UNIVERSITY OF ALBERTA

The Relationship Between Atopy and Respiratory Symptoms in Alberta Farmers

by

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ABSTRACT

Farming is the commonest occupation in the world and has been associated with several respiratory syndromes. These syndromes include asthma, chronic bronchitis, non-specific airflow limitation, extrinsic allergic alveolitis, organic dust toxic syndrome and mucous membrane irritation syndrome.

Certain host factors such as atopy to environmental antigens may predispose an individual to be susceptible to some of these syndromes.

Among 781 farmers from two counties in East-Central Alberta, respiratory symptoms were found to occur commonly. Skin atopy to environmental antigens was strongly correlated with asthma and symptoms consistent with asthma, whereas symptoms of chronic bronchitis were not associated with atopy.

When prevalence of respiratory symptoms was compared for 781 farmers and 151 oil workers no difference in frequency of respiratory symptoms were noted when age and smoking history were controlled for. The prevalence of atopy to environmental antigens was significantly lower in farmers than in oil workers. This would suggest that farmers who are atopic select themselves out of the occupation (healthy worker effect).

In non-smoking farmers who reported respiratory symptoms and who had specific and non-specific bronchoprovocation studies performed, the farmers who reported asthma or symptoms consistent with asthma, were more likely to have a positive bronchoprovocation test when compared with farmers reporting chronic bronchitis symptoms. Farmers with atopy to agricultural antigens were more likely to have a positive specific bronchoprovocation test. Correlation between specific

and nonspecific bronchoprovocation test were low (OR = 1.66 p = 0.68), suggesting that the most widely used method of identifying those airway reactivity may not be the most sensitive method in this group of workers. Farmers who report symptoms consistent with asthma had responses to the challenge test that were similar to those with asthma and therefore may represent a pool of individuals that may have asthma or occupationally induced asthma.

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CHAPTER I

GENERAL INTRODUCTION

Introduction

Farming is the commonest occupation in the world. It has also been associated with respiratory diseases. The first description of an occupational disease in agricultural workers was by Ramazzini in 1613 (1), describing respiratory disease in grain workers. There is a long and well documented connection between agricultural practices and the development of respiratory illnesses.

The exposures on a farm are multiple and vary in intensity and duration. They include grain dust, hay, animals and animal products, fertilizers, fuels, and chemicals such as pesticides and herbicides (2).

The respiratory syndromes that have been shown to be related to the agricultural industry include asthma, chronic bronchitis, non-specific airflow limitation, extrinsic allergic alveolitis, organic dust toxic syndrome and mucous membrane irritation syndrome (2).

The question of whether host (genetic) factors predispose to the development different respiratory syndromes has been extensively discussed. The British hypothesis states that an individual will develop asthma or chronic bronchitis if exposed to certain agents for long enough duration and in high enough concentrations, whereas the Dutch hypothesis states that there is there an underlying genetic predisposition that results in the development of symptoms and disease following exposure (3).

One identifiable host factor for the development of certain respiratory syndromes is atopy (4). In children at high risk for atopy (5), CD4+ cell function was significantly different from 'normal' children. IL-4 production was significantly lower in high risk children. The suggestion being that immune responses to environmental allergens in early childhood occur against a background of maturational deficiency in CD4+ T-cell function and that this difference may account for different responses to environmental allergens.

Although the weight of current evidence favours the Dutch hypothesis, the amount of exposure (whether measured as length of time or concentration) plays a role in determining pulmonary response to inhaled substances. With grain dust, those with prolonged and persistent exposures (i.e grain handlers) have shown a stronger association with certain respiratory syndromes (6,7). Farmers' exposures to grain dust are relatively intermittent and probably result in lower cumulative doses. Also, farmers are exposed to numerous other agents which may confound the association between grain dust exposure and the development of respiratory syndromes.

The objectives of this study are to: 1) document the relationship between atopy and respiratory symptoms in farmers; 2) determine whether respiratory symptoms in farmers are more common than expected; and 3) determine if the presence of these symptoms are associated with airway hyperreactivity to specific or non specific challenge testing.

A series of papers will be presented to answer the objectives. The first paper deals with the relationship of respiratory symptoms in farmers with skin atopy to environmental antigens. In particular this paper will attempt to assess the relationship between atopy to either common environmental antigens or occupationally associated antigens and respiratory symptoms. If an association between atopy and both asthmalike respiratory symptoms and asthma is found, it would support the role of genetic predisposition in the development of certain respiratory illnesses and clarify the significance of asthmalike symptoms in the absence of a diagnosis of asthma. This paper will explore whether atopy to agricultural antigens occurs in individuals who are atopic to common environmental antigens, or whether atopy to agricultural and common environmental antigens occur independently.

The next paper compares the prevalence of respiratory symptoms in farmers and a non-exposed comparison group. This is to determine whether respiratory symptoms occur more frequently in farmers and to compare the relationship between symptoms and atopy in the two groups. Affected workers often remove themselves from certain occupations if symptoms develop as a result of being in a work environment. Atopy to common environmental antigens could be used as a marker for a self selection process.

The last paper explores the relationship between respiratory symptoms and bronchial reactivity. Non-smoking farmers with respiratory symptoms had specific and non-specific bronchoprovocation tests performed. This was to determine whether those reporting asthmalike symptoms do in fact have increased airway hyperreactivity as seen in asthmatics. Also the issue of whether this increased airway reactivity was induced by an agricultural exposure was explored.

Farm Exposures

The exposures on a farm are multiple and vary in intensity and duration, they include grain dust, hay, animals and animal products, fertilizers, fuels, and chemicals such as pesticides and herbicides.

The grains include a variety of cereal grains such as wheat, barley, oats, rye, and oil seeds such as canola, mustard and sunflower (2).

From an occupational health perspective, grain consists of grain kernels and husks, weed seeds, storage mites, insects, bacteria, moulds, inorganic material, chemicals, and animal matter (including weevils, particles and excrement of rodents, insects and birds) (2).

Analyses of cattle barns reveal aeroallergens such as fungi, moulds, insects, cattle, rats and grasses (8).

Hog barns include many of the above aeroallergens as well as dander from the hogs, and ammonia and hydrogen sulfide gas (9).

The grain dust microflora changes through handling and storage and is often dependent on the conditions at the time of storage. During harvest, Cladosporium sp.and Alternaria sp. are often found and vary in quantity. Depending on storage conditions (such as grain dampness and aeration) fungi are found in varying concentrations. These include Ustilago sp., Aspergillus sp. and Mucor sp. and the above mentioned moulds and, if the grain overheats, Thermophillic actinomycetes species (10).

Gram negative bacteria such as Enterobacter sp. Pseudomonas sp., Serratia, and Acinetobacter have been identified (11).

Grains also contain mites that have antigenic potential for causing illness. These include Sitphilus granarius, Glycophagus, Tyrophagus, Acarus, and Goheria. The concentration of these mites is dependent on the water content of the grain: the dryer the grain, the fewer mites found (2,10).

Inorganic dust also are a component of grain dust and have been detected in tractor cabs in Alberta (12). The majority of these particles were respirable (< 5 microns). Free silica varied from 1 to 17% of mass, but no asbestos, tremolite or zeolite were identified. At large coastal terminals, the inorganic content of the dust is about 2.1% whereas in country elevators the content is about 6.5% (13).

Atopy and Respiratory Syndromes

Atopy is defined as a sensitivity to environmental antigens. One manifestation of this is an immediate skin reaction to the antigen (14). In order for this reaction to occur, the subject must have been previously been exposed to the antigen. Either lymphocytes or plasma cells are stimulated to produce antibodies that, in turn, stimulate effector cells such as mast cells and eosinophils to release mediators. These mediators include substances such as histamine, that cause vascular dilation and increase vascular permeability. The outcome is the development of an itchy skin wheal within minutes after antigen exposure (15,16,17). For an immediate skin reaction to occur, the above mentioned cascade must be functional.

The class of immunoglobulins produced to create such a reaction are predominantly IgE (17). The effector cells identified with this reaction include eosinophils and mast cells (16,17), with eosinophils being present in the circulatory system while mast cells reside within organs (18,19).

To determine if there is in fact a genetic predisposition to development of certain respiratory syndromes such as asthma, several studies have investigated the association between respiratory syndromes and skin atopy, serum IgE levels, and circulating eosinophil levels (6,14,15,20,21,22).

Eosinophils have long been noted to be increased in severe asthma (19). The level of eosinophilia increases with severity of asthma, and the level of eosinophils increases with the development of a late asthmatic response. A survey exploring the relationship between eosinophilia and FEV1 in a cross-sectional study showed that there was a significant relationship between the level of blood eosinophilia and reduction in FEV1, but a longitudinal study of the same population did not confirm this fact (22). Burrows et al showed a significant relationship between FEV1 and eosinophilia that disappeared once asthmatics were removed from the analysis (21). This would suggest that atopy alone is not the cause of decline in FEV1, but because of the strong association between atopy and asthma, lower spirometry measurements are noted in atopic individuals.

IgE has been associated with the allergic phenomenon (20). Atopic subjects tend to have higher IgE levels than nonatopics. The peak level of IgE is found in children age 10 years, and there is a rapid decline with age. IgE tends to be higher in smokers. Burrows et al (20,23) indicated that when controlled for age, IgE levels are consistently higher in asthmatics. In subjects older than 35 years, after controlling for age and smoking history, there was a relationship between the elevation of IgE and decline in FEV1 and again, this association disappeared once asthmatics were removed from the analysis. In spite of this only a small proportion of subjects with elevated serum IgE levels have clinical asthma.

Skin atopy to common aeroallergens has been long recognized as being associated with respiratory syndromes. One syndrome, hay fever, is strongly correlated with skin atopy (14,20,21,23). In community based surveys skin atopy is common, occurring in up to 50% of the population tested. The distribution has a peak in prevalence at age 30 and then falls with age. Longitudinal studies confirm this as well as noting that skin atopy in individuals is not static. As one ages, there tends to be a fall in skin test response to common aeroallergens. With increasing age the likelihood of converting ones skin test from negative to positive declines as well. Smokers tend to less atopic but exsmokers tend to be more atopic than either current smokers or nonsmokers.

In the Tuscon study (4,24), respiratory symptoms such as wheeze, family history of allergy and self reported asthma were correlated with skin atopy. In children a history of chronic cough and recurrent respiratory tract infections were correlated with skin atopy, while in adults chronic cough was more closely associated with smoking. It should be noted that although the sensitivity of the skin test in identifying people with asthma is high, the specificity is rather low. This means that persons with reported asthma are likely to have a positive skin test to common aeroallergens, but a positive skin test does not necessarily imply the presence of asthma.

Ventilatory impairment does appear to be weakly correlated with skin atopy (4), although this association appears to be mainly due to the relationship between atopy and asthma. However, the association between ventilatory impairment and atopy may be under estimated in population based studies because, while ventilatory impairment is most often noted in the elderly, this group is known to have a lower prevalence of skin atopy. One form of ventilatory impairment, asthmatic bronchitis does appear to be correlated with skin atopy. Because atopy is largely determined genetically, this would help confirm the Dutch hypothesis that genetic predisposition plays an important role in the development of different forms of ventilatory impairment.

Several studies have been performed examining the correlation between skin atopy and IgE levels. Barbee et.al. in a large community based survey compared mean IgE levels and skin atopy controlling for age and sex (20). Across both sex and age categories the mean IgE levels were higher in atopic individuals but the variation in IgE levels amongst individuals was so large that confidence limits were difficult to construct.

A survey of 363 French policemen comparing FEV1 levels, skin atopy and blood eosinophil levels found a statistically significant relationship between skin atopy and percent blood eosinophils but this relationship did not hold if absolute eosinophil count was compared to skin atopy (22).

In a survey comparing 207 newly hired Saskatchewan grain handlers (25) to agricultural students a lower prevalence of atopy to common antigens (21.4% vs 33.3%) was noted for the grain handlers. When testing was repeated an average of 1.34 years after commencing employment, those that dropped out of the industry and the control dropouts had similar rates of atopy (26.7% vs 24.4%) respectively. The atopy rate for those that remained in the industry was 18.7% vs 33.3% in controls. Of those who reported wheeze on job entry, those who dropped out had an atopy rate of 41.2 % vs 18.2% in those with wheeze who remained in the industry. Subjects with other symptoms such as cough and phlegm production did not exhibit similar drop out rates. This study would indicate that atopic individuals are more likely to report symptoms suggestive of asthma and are more likely to remove themselves from the industry (healthy worker effect).

Respiratory Syndromes

Several respiratory syndromes have been shown to be associated with exposures in the farming environment.

1) Extrinsic allergic alveolitis (also known as farmers lung) refers to a syndrome that presents with symptoms of cough, chest tightness, fever, and pain in the extremities followed by the development of respiratory symptoms such as increasing shortness of breath (26,27). On examination basal crepitations are often heard. The chest x-ray shows a diffuse miliary pattern that can lead to pulmonary fibrosis.

Pulmonary function testing usually reveals a restrictive pattern with a reduction in PaO_2 and a reduction in diffusing capacity (26).

On bronchoscopy, infiltration with lymphocytes and macrophages is noted, but if samples are taken very soon after the initial febrile episode they often show a granulocytic predominance.

Precipitating antibodies are noted with fungi that have spores less than 5 microns. These include Alternaria, Thermophilic actinomycetes, Micropolyspora feani, and Aspergillus.

From Swedish studies, the yearly incidence in 4,373 full time farmers was estimated to be 3/10,000 (27) .

It was initially felt that treatment and avoidance of exposure to the offending agent, could prevent permanent pulmonary fibrosis. Terho (28) in a recent longitudinal study has suggested that the degree of pulmonary fibrosis is not affected by treatment with steroids or being removed from the workplace, but that with steroids there is a more rapid resolution of the pulmonary abnormalities.

There does not appear to be any correlation between extrinsic allergic alveolitis and atopy.

2) Organic dust toxic syndrome (ODTS) refers to a syndrome noted by doPico to occur in high frequency in farmers (26). It is manifested by symptoms of fever and dyspnea, dry cough, headache, joint and muscle pain, fatigue, and nausea that develop shortly after exposure to mouldy dust. The symptoms generally are short lived, affected individuals may show a transient fall in diffusing capacity, and may have fleeting infiltrates on chest x-ray.

Bronchoscopy, if performed shortly after exposure, may show a neutrophilic infiltrate. Although the presence of neutrophils in the lungs is often associated with the development of pulmonary fibrosis, this is not noted in those with ODTS.

The exposure noted is often extremely mouldy grain.

In Sweden, ODTS occurs commonly with an annual incidence estimated to be 1/100 farmers/year (27).

The importance in differentiating between ODTS and extrinsic allergic alveolitis is that extrinsic allergic alveolitis may lead to permanent irreversible pulmonary fibrosis whereas ODTS is unlikely to lead to permanent disability.

Again, no noted association between ODTS and atopy has been documented.

3) Mucous membrane irritation syndrome refers to a syndrome of symptoms reflective of irritation of the mucous membranes following exposure to organic dusts. Symptoms include dry or itchy eyes, and sore or itchy throat and nose. In a Manitoba survey of farmers, the rate ratio of nasal symptoms was 1.8 in current as opposed to former farmers (29). The long term significance of this syndrome is not known.

4) Chronic bronchitis is defined by symptoms of cough and phlegm production for more than three months in a year for two consecutive years (3). There are two components to this disorder, hypersecretion of mucous that can lead to more frequent infections, and airflow obstruction that can lead to permanent respiratory disability. Although airflow obstruction is often found in those

with chronic bronchitis, this is thought to be related most often to underlying emphysema (30). The suggested reason for the common co-existence between chronic bronchitis and airflow obstruction is the relationship between both of these conditions and cigarette smoking. The prevalence of chronic bronchitis varies based on smoking history and ambient air pollution levels, especially particulate air pollution (46) . In smokers living in a high pollution area the prevalence is estimated to be 15% whereas in non smokers living in low pollution areas, the prevalence is estimated to be about 2-3%. The importance of this diagnosis rests in its association with an increase in both morbidity and mortality. The symptoms and rate of decline in spirometry measurements improve when the inciting agent is removed (e.g. when smokers stop smoking).

Symptoms of chronic bronchitis have been demonstrated in agricultural workers.

In a study of 1685 Danish farmers, the prevalence of chronic bronchitis was 23.6% (32). The prevalence was increased in older farmers, smokers and those that were involved in raising hogs.

A survey in Saskatchewan compared 90 nonsmoking farmers to matched controls (town residents)(33). The prevalence of symptoms of chronic bronchitis was significantly higher in the farmers (23.1% vs 3.3%). Relationships between atopy and respiratory function were not explored. There was an association between years of agricultural exposure and reduction in MMFR and Vmax50, but because of the small numbers in each cell, no comparison to type of respiratory symptoms and physiologic measurements could be made.

In a survey of 824 farmers in Slavonia (34) Milosevic found the prevalence of chronic bronchitis symptoms to be 27.1% (14.5% in non smoking farmers n = 43). Cattle breeders had the highest prevalence at 47.4%.

A survey of 250 French dairy farmers matched with 250 administrative workers (35) found the prevalence of chronic bronchitis to be 14.8% in the farming group. Comparing the two groups, there was a significant odds ratio of 2.13 (CI 1.01,3.25) overall, and 7.56 (CI 1.70,13.42) in non smokers. Respiratory function was lower in the farming group, but this was not correlated with either respiratory symptoms or atopic status.

In a survey of 833 Manitoba farmers (36), 23% reported symptoms of chronic bronchitis, 18% in non smokers. There was a slight increase in cattle farmers compared to non-cattle farmers (27% vs 22% n.s.). A weak association between skin atopy and chronic bronchitis symptoms was found.

In a survey of 300 grain elevator workers (37) in Wisconsin, doPico found a prevalence of chronic bronchitis of 37% (42% in smokers and 30% in non smokers). No correlation between chronic bronchitic symptoms and either atopy to work related aeroantigens (fungi, bacteria grain and grain dust) or measurements of respiratory function (FEV1, FVC and DLCO) were found.

It would appear, on the basis of these studies that symptoms of chronic bronchitis are more prevalent in persons working in the agricultural industry, and that amongst farmers, working with confined animals increased this prevalence.

There does not appear to be an association between chronic bronchitic symptoms and skin atopy. There has been no documentation of farmers having chronic bronchitic symptoms developing a more rapid decline in respiratory function.

5) Asthma is defined by the American Thoracic Society (ATS) (38) as a syndrome with paroxysms of dyspnea, wheezing and cough, which may vary from mild and almost undetectable to severe and unremitting. A characteristic of asthma is airway hyperresponsiveness resulting in variable airway obstruction. Because of the variability in lung function and symptoms, the prevalence of asthma is difficult to estimate by physiologic measures alone (39,40,41). Single measurements of respiratory function often do not document the variability and in fact, unless the subject is having an exacerbation of asthma, lung function may be normal. This may hold true even if repeated measurements of lung function are made.

Diagnosis of asthma can be made by several means (39,41). These include clinical evaluation, by questionnaire (looking for a history of diagnosis or history of symptoms), by pulmonary function testing (identifying the level and variability of respiratory function), airway responsiveness to bronchodilators, and by both specific and non-specific bronchial challenge testing (43,44).

Because of the difficulty in developing a diagnostic test for asthma that has high sensitivity and specificity, and that is simple and safe to administer in the epidemiologic setting, estimates of the prevalence of asthma have been based on a positive response to the question "Have you ever been diagnosed as having asthma by a physician?" (41).

Based on the Second National Survey of Morbidity in General Practice in Britain, it estimated that up to age 15, 2-3 % of boys and 1-2 % of girls have asthma. For adults, the estimated prevalence is about 1-2 % (46,52).

From the Second National Health and Nutrition Examination Survey (1976-1980) in the U.S.(47), where asthma was defined as physician diagnosed asthma or as having asthma and/or frequent problems with wheezing in the past 12 months, the overall prevalence was estimated to be 10.6%. In terms of age distribution, between the ages 3-11 years the asthma prevalence was 10.2%, from 12-44 it was 9.9%, from 45-64 11.8% and from 65-74, 12.4%.

In other North American surveys using questionnaires the prevalence of asthma has been estimated to range from about 10% in male children to about 4-5 % in the adult population(45,46,47,48,49,50,). There have been no recent studies estimating the prevalence of asthma in Canada.

Occupational asthma is defined as variable airflow obstruction caused by a specific agent at the workplace (53). The prevalence of occupational asthma is again difficult to estimate, but one survey in Japan estimated that approximately 15% of adult male asthma was due to an occupational exposure. Often there is an under estimation of the prevalence of occupational asthma in cross sectional studies due to the fact that asthmatics may self select themselves out of an environment that is causing them problems.

The diagnosis of occupational asthma can be made by several methods (53). The first is by questioning and noting changes in respiratory symptoms related to exposure. More objective means of diagnosis include peak flow measurements (PEF) over time, pre and post shift spirometry measurements and specific and non specific challenge tests. Many agents have been implicated in causing occupational asthma (over 200) but only a few have been studied in detail. These agents can be divided into low and high molecular weight compounds. Examples of low molecular weight compounds (< 1000 Daltons) include isocyanates, plicatic acid and acid anhydrides. High molecular weight compounds include proteins, polysaccharides and peptides, such as grain and cotton dust, and animal dander (53).

The importance of identifying asthmatics is that there is a link between acute asthma and airway hyperreactivity, and chronic respiratory changes (3,51,54). In several industries (grain handling and cotton industries) persons documented as having the greatest acute changes in spirometry measurements after exposure to the agent have been found to have the greatest chronic reductions in spirometry measurements when tested years later. On the other hand, when comparing the rate of fall in spirometry measurements between persons in the general population with COPD vs asthmatic bronchitis, the persons with COPD on average had an annual fall in FEV1 of about 70 ml/yr while those with asthmatic bronchitis had an average annual fall of only 20 ml/yr with treatment (4). This information would indicate that persons with asthma or asthmatic bronchitis are susceptible to a greater annual decline in respiratory function that can lead to a permanent respiratory impairment that can be prevented if recognized and treated. The association between asthma and agricultural work has been long recognized and the prevalence of asthma has been estimated in a few studies. Because of the difficulty in diagnosing asthma, the various reports have led to different conclusions.

Iverson, in 1685 Danish farmers, noted a prevalence of asthma of 7.7%. The prevalence increased in the older age groups (32). In those between the ages of 51 and 70 the prevalence was 11.8% while in the less than 30 age group it was 1.0% . This pattern of increasing prevalence in the older age categories is common for occupational asthma. There was no correlation made with skin atopy.

Cuthbert, in a survey of 220 Orkney farmers noted the prevalence of asthma in their farming population to be 15%. Those who stated that symptoms worsened on exposure to agricultural products had a higher rate of skin atopy to storage mites than local townspeople (55).

In the grain handling industry Chan-Yeung estimated the prevalence of asthma in grain workers to be 2.4% as opposed to 2.7% in civic workers (56). When comparing skin atopy rates in non-exposed civic workers and exposed grain handlers, the civic workers had an atopy rate of 28.1 % whereas grain handlers had a rate of 16.2 %. Longitudinally as the mean level of grain dust fell in the port of Vancouver grain terminals, the prevalence of skin atopy and persons with self reported asthma increased, suggesting that atopic individuals were able to remain in the industry as dust exposure was reduced (7,57). These studies suggest that there may be a selection process that eliminates people with asthma or asthma like symptoms from this environment (healthy worker effect).

Because of the reliance on self reported asthma, there is a concern that the prevalence of asthma may be under estimated. Persons exposed to potentially asthmagenic substances may have undiagnosed asthma. Therefore the occurrence of acute respiratory symptoms has been evaluated in agricultural workers as a marker for undiagnosed asthma. These symptoms have been correlated with atopy and airway hyperreactivity .

In a survey of 610 elevator workers in Vancouver, symptoms of wheeze and cough were more common in atopic elevator workers when compared to atopic civic workers (56). Therefore a proportion of subjects with asthma like symptoms exhibit features of asthma such as increased bronchial reactivity and an increased prevalence of skin atopy. These people could represent a pool of undiagnosed asthma or represent a mild form of the syndrome. Since asthmatics when chronically exposed to an agent to which they are sensitized are more likely to have a rapid decline in respiratory function, undiagnosed asthmatics who are continually exposed to the sensitizing agent are at even greater risk for rapid fall in lung function.

In a study of 90 non smoking Saskatchewan grain handlers 33% of workers reported symptoms of wheeze, whereas only 10.0 % of non grain handlers did ($p < .001$). No correlation with atopic status was made (33).

Iverson et al. studying 1175 Danish farmers (61) noted that in those reporting having asthma 95% (36/38) had a positive methacholine test. Of those reporting asthmalike symptoms (wheeze, shortness of breath or cough without phlegm), 66% (40/61) had a positive methacholine challenge and in those reporting no respiratory symptoms, 59% (20/34) had a positive challenge test.

DoPico in a survey of 300 grain handlers reviewed respiratory symptoms, lung function and atopic status (37). 42% had symptoms of wheeze, and 76% had cough on exposure. 27.6% had a positive skin test to pollens, insects, alternaria, cat hair or flax. 17% reacted to rye, oats, barley or wheat. Respiratory symptoms (wheeze on exposure, chest tightness, histoty of wheeze) were more common in skin reactors. A larger number of abnormal Vmax 50 and Vmax 75 measurements occurred in the atopic individuals.

In Manitoba farmers (36) acute shortness of breath was noted in 41% and was more common in smokers. Those who had a positive skin test to common antigens had a higher mean IgE level. Persistent wheeze was also more common in the atopic group.

Non-specific challenge testing using substances such as methacholine and histamine is often used to document airway hypersensitivity (43,44). Although airway hyperreactivity is not exclusively seen in asthmatics, it is a major component of asthma. In an occupational setting, these tests are often used to document changes in hypersensitivity when a worker moves from a relatively innocuous environment to an environment that is potentially asthmagenic.

Specific challenge testing involves controlled exposure to an agent that is suspected to be causative for their asthma (69). In a controlled environment, lung function measurements are performed before and after the subject is exposed to the agent. A drop of at least 20% in either peak flow or FEV1 is required to demonstrate a causal relationship. Care must be taken when performing these tests so that adverse reactions do not occur. It should be noted that in an environment of concern there may be multiple exposures, one or more of which may be responsible for the development of asthma and therefore the causal agent may not be tested for.

When looking at predictors of methacholine reactivity in Vancouver grain handlers, presence of atopy yielded an odds ratio of 2.10 ($p < 0.05$). Years of employments also showed a significant association (OR=1.38). There was no correlation with smoking history (64). Those with a physician's diagnosis of asthma showed the greatest response to methacholine: 60.5% had a response to less than 8 mg/ml of methacholine and 39.5% responded to less than 2 mg/ml of methacholine. In those with sypmtoms of chronic bronchitis 31.4% responded to less than 8 mg/ml and 10% responded to less than 2 mg/ml. In persons reporting no respiratory symptoms only 10.5% had a response to less than 8 mg/ml of methacholine and 2.4% to less than 2 mg/ml (64). Of those reporting symptoms of wheeze and breathlessness, 12.6% responded to less than 2 mg/ml of methacholine and, using Brooks' criteria for asthma (i.e. positive response to at least 4 questions- regular wheeze, cough, phlegm, breathlessness, cough on most days, persistent wheeze, attacks of chest tightness with breathlessness, or breathlessness on hurrying up a hill), 32.7% responded to at least 8 mg/ml of methacholine and 12.7% responded to less than 2 mg/ml. This study did not correlate respiratory symptoms and bronchial reactivity with atopic status.

Therefore a proportion of persons with asthma-like symptoms respond to methacholine in the same way that asthmatics do and may represent cases of undiagnosed asthma.

6) Non-specific airflow limitation refers to a fall in spirometry measurements over time in persons who either do not have symptoms or are not diagnosed as having a respiratory disorder. This phenomena as been documented in grain handlers (6,59,70). Unless testing is performed, this loss in lung function may not be recognized. An explanation for the lack of symptoms is that these subjects are otherwise healthy and often young with a large respiratory reserve. With continued exposure and time, however, permanent disability may develop.

Heller et.al. in a study of 146 farmers did not demonstrate an excess in respiratory symptoms but noted an increase in the proportion of farmers with an decreased FEV1/FVC ratio (60). No correlation was made with either respiratory symptoms or atopic status.

Non-smoking farmers in Saskatchewan had a lower mean mid expiratory flow rates and MEF 50 than controls (62,66).

DoPico in a longitudinal study of 146 farmers did not notice any relation between length of farming and decline in respiratory function (37).

In his survey of Manitoba farmers Warren found that smokers had reduced respiratory function as compared to non farming smokers but associations with type of respiratory symptoms and atopy were not noted to be significant (36).

Broder in a survey of 441 grain workers (63) in Thunder Bay noted a small decrease in FVC and FEV1 when comparing grain workers to civic workers. As well about 1% of civic workers reported a positive skin test to grain antigens whereas between 4 and 6% of grain handlers were positive. The civic workers when compared to two groups of grain handlers, also reported a greater frequency of positive skin tests to moulds or pollen (13% vs 4% and 10%) and reported a greater frequency of asthma (19% vs 13% and 10%). This may be indicative a selection process (i.e healthy worker effect), thereby underestimating the effect of grain dust on respiratory function.

Several reports have been compiled on grain workers at the port of Vancouver. Chan-Yeung et. al. studied 610 grain workers and compared these to 136 civic workers(56,64,65,72). Amongst the grain workers, 17.5% had a positive skin test to common antigens, 13.6% positive to Dermatophagoides farinae and 8.8% positive to grass pollen whereas in the civic workers 28.1% had a positive skin test to common antigens, 17% to D. farinae and 18.5 % to common grass pollen. Among non smokers, the percent of predicted FEV1 in grain workers was lower than in civic workers (100% vs 104%). The same phenomenon was seen for FVC measurements (99.8 % vs 104.7 %). The grain workers also had significant cross shift declines in FEV1 and FVC that were not seen in a comparable group of sawmill workers (66). Despite the likely presence of a healthy worker effect (reflected by a lower rate of atopy to common antigens) there was a demonstrable decline in spirometry measurements and increased bronchial reactivity.

In a nested cohort study, those grain workers with the greatest declines in FEV1 over a 6 year period were analyzed (6). The greatest declines were seen in workers with the highest dust exposure levels. Other host factors were analyzed and found not to be significant (atopy, asthma, bronchitis, and other respiratory symptoms). This fall in FEV1 was seen with dust levels that were persistently elevated above 5 mg/m^3.

Amongst the same workers, a cohort study of those with increased bronchial reactivity was performed (58). In those workers with a demonstrable reactivity to methacholine, a greater cross shift change in FEV1 was seen as was the greatest decline in FEV1 (13 vs 26 ml/yr) over a six year period. Also those who had a positive response to a controlled grain dust challenge had an even more pronounced fall (78 ml/yr). Workers who had a positive methacholine challenge at the beginning of the survey had the lowest percent predicted FEV1 (65% vs 93% in those who did not respond to methacholine). This level of FEV1 was similar to those with a positive response to a grain dust challenge (66%). Therefore there appears to be an especially detrimental effect of grain dust on respiratory function in workers with reactive airways, more so when they are found to be specifically sensitive to grain dust.

In another longitudinal study of these grain workers, the change in spirometry was correlated with dust exposure levels. Civic workers (comparison group) had a decline in FEV1 of 21.1 ml/yr and 24.7 ml/yr in FVC. Those chronically exposed to dust levels greater than 9 mg/m^3 had a decline in FEV1 of 34.1 ml/yr and in FVC of 41.9 ml/yr. This decline was greater for workers exposed to between 4 and 9 ml/m^3. Workers exposed to less than 4 mg/m^3 had the smallest annual decline. These data support a dose response relationship between dust exposure and decline in respiratory function (6,57).

The conclusions drawn from the Vancouver studies are: 1) that chronic grain dust exposure leads to a more rapid decline in respiratory function and more respiratory symptoms; 2) there appears to be a dose dependent effect on respiratory function; 3) those with demonstrable airway hyperreactivity (especially to the specific exposure), when chronically exposed have a more rapid decline in respiratory function; 4) persons with reported asthma and atopy are proportionally less well represented in the grain handling industry, but, as dust levels are being reduced, they are being increasingly represented suggesting a healthy worker effect, in that those who can tolerate the exposure remain in the industry while those not able to withstand the exposure remove themselves from the industry.

This relationship between grain dust exposure and change in respiratory function is not as well documented in farmers. Reasons for this may include the fact that farmers are more difficult to identify and study and possibly that farmers are exposed to lower levels of grain dust.

Conclusions

A number of studies have investigated the respiratory effects of grain dust on grain handlers. As the exposure to grain dust increases so does the rate of decline in respiratory function. In longitudinal studies, as the dust level increases, the proportion of workers with reported asthma or skin atopy declines, suggesting a process of healthy worker selection. Those individuals with the greatest documented bronchial reactivity, have the greatest decline in respiratory function if they continue to work in the industry. The conclusions from this body of evidence would be that grain dust is potentially hazardous to the respiratory health of workers and that the greatest risk is to those individuals with asthma, airway hyperreactivity or atopy.

The studies to date on the respiratory health of farmers especially in association with atopic status are unclear. The studies have been cross-sectional and case-control studies. There have been no long term longitudinal studies. In spite of this it appears that asthma and atopy to agricultural antigens in farmers is increased when compared to non farming populations.

The long term fall in respiratory function noted in grain handlers that is more pronounced in those with bronchial reactivity has not been documented or studied in the farming population. If a similar longitudinal fall in lung function can be documented in farmers, then the potency of grain dust as an asthmagenic agent could be confirmed, since farmers are exposed to grain dust on a less frequent basis than grainhandlers. Studies of farmers to date do not show any relationship between either atopic status or asthma and a more rapid decline in lung function.

The exposures on the farm are to a multitude of agents, and the exposures vary in duration. Exposure to grain dust may not be a daily occurrence, but may be intense during harvesting and planting. Some farmers grind grain for feed, resulting in further exposures. Other exposure include animals, chemicals and grass crops. Because most farmers are self employed, exposures might change due to symptoms, e.g. certain grain crops will not be grown or the farmer may get out of hog or chicken production. There may also be a selection process occurring. Because farms are often passed from generation to generation the child that develops respiratory symptoms may choose not to remain on the farm.

These factors complicate the assessment of the association between farming and respiratory health.

CHAPTER II

RESPIRATORY SYMPTOMS AND ATOPY IN ALBERTA FARMERS

Respiratory Symptoms and Atopy in Alberta Farmers

Farming is the commonest occupation in the world and exposure to grain dust has long been recognized as being a causative factor in the development of lung disease (1). Other studies of populations exposed to grain dust have demonstrated adverse changes in pulmonary function and respiratory symptoms (2,54). Respiratory syndromes associated with grain dust exposure include asthma, chronic bronchitis, non-specific airflow limitation, extrinsic allergic alveolitis, organic dust toxic syndrome and mucous membrane irritation syndrome.

The prevalence of asthma in the general adult population is approximately 5% but in surveys in farming communities, the prevalence has been reported to be as high as 15 percent (55). Symptoms of chronic bronchitis (cough and phlegm production for more than 3 months over a two year period) occur in 4 - 15 percent of the general population dependent on smoking history and ambient air pollution levels (3,24). Most studies indicate that chronic bronchitis is twice as common in farmers as non-farmers (34,35,36).

Grain handlers in the port of Vancouver were studied in both case-control and cohort studies (6,56). In both study designs exposed workers were found to have more respiratory symptoms and a lower FEV1 than non-exposed workers. This in spite of the fact that grain handlers have a much lower prevalence of self-reported asthma and atopy than the general population.

To date, the data on respiratory function changes in farmers are inconclusive . Two case-control studies have been performed, one indicating that farmers do have evidence of airflow obstruction (73), and the other not showing this effect (60).

Atopy to common environmental antigens occurs in up to 40 percent of the general population (14), and although reactivity to these antigens does not necessarily predict the development of respiratory symptoms, several authors indicate that almost all persons with hay fever syndrome and asthma appear to be atopic (4,15): atopy being defined as having skin reactivity to at least one antigen, or by having elevated blood IGE levels. Therefore there is the suspicion that atopy may be important in identifying individuals who are more susceptible to developing certain respiratory syndromes such as asthma (4), the presence of asthmalike symptoms (65), bronchial reactivity (68), mucous membrane irritation syndrome (36), or a more rapid loss of pulmonary function (4).

To further understand and to quantify the risk of developing respiratory problems in mixed agricultural farmers in Alberta, a cross-sectional survey was performed, to establish the prevalence of respiratory symptoms, pulmonary function abnormalities, and reactivity to common environmental antigens.

The goal of this project was to quantify the prevalence of respiratory symptoms in Alberta farmers and host factors (i.e. atopy) associated with these symptoms, and specifically to determine whether asthmalike symptoms and chronic bronchitis in farmers are associated with atopy in a manner similar to the way asthma is associated with atopy.

Methods

A survey instrument was developed based on the American Thoracic Society respiratory symptom questionnaire (74) (appendix 1). Additions to the questionnaire included items or sections on mucous membrane irritation syndrome, symptoms suggestive of either extrinsic allergic alveolitis or organic dust toxic syndrome, questions on past medical history and family history, and medication use. Detailed enquiry was made about the occupational history, and in particular, the type and extent of exposure to various agricultural products. For instance, the extent of exposure to different grains was explored as well as exposure to livestock and chemicals.

Testing of skin reactivity was performed by the skin prick method. A drop of antigen was placed on the skin and a small scratch was made with a sterile needle. The largest diameter of the skin wheal was measured 15 minutes after exposure and a measurement of 3 mm or greater was interpreted as positive. The antigens used included wheat, rye grain, house dust, alternaria, cat dander and birch tree.

In Camrose and Wetaskiwin counties in East-Central Alberta, a list of farmers from the federal fertilizer rebate program was obtained from the district agriculturalists. This was felt to be the most complete listing of farmers in the area. The farmers were then contacted by telephone and were asked about eligibility. White males between the ages of 18 and 65 who spent at least 80% of their time farming were invited to participate in the survey.

Several testing sites were set up within the counties. Farmers were contacted by telephone (at least 4 attempts were made) and invited to attend the testing site. Those who expressed a willingness to participate but did not attend were called again and their appointments were rescheduled. The participation rate was 76%.

Upon the subject's arrival to the testing site, a trained interviewer informed the subject about the survey and obtained informed consent. The questionnaire was administered and skin tests were performed.

Incoming questionnaires were reviewed for completeness and consistency. The data were then coded, double entered and checked for valid codes and internal consistency. Deficiencies were corrected.

All subjects were contacted by mail explaining the individual findings. Those with either abnormal spirometry (FEV1 less than 80% predicted) or remarkable symptoms were contacted by telephone by a physician and follow-up arrangements were made.

Bivariate analyses were performed using the chi-square test for categorical variables (e.g. presence of symptoms). Multivariate categorical analyses were performed using unconditional logistic regression methods. Forward stepwise selection using likelihood ratios was employed to select the most strongly associated variables. Cigarette smoking and age were the factors most commonly controlled in the multivariate analyses.

Respiratory symptoms were defined as follows:

1) Asthma, positive responses to the questions "Have you ever had asthma" and "do you still have asthma".

2) Cough, positive responses to the questions "Do you usually have a cough" and "Do you usually cough like this for 3 consecutive months or more during the year for 2 or more years".

3) Phlegm, positive responses to the questions "Do you usually bring up phlegm from your chest" and "Do you bring up phlegm like this for 3 consecutive months or more during the year for 2 or more years".

4) Dyspnea, positive response to the question "Are you troubled by shortness of breath when hurrying on the level or walking up a short hill".

5) Wheezing, positive response to the question "Does your chest ever sound wheezy or whistling occasionally apart from colds".

6) Chest tightness, positive response to question "Does your chest ever feel tight and is this associated with difficulty in breathing".

7) Attacks of wheeze, positive response to question "Have you ever had an attack of wheezing that has made you feel short of breath".

Subjects were classified as: non smokers,(never smoked before); current smokers, (smoked at least one cigarette per day over last month);or ex smokers,(did not smoke at least one cigarette per day over the last month).

Results

A total of 871 farmers was interviewed and 781 met the eligibility criteria.

Less than one quarter of the farmers (21.6%) were less than 35 years of age and about forty percent (41.0%) were age 50 or older (table 1).

More than half the farmers (53.7%) were lifelong non smokers, 28.5% were exsmokers and 17.6% were current smokers (table 2).

Skin atopy (table 3) to any one of the six antigens was 19.7 percent, the prevalence of atopy to common grain antigens was 9.7% and to common environmental (non grain) antigens 15.5%. The rates of atopy to each antigen ranged from 3.8% for cat epidermal antigen, to 8.9% for housedust.

Being atopic to one antigen increased the likelihood of having a positive reaction to another antigen (table 4). The strongest association was between wheat and rye. The odds ratio for positivity to rye given positivity to wheat was 62.0. The weakest association was between wheat and house dust (OR 7.3). Atopy rates did not change with age (table 5) and atopy tended to be more prevalent in smokers (table 6).

Chronic phlegm production (definition of chronic bronchitis) was seen in 15.7% overall (table 7), in 13.5% of non smokers (table 8) and in 16.0% of those less than age 35 (table 9). Those from age 50 to 65 reported a prevalence of 12.5%.

Dyspnea was defined as shortness of breath while walking on the level for more than two blocks. Overall, the prevalence of dyspnea was 23.7%. Among non-smokers it was reported in 16.4%, and was reported in 10.1% under age 35 and in 35.9% in those age 50 and older.

Asthma was reported by 4.4% of respondents (table 7) and increased in frequency with age (table 9)(from 1.2% in the under 35 category to 5.4% in those 50 and older). Amongst lifelong non-smokers the prevalence of asthma was 2.4% (table 8).

The prevalence of symptoms that suggest asthma (wheeze, chest tightness with shortness of breath and attacks of wheeze) was noted to be high (table 7). Among non smokers these symptoms were reported by 8.7% to 10.8% of respondents. Wheeze apart from colds was reported with the highest frequency, and this frequency increased with age, from 11.8% under age 35 to 21.3% for those age 50 or older. When those with asthma were removed from the analysis, 8.2% and 15.9% of the remaining farmers had respiratory symptoms suggestive of asthma (table 14).

When age and smoking history were controlled, associations remained between both asthma and respiratory symptoms suggestive of asthma and atopy to either common environmental antigens or grain antigens, but not for chronic phlegm, cough, or dyspnea (Tables 10,11 and 12).

In subjects with self reported asthma, there was an association with a positive skin test to at least one common environmental antigen (OR = 2.83) (table 12).

Respiratory symptoms suggestive of asthma included attacks of wheeze, wheeze, and chest tightness associated with shortness of breath. These symptoms were all associated with atopy (wheeze OR=1.9, attacks of wheeze OR=3.82, and chest tightness with dyspnea OR=1.7) (table 12). Symptoms such as shortness of breath, and chronic cough and phlegm production were not associated with atopy (either to common antigens or grain antigens).

When persons with asthma were removed from the analysis (table 13), the respiratory symptom 'attacks of wheeze' remained significantly associated with atopy to grains (OR=3.0). Odds ratios for chronic cough and phlegm production did not change appreciably. This suggests that chronic bronchitis symptoms are not related to asthma.

Conclusions

Among farmers in a temperate climate respiratory symptoms occurred commonly and skin atopy correlated strongly with asthma and with symptoms suggestive of asthma, whereas symptoms of chronic bronchitis were not associated with a atopy. With atopy being a marker for a genetically based susceptibility, the association between atopy and asthma (and symptoms suggestive of asthma) and not chronic bronchitis in farmers from East-Central Alberta may indicate that a genetic predisposition has a role in the development of respiratory syndromes in response to environmental aeroallergens. This would be consistent with the Dutch hypothesis which states that individuals who are genetically predisposed will be more likely to develop respiratory syndromes following exposure (3).

It was noted that there was an association between symptoms suggestive of asthma and skin atopy in this population. It was found that wheeze, attacks of wheeze and chest tightness associated with shortness of breath were associated with atopy. When asthmatics were removed, the strongest association was with the symptom 'attacks of wheeze'. These symptoms may be indicative of a reservoir of undiagnosed asthmatics (especially those who report 'attacks of wheeze') who, if chronically exposed to aggravating aeroallergens may be susceptible to more rapid decline in respiratory function (58,70). Further study of individuals using non specific and specific challenge testing would be helpful in discerning the significance of these symptoms in the absence of a diagnosis of asthma.

In the grain handling industry respiratory symptoms are more common than in the general population and atopic individuals appear to select themselves out of the industry (25,56,71). For lung function there appears to be a dose related effect in that with greater dust exposure there is a greater decline in respiratory function (7). Those individuals shown to have the greatest response to either methacholine or grain dust have shown the greatest longitudinal fall in respiratory function when chronically exposed to grain dust (58).

The same effect has not been demonstrated consistently in the farming population. This may be a reflection of a dose effect, i.e. that farmers are not consistently exposed as much as grain handlers to an agent that can cause respiratory problems. There may also be a self selection process involved, where, in a family farm, bronchial 'challenges' to grain and other substances occur from a young age. The child who exhibits respiratory symptoms often chooses a different career.

The data indicate that respiratory precautions such as avoiding dust exposure or using dust masks when exposure is unavoidable should be employed, especially in sensitive subjects. Farmers reporting asthma or asthmalike symptoms should be investigated to rule out occupationally induced asthma.

Table 1: Distribution of farmers by age category

	Number positive	percent
≤ 35 years	169	21.6
36 to 50 years	292	37.4
> 50 years	320	41.0
Totals	781	100

Table 2: Distribution of farmers by smoking category

	Number positive responses	percent
Non smokers	415	53.2
Ex smokers	225	28.8
Current smokers	140	17.9
Total	780	100

Table 3: Number and percent of farmers reacting to specific antigens and to one of several grouped antigens

	(n=778)	
Antigen	Number	Percent
Wheat	65	8.4
Rye	43	5.5
Birch	46	5.9
Cat	30	3.9
Alternaria	39	5.0
House dust	69	8.9
Atopy to any antigen (1)	154	19.8
Atopy to common antigens (2)	121	15.5
Atopy to grain antigens (3)	76	9.8

(1) house dust, cat epidermis, birch, alternaria, wheat, rye

(2) house dust, cat epidermis, birch, alternaria

(3) wheat, rye

Table 4: Odds ratios [95% confidence intervals] for associations between positive skin reactions to pairs of antigens

	Rye	Birch	Cat	Alternaria	Housedust
Wheat	62.0 [28.9-134]	13.0 [6.9-25.4]	12.0 [5.6-26.0]	12.6 [6.3-25.4]	7.3 [4.0-13.2]
Rye		20.8 [10.2-42.6]	13.0 [5.7-29.6]	11.8 [5.6-25.4]	10.9 [5.6-21.2]
Birch			11.8 [5.2-26.8]	10.7 [5.1-23.0]	9.6 [5.0-18.5]
Cat				12.4 [5.3-29.0]	12.9 [6.0-27.8]
Alternaria					9.0 [4.5-18.1]

Table 5: Number and percent of farmers with skin reactivity to groups of antigens* by age category

	≤ 35 years		36 to 50 years		> 50 years	
	N	%	N	%	N	%
	(n=169)		(n=290)		(n=320)	
Atopy to any antigen (1)	37	21.9	58	20.0	59	18.4
Atopy to common antigens (2)	27	16.0	45	15.5	49	15.3
Atopy to grain antigens (3)	21	12.4	31	10.7	24	7.5

(1) house dust, cat epidermis, birch, alternaria, wheat, rye

(2) house dust, cat epidermis, birch, alternaria

(3) wheat, rye

Table 6: Number and percent of farmers with skin reactivity to groups of antigens* by smoking category

	Non smoker		Ex smoker		Current smoker	
	N	%	N	%	N	%
	(n=414)		(n=224)		(n=140)	
Atopy to any antigen (1)	76	16.9	51	22.8	33	23.6
Atopy to common antigens (2)	56	13.5	36	16.1	29	20.7
Atopy to grain antigens (3)	34	8.2	24	10.7	18	12.9

(1) house dust, cat epidermis, birch, alternaria, wheat, rye

(2) house dust, cat epidermis, birch, alternaria

(3) wheat, rye

Table 7: Number and percent of farmers reporting respiratory symptoms

	Number	percent
Asthma	34	4.4
Wheeze	145	18.6
Attacks of		
Wheeze	87	11.1
Chest tightness	123	15.7
Dyspnea	185	23.7
Cough	101	12.9
Phlegm	123	15.7

Table 8: Number and percent of farmers reporting respiratory symptoms by smoking category

	non smoker		ex smoker		current smoker	
	N	%	N	%	N	%
	(n=415)		(n=225)		(n=140)	
Asthma	10	2.4	18	8.1	6	4.3
Wheeze	44	10.6	45	20.1	56	40.3
Attacks of wheeze	36	8.7	35	15.6	15	10.7
Chest tightness	45	10.8	50	22.2	27	19.3
Dyspnea	68	16.4	77	34.2	39	27.9
Cough	37	8.9	23	10.3	41	29.3
Phlegm	56	13.5	27	12.1	40	28.8

Table 9: Number and percent of farmers reporting respiratory symptoms by age category

	≤ 35 years N	%	36 to 50 years N	%	> 50 years N	%
	(n=169)		(n=291)		(n=320)	
Asthma	2	1.2	15	5.2	17	5.4
Wheeze	20	11.8	57	19.7	68	21.3
Attacks of wheeze	12	7.1	30	10.3	45	14.1
Chest tightness	20	11.8	39	13.4	64	20.0
Dyspnea	17	10.1	53	18.2	115	35.9
Cough	13	7.7	37	12.7	51	15.9
Phlegm	27	16.0	48	16.5	48	15.0

Table 10: Odds ratios [95% confidence intervals] for associations between respiratory symptoms and skin reactivity to specific antigens

	Wheat	Rye	Birch	Cat	Housedust	Alternaria
Asthma	3.1	3.2	4.1	3.7	2.4	2.7
	[1.4-7.5]	[1.2-8.9]	[1.6-10.5]	[1.2-11.5]	[.94-5.6]	[0.91-8.2]
Wheeze	1.9	2.8	2.0	2.7	1.9	1.8
	[1.1-3.4]	[1.5-5.3]	[1.04-3.9]	[1.2-5.7]	[1.1-3.3]	[0.87-3.7]
Attacks of wheeze	3.3	4.4	2.4	3.7	2.3	2.2
	[1.8-6.1]	[2.2-8.8]	[1.2-5.0]	[1.6-8.5]	[1.2-4.3]	[0.97-4.9]
Chest tightness	1.7	2.2	1.3	2.0	1.9	1.2
	[0.93-1.26]	[1.1-4.5]	[0.63-2.9]	[0.88-4.7]	[1.1-3.4]	[0.52-2.8]
Dyspnea	0.71	0.73	0.38	0.98	1.5	0.83
	[0.37-1.4]	[0.33-1.6]	[0.15-0.97]	[0.42-2.3]	[0.85-2.5]	[0.37-1.8]
Cough	1.1	0.89	0.82	1.04	1.3	0.55
	[0.52-2.3]	[0.34-2.3]	[0.31-2.1]	[0.35-3.0]	[0.67-2.6]	[0.17-1.8]
Phlegm	1.1	1.0	0.95	1.3	1.4	0.77
	[0.55-2.1]	[0.45-2.4]	[0.41-2.2]	[0.54-3.4]	[0.75-2.6]	[0.30-2.0]

Table 11: Odds ratios [95% confidence interval] for associations between respiratory symptoms and skin reactivity to groups of antigens*

	Atopy to any antigen (1)	Atopy to common antigens (2)	Atopy to grain antigens (3)
Asthma	2.4	2.9	3.1
	[1.2-5.0]	[1.4-6.1]	[1.4-7.2]
Wheeze	1.9	2.0	1.9
	[1.3-2.9]	[1.3-3.2]	[1.1-3.3]
Attacks of wheeze	2.5	2.4	3.4
	[1.5-4.0]	[1.4-4.0]	[1.9-6.1]
Chest tightness	1.6	1.7	1.7
	[1.0-2.5]	[1.1-2.8]	[0.93-3.0]
Dyspnea	0.85	1.02	0.64
	[.56-1.3]	[0.65-1.6]	[0.34-1.2]
Cough	0.94	0.87	0.91
	[0.55-1.6]	[0.48-1.6]	[0.43-1.9]
Phlegm	0.86	0.92	0.89
	[0.52-1.4]	[0.53-1.6]	[0.46-1.7]

(1) house dust, cat epidermis, birch, alternaria, wheat, rye

(2) house dust, cat epidermis, birch, alternaria

(3) wheat, rye

Table 12: Odds ratios for association between respiratory symptoms and atopy, smoking and age in farmers

	Common antigens*	Grain antigens**	Smoking non	Smoking ex	Smoking current	Age
Asthma	2.83	-	0.52	2.00	0.95	-
Wheeze	1.90	-	0.45	0.94	2.36	-
Attacks of wheeze	-	3.82	-	-	-	1.30
Chest tightness	1.70	-	0.62	1.30	1.20	1.02
Dyspnea	-	-	0.62	1.3	1.28	1.71
Cough	-	-	0.63	0.58	2.70	1.03
Phlegm	-	-	0.76	0.67	1.95	-

[Forward stepwise selection procedure was used with a p value fop entry of 0.05. Dashes indicate terms not entered into the model.]

* house dust, cat, birch, alternaria

** wheat, rye

Table 13: Odds ratios for association between respiratory symptoms and atopy, smoking and age in farmers with asthma removed

	Common antigens*	Grain antigens**	Smoking non	ex	current	Age
Wheeze	-	-	0.45	0.76	3.00	1.22
Attacks of wheeze	3.00	-	-	-	-	1.27
Chest tightness	-	-	0.59	1.20	1.33	1.02
Dyspnea	-	-	0.66	1.18	1.28	-
Cough	-	-	0.69	0.48	2.80	1.03
Phlegm	-	-	0.78	0.65	1.95	-

[Forward stepwise selection procedure was used with a p value for entry of 0.05. Dashes indicate terms not entered into the model.]

* house dust, cat, birch, alternaria

** wheat, rye

Table 14: Number and percent of farmers with respiratory symptoms with those with asthma removed

(N= 736)

	number	percent
Wheeze	117	15.9
Attacks of wheeze	60	8.2
Chest tightness	102	13.9
Dyspnea	161	21.9
Cough	89	12.1
Phlegm	114	15.5

CHAPTER III

RESPIRATORY SYMPTOMS AND ATOPY IN FARMERS AND OILWORKERS

Respiratory Symptoms and Atopy in Farmers and Oil Workers

It has long been recognized that respiratory illnesses are associated with agricultural work (1). Ramazzini in 1713 described an illness in those who sift grain in which a persistent cough develops, they become short of breath, and subsequently die prematurely. This description likely represents occupationally induced asthma resulting in reduced lung function and then respiratory failure. This adverse change in respiratory function in agricultural workers has been noted in several recent studies (2,54,7).

Several respiratory syndromes have been associated with the agricultural industry. These include asthma, chronic bronchitis, non-specific airflow limitation, extrinsic allergic alveolitis, organic dust toxic syndrome, and mucous membrane irritation syndrome (2).

Asthma has been estimated to occur in about 5 percent in the general adult population, but in farming communities the prevalence varies widely. Prevalence rates as high as 15 percent have been reported (55).

The prevalence of chronic bronchitis (defined as cough and phlegm production for greater than 3 months over a two year period) in different communities varies depending on the prevalence of smoking in that community and ambient air pollution levels(5,6). The frequency of chronic bronchitis in the general adult population varies from 4 to 15 percent. Studies of farming communities generally indicate that chronic bronchitis is twice as common as in non farming communities (34,35,36).

Grain handlers from the port on Vancouver have been extensively studied for changes in respiratory symptoms and function (6,56,72). In both case-control studies and cohort studies workers exposed to grain dust were found to have more respiratory symptoms and lower FEV1 than non exposed workers. These differences were noted even though there was a lower prevalence of self reported asthma and atopy in grain handlers compared to controls (civic workers).

The studies performed to document respiratory function changes in farmers have been inconclusive (60,73). Only two studies using a comparison have been performed, one indicating evidence of airflow obstruction in farmers while the other study did not document any respiratory function changes.

Atopy may represent a genetic marker of increased risk for the development of respiratory problems in populations exposed to aeroallergens. Atopy is defined as increased sensitivity to environmental antigens manifested by skin reactivity to these antigens, having an elevated IgE level, or increased blood eosinophil counts. The prevalence of atopy in the general population has been noted to be up to 40 percent (14), but not all atopic individuals have respiratory problems. Conversely, several authors have noted that almost all individuals with hay fever or asthma appear to be atopic (4). The respiratory syndromes that appear to be associated with atopy include asthma (4), the presence of asthmalike symptoms (68), bronchial hyperreactivity (64), mucous membrane irritation syndrome (29), and more rapid loss of lung function (6).

To further understand and to quantify the risk of having respiratory problems in mixed agricultural farmers in Alberta, a cross-sectional survey was performed, comparing farmers to a group of non-exposed blue collar workers for the prevalence of respiratory symptoms, pulmonary function abnormalities, and reactivity to common environmental antigens.

The goal of this study was to quantify the prevalence of respiratory symptoms in Alberta farmers and to identify occupational and host factors associated with these problems.

Methods

A survey instrument was developed based on the American Thoracic Society respiratory symptom questionnaire (74). Additions to the questionnaire included items or questions on mucous membrane irritation syndrome, symptoms suggestive of either extrinsic allergic alveolitis or organic dust toxic syndrome, questions on past medical history and family history, and medication use. Detailed enquiry was made about the occupational history, and in particular, the type and extent of exposure to various agricultural products. For instance, the extent of exposure to specific grains was explored as well exposure to livestock and chemicals.

Testing of skin reactivity was performed by the skin prick method. A drop of antigen was placed on the skin and a small scratch was made with a sterile needle. The largest diameter of the skin wheal was measured 15 minutes after exposure and a measurement of 3 mm or greater was interpreted as positive. The antigens used included wheat, rye grain, house dust, alternaria, cat dander and birch tree.

In Camrose and Wetaskiwin counties in East-Central Alberta, a list of farmers from the federal fertilizer rebate program was obtained from the district agriculturists. This was felt to be the most complete listing of farmers in the area. The farmers were then contacted by telephone and were asked about eligibility. White males between the ages of 18 and 65 who spent at least 80% of their time farming were invited to participate in the survey.

Several testing sites were set up within the counties. Farmers were contacted by telephone (at least 4 attempts were made) and invited to attend. Those who expressed a willingness to participate but did not attend were called again and their appointments were rescheduled.

Incoming questionnaires were reviewed for completeness and consistency. The data were then coded, double entered and checked for valid codes and internal consistency. Deficiencies were corrected.

All subjects were contacted by mail explaining the individual findings. Those with either abnormal spirometry (FEV1 less than 80% predicted) or remarkable symptoms were contacted by telephone by a physician and follow-up arrangements were made.

A comparison group of oilfield and gasplant workers was identified in west central Alberta. All white male workers employed by either of two companies between the ages of 18 and 65 and who had not an exposure to hydrogen sulfide intense enough to cause loss of consciousness were eligible. They were tested by the same field team using the same protocol and equipment.

Bivariate analyses were performed using the chi-square test for categorical variables (e.g. presence of symptoms). Multivariate categorical analyses were performed using unconditional logistic regression methods. Forward stepwise selection using likelihood ratios was employed to develop models and to provide a best fit regression equation. Cigarette smoking and age were the factors most commonly controlled in the multivariate analyses.

Respiratory symptoms were defined as follows:

1) Asthma, positive responses to the questions "Have you ever had asthma" and "do you still have asthma".

2) Cough, positive responses to the questions "Do you usually have a cough" and "Do you usually cough like this for 3 consecutive months or more during the year for 2 or more years".

3) Phlegm, positive responses to the questions "Do you usually bring up phlegm from your chest" and "Do you bring up phlegm like this for 3 consecutive months or more during the year for 2 or more years".

4) Dyspnea, positive response to the question "Are you troubled by shortness of breath when hurrying on the level or walking up a short hill".

5) Wheezing, positive response to the question "Does your chest ever sound wheezy or whistling occasionally apart from colds".

6) Chest tightness, positive response to question "Does your chest ever feel tight and is this associated with difficulty in breathing".

7) Attacks of wheeze, positive response to question "Have you ever had an attack of wheezing that has made you feel short of breath".

Subjects were classified as: non smokers,(never smoked before); current smokers, (smoke at least one cigarette per day over last month);or ex smokers,(did not smoke at least one cigarette per day over the last month).

Results

A total of 871 farmers was interviewed and 781 met the eligibility criteria. Of the 176 oil workers who were identified and interviewed, 151 met eligibility criteria. The response rate in the farming group was 76% and 80% in the oil workers.

The farmers tended to be older (mean age 45.6 years s.d. 11.6) than the oilfield workers (35.0 years s.d. 8.3 $p < 0.001$) (table 1) and farmers tended to smoke less, with current smokers representing 17.9% of farmers and 29.1% of the oil workers ($p = 0.043$) (table 2).

Unadjusted for age or smoking history, only the symptom of shortness of breath was statistically different between farmers and oilfield workers (OR =2.3 CI 1.3-3.6) (table 3).

The prevalence of skin atopy to each individual antigen was significantly higher in the oil workers (table 4). Atopy to any of the common environmental antigens (one of:birch, cat epidermal antigen, alternaria, or house dust) was also more common in oil workers (OR 0.51 ol 0.34-0.76), but atopy to any grain antigens (wheat and rye) was not significantly different (OR =0.70 CI 0.41-1.2) between the two groups. These associations were present when age and smoking history were controlled (table 5).

No significant differences in the frequency of any of the respiratory symptoms were noted between farmers and oil workers (table 3), and no associations between farming and respiratory symptoms were noted when age, atopy and smoking history were included in the model (table 7).

There were significant associations between atopy and several respiratory symptoms (table 6). Atopy was associated with asthma, wheeze, attacks of wheeze and chest tightness, but not chronic cough or phlegm production.

Chronic bronchitis was not associated with atopy but appeared to be correlated with current smoking (OR= 2.14) (table 7).

Self reported asthma was associated with atopy (OR =3.3) and being an ex smoker (OR=1.80). Asthmalike symptoms (attacks of wheeze, chest tightness with shortness of breath, and wheeze) were all associated with atopy, but with lower odds ratios than asthma (table 7).

When comparing respiratory symptoms and associated variables in farmers and oilfield workers separately (tables 8 and 9), the association of asthma and asthmalike symptoms to atopy remains, while chronic bronchitis symptoms remain correlated only with current smoking.

When asthmatics were removed from the analysis, in both farmers and oilfield workers, some of the asthmalike symptoms remained associated with atopy (tables 10 and 11). In farmers, attacks of wheeze were correlated with atopy (OR=3.0) and in oil workers, wheeze (OR=5.9) and attacks of wheeze (OR=9.9) were associated with atopy.

Conclusions

When controlling for factors that may confound the association, no statistically significant difference in the frequency of any respiratory symptom was noted in those working in the farming industry compared to oil workers.

Chronic bronchitis symptoms (chronic cough and phlegm production) were strongly associated with being a current smoker. There does not appear to be any association between these symptoms and atopy to any of the tested antigens. These findings are consistent with other population based surveys in which chronic bronchitis was not associated with atopy (24,30).

Asthma was correlated with atopy to common environmental antigens (house dust, cat, birch and alternaria) and being an ex smoker.

Asthmalike symptoms (wheeze, attacks of wheeze and chest tightness with shortness of breath) were associated with atopy and remained associated with atopy when those with self reported asthma were removed from the analysis. The symptom 'attacks of wheeze' has the strongest association with atopy. These symptoms may therefore represent a reservoir of undiagnosed asthmatics and the symptom 'attack of wheeze' may be the most sensitive indicator.

Asthma is strongly associated with airway hyperreactivity and grain handlers with documented airway hyperreactivity when continually exposed to grain dust, have the greatest decline in respiratory function (58). Therefore the identification of individuals

with airway hyperreactivity who are sensitive to an aeroallergen and who are likely to have continued exposure to that aeroallergen is important in preventing long term respiratory problems.

Since asthma is often difficult to diagnose, asthmalike symptoms in the absence of a diagnosis of asthma may indicate the presence of asthma. Atopy may be a marker for asthma in those with certain symptoms.

It also appears that there is a self selection process among farmers. Using atopy as a marker of susceptible individuals, it was noted that farmers have a lower frequency for atopy when controlled for age. This is consistant with the "healthy worker effect" .

To confirm the effect that respiratory symptoms and atopy have on airway hyperreactivity and the long term consequences in Alberta farmers further, longitudinal studies of lung function and specific and non-specific bronchial challenge testing would be helpful.

For those farmers reporting respiratory symptoms it would be useful to evaluate them further to confirm specific allergen sensitivity so that they can avoid exposure to the offending agent as much as possible (e.g. avoidance of working in grain bins, use of masks and devices to reduce dust levels).

Table 1: Number and percent of farmers and oil workers by age category

	Farmers		Oil workers	
	N	%	N	%
≤ 35 years	169	21.6	90	59.6
36 to 50 years	292	37.4	50	33.1
> 50 years	320	41.0	11	7.3
Totals	781	100	151	100

$p < 0.001$

Table 2: Number and percent of farmers and oil workers by smoking category

	Farmers		Oil workers	
	N	%	N	%
Current smoker	140	17.9	44	29.1
Ex smoker	225	28.8	43	28.5
Non smoker	415	53.1	64	42.2
Total	780	100	151	100

$p < 0.05$

Table 3: Prevalence of respiratory symptoms with odds ratios (OR) and 95% confidence intervals (CI) for farmers and oil workers

	Oil workers (n=151)		Farmers (n=780)		OR	CI
	N	%	N	%		
Asthma	5	3.3	34	4.4	1.35	0.52-3.51
Wheeze	31	20.5	145	18.6	0.88	0.57-1.40
Attacks of wheeze	14	9.3	87	11.1	1.20	0.68-2.20
Chest tightness	21	14.1	123	15.7	1.10	0.69-1.90
Dyspnea	19	12.6	185	23.7	2.30	1.30-3.60
Cough	17	11.3	101	12.9	1.17	0.67-2.02
Phlegm	19	12.6	123	15.8	1.30	0.78-2.20

Table 4: Distribution of atopy to individual and grouped antigens with odds ratios (OR) and 95% confidence intervals (CI) for farmers and oil workers

	Oil workers (n=151)		Farmers (n=781)		OR	CI
	N	%	N	%		
Wheat	18	11.9	65	8.3	0.67	0.39-1.17
Rye	9	6.0	43	5.5	0.92	0.44-1.93
Birch	22	14.6	46	5.9	0.37	0.21-0.63
Cat	22	14.6	30	3.8	0.23	0.13-0.42
Alternaria	15	9.9	39	5.0	0.47	0.26-0.89
House dust	17	11.3	69	8.8	0.76	0.44-1.34
Atopy to any antigen (1)	45	30.0	154	19.8	0.57	0.39-0.85
Atopy to common antigen (2)	40	26.7	121	15.5	0.51	0.34-0.76
Atopy to grain antigen (3)	20	13.3	76	9.8	0.70	0.41-1.2

(1) house dust, cat epidermis, birch, alternaria, wheat, rye

(2) house dust, cat epidermis, birch, alternaria

(3) wheat, rye

Table 5: Odds Ratios for associations between atopy categories and farming, age and smoking categories

	Atopy to any antigen (1)	Atopy to common antigens (2)	Atopy to grain antigens (3)
Farming	0.66*	0.56*	0.88
Age	0.99	0.99	0.98
Smoking			
never	0.87	1.13	0.79
ex	1.20	1.14	1.13
current	0.96	0.78	1.11

* denotes $p < 0.05$

(1) house dust, cat epidermis, birch, alternaria, wheat, rye

(2) house dust, cat epidermis, birch, alternaria

(3) wheat, rye

Table 6: Odds ratios for associations between atopy to common antigens and farming, age, smoking category and respiratory symptoms

	Farming	Age	Smoking			Symptom
			non	ex	current	
Asthma	0.54*	0.99	1.05	1.02	0.93	3.50*
Wheeze	0.56*	0.99	1.00	1.12	0.89	2.50*
Attacks of wheeze	0.54*	0.99	0.92	1.02	0.90	3.20*
Chest tightness	0.56*	0.99	0.91	1.04	1.05	1.86*
Dyspnea	0.57*	0.99	0.90	1.05	0.85	1.04
Cough	0.56*	0.99	0.88	1.04	1.08	0.83
Phlegm	0.56*	0.99	0.89	1.06	1.06	0.96

* denotes $p < 0.05$

Table 7: Odds ratios for association between respiratory symptoms and atopy, smoking and age

	Common antigens*	Grain antigens**	Smoking non	ex	current	Age	Farming
Asthma	3.30	-	0.55	1.80	1.02	-	-
Wheeze	2.50	-	0.48	0.82	2.51	1.02	-
Attacks of wheeze	2.38	2.34	-	-	-	1.02	-
Chest tightness	1.85	-	0.72	1.17	1.17	1.02	-
Dyspnea	-	-	0.67	1.15	1.30	1.06	-
Cough	-	-	0.58	0.57	3.00	1.03	-
Phlegm	-	-	0.71	0.65	2.14	-	-

[Forward stepwise selection procedure was used with a p value for entry of 0.05. Dashes indicate terms not entered into the model.]

* house dust, cat, birch, alternaria

** wheat, rye

Table 8: Odds ratios for association between respiratory symptoms and atopy, smoking and age in farmers

	Common antigens*	Grain antigens**	Smoking non	Smoking ex	Smoking current	Age
Asthma	2.83	-	0.52	2.00	0.95	-
Wheeze	1.90	-	0.45	0.94	2.36	-
Attacks of wheeze	-	3.82	-	-	-	1.30
Chest tightness	1.70	-	0.62	1.30	1.20	1.02
Dyspnea	-	-	0.62	1.30	1.28	1.71
Cough	-	-	0.63	0.58	2.70	1.03
Phlegm	-	-	0.76	0.67	1.95	-

[Forward stepwise selection procedure was used with a p value for entry of 0.05. Dashes indicate terms not entered into the model.]

* house dust, cat, birch, alternaria

** wheat, rye

Table 9: Odds ratios for association between respiratory symptoms and atopy, smoking and age in oil workers

	Common antigens*	Grain antigens**	Smoking non	Smoking ex	Smoking current	Age
Asthma	12.10	-	-	-	-	-
Wheeze	6.75	-	0.59	0.58	2.90	-
Attacks of wheeze	13.46	-	-	-	-	-
Chest tightness	-	-	-	-	-	-
Dyspnea	-	-	-	-	-	-
Cough	-	-	0.22	0.70	6.40	-
Phlegm	-	-	0.31	0.73	4.40	-

[Forward stepwise selection procedure was used with a p value for entry of 0.05. Dashes indicate terms not entered into the model.]

* house dust, cat, birch, alternaria

** wheat, rye

Table 10: Odds ratios for association between respiratory symptoms and atopy, smoking and age in farmers with asthma removed

	Common antigens*	Grain antigens**	Smoking non	ex	current	Age
Wheeze	-	-	0.45	0.76	3.00	1.22
Attacks of wheeze	3.00	-	-	-	-	1.27
Chest tightness	-	-	0.59	1.20	1.33	1.02
Dyspnea	-	-	0.66	1.18	1.28	-
Cough	-	-	0.69	0.48	2.80	1.03
Phlegm	-	-	0.78	0.65	1.95	-

[Forward stepwise selection procedure was used with a p value for entry of 0.05. Dashes indicate terms not entered into the model.]

* house dust, cat, birch, alternaria

** wheat, rye

Table 11: Odds ratios for association between respiratory symptoms and atopy, smoking and age in oil workers with asthma removed

	Common antigens*	Grain antigens**	Smoking non	Smoking ex	Smoking current	Age
Wheeze	5.90	-	0.55	0.58	3.07	-
Attacks of wheeze	9.90	-	-	-	-	-
Chest tightness	-	-	-	-	-	-
Dyspnea	-	-	-	-	-	-
Cough	-	-	0.23	0.71	5.70	-
Phlegm	-	-	0.30	0.73	4.56	-

[Forward stepwise selection procedure was used with a p value for entry of 0.05. Dashes indicate terms not entered into the model.]

* house dust, cat, birch, alternaria

** wheat, rye

CHAPTER IV

GRAIN DUST CHALLENGE IN ALBERTA FARMERS

Grain Dust Challenge in Alberta Farmers

Respiratory disease has long been recognized as an occupational hazard for agricultural workers. Ramazzini in 1713 described an illness in those that were involved the sifting of grains (1). The description given was: "The throat, lungs and eyes are keenly aware of serious damage, the throat is choken and dried up with dust, the pulmonary passages become coated with crust formed by 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 or measuring grain are short of breath and cachectic and rarely reach old age". This likely is a description of occupationally induced asthma with a rapid decline in respiratory function resulting in disability and premature death.

From studies of grain handlers in the port of Vancouver, it has been noted that atopic individuals and persons with self reported asthma were less likely to be in and remain in the grain industry. Compared to matched controls (civic workers), grain handlers had slightly lower spirometry measurements (56). Also a more rapid decline in respiratory function was noted in workers who were exposed to the highest dust levels (7). Workers exhibiting the greatest degree of bronchial hyperreactivity to grain dust when chronically exposed to grain dust had the greatest longitudinal fall in respiratory measurements (58).

Burrows et al in a large population based survey in Arizona noted that asthma appeared to be related to atopic status manifested by either an immediate reaction to antigens on skin testing, an elevated IgE level, or an elevation in serum eosinophil levels (4). When these individuals were identified and treated they had a longitudinal decline in respiratory function similar to non smokers, but if unidentified and untreated had a more rapid and fixed decline in respiratory function. Therefore it appears that the identification and treatment of individuals who have asthma or asthmatic bronchitis affords an important opportunity for prevention of respiratory disease.

After completing a survey of the respiratory health of 781 mixed grain and livestock farmers from East Central Alberta, it was noted that: 1) respiratory symptoms were common amongst these workers; 2) self reported asthma was associated with skin atopy to environmental antigens and 3) that asthmalike symptoms were associated with atopy.

To better understand the relationship of the respiratory symptoms to bronchial hyperreactivity, asthma, and atopy those non smoking farmers reporting respiratory symptoms were asked to have further studies performed. These included a larger battery of skin tests to common agricultural antigens and bronchial challenge testing with both methacholine and grain dust.

Methods

A survey of the respiratory health of mixed grain and livestock farmers from East Central Alberta was performed from November 1989 to March 1990. A total of 871 male farmers between the ages of 18 and 65 participated (representing 76% of eligible respondents). The survey included a questionnaire on respiratory symptoms (based on the ATS questionnaire), smoking and occupational histories, allergy skin tests and spirometry.

From this survey 109 non-smoking farmers with respiratory symptoms or abnormal spirometry were identified. The symptoms or syndromes of interest included asthma (self reported), chronic bronchitis (defined as phlegm production for greater than three months for two years) or symptoms suggestive of asthma (wheeze, wheeze that occurs in attacks, or chest tightness associated with shortness of breath).

These farmers were then contacted and asked to participate in a three day protocol to assess the association between respiratory symptoms and non-specific and specific bronchial reactivity. The testing included further allergy skin tests, a methacholine challenge test, a specific airway challenge test with grain dust, and for a subset, bronchoscopy. Prior to any testing informed consent was obtained.

The skin tests involved placing a drop of antigen on the skin, making a small scratch with a needle and measuring the largest diameter of the wheal after 15 minutes. A wheal at least 3 mm greater than the control wheal (normal saline) was considered a positive reaction. The antigens tested included: cattle hair and dander, grain mill dust, chicken feathers, turkey feathers, barley, oats, rye, wheat, Aspergillus fumigatus, Aspergillus glaucus, barley smut, wheat smut, oat smut, D. farinae, and several common environmental antigens: cat dander, house dust, alternaria and birch.

On the first day a methacholine challenge test was performed. The method was that described by Cockcroft (43). First spirometry measurements were made using a 13 liter Collins Bell spirometer and FEV1 and FVC were calculated. Several readings were taken, and corrected to BTPS. The ATS criteria were applied to all spirometric tests (74). The largest of the FEV1 and FVC readings were used, regardless of whether they came from the same tracing.

The starting dose for the methacholine challenge was 0.5 mg/ml and the testing stopped when a 20% decline in FEV1 was noted or a dose of 8 mg/ml was reached.

The subject was instructed in the use of a Wright peak flow device, and asked to perform and record 3 measurements: 1) every two hours while awake 2) any time the subject was woken at night; and 3) upon development of any respiratory symptoms. Arrangements were made for these subjects to stay in a hostel adjacent to the University Hospital. If any respiratory symptoms developed, subjects were asked to report these to the physician responsible and if severe symptoms developed, to go immediately to the Emergency Department.

On the second day of testing, a specific aerosolized grain dust challenge test was performed using a grain dust generating chamber (75). This chamber had approximately 36 litre capacity, had a filtered air intake opening, ports to inject grain dust and to measure dust levels, and an exhalation port. The subject was attached to the chamber with a 3 cm hose and a tight fitting mask. Dust levels were monitored using a Miniram dust monitoring device that measured the concentration of dust particles. Three electrical fans kept the dust circulating within the chamber. Dust levels were kept between 5 and 10 mg/m^3 by injecting crude grain dust into the injection ports periodically, dust levels were monitored and recorded every 30 seconds. The dust used was obtained from commercial grain elevators in the home area of these farmers. The dust was sifted to remove large particles and then analyzed by an occupational hygienist for particle size distribution.

The subject was then exposed to the grain dust for 5 minutes. The exposure was discontinued if severe respiratory symptoms were reported. After a 5 minute exposure spirometry measurements were made every minute for the first 5 minutes and every 5 minutes for the next 25 minutes. Multiple readings were taken at each interval, and two of these had to be within 5% of each other to be considered accurate. The largest of the readings for FEV1 and FVC were used for analysis.

If the subject did not have any untoward effects from the 5 minute exposure, and the FEV1 did not fall by more than 20% a 30 minute exposure challenge using the same methodology was performed. This followed the same procedure, with spirometry being performed over a 30 minute period post exposure. Again the testing was terminated if severe respiratory symptoms developed and ventolin was administered. This occurred in one subject. If post exposure spirometry showed a 20% drop in FEV1 ventolin was administered.

The subject was then given the Wright peak flow meter, and asked to perform and record three peak flow measurements every 15 minutes for the first three hours and then every two hours or if respiratory symptoms developed or if they were woken at night. If there was a drop in peak flow greater than 20% from baseline (peak flow measurements taken just prior to dust exposure) or respiratory symptoms developed the subject was to take and record ventolin inhalation with a metered dose inhaler. The subject was to report these symptoms to the responsible physician and if symptoms persisted to be seen in the Emergency Department. These instructions were given to the subject verbally and in written form.

For analysis spirometry measurements were corrected for BPTS, and the percent drop in measurements for spirometry pre and post exposure was calculated. The percent drop in peak flow measurements was calculated from the difference between each reading and the reading taken from the same time of day on the previous day to account for diurnal variation. The spirometry measured the immediate airway hyperresponsiveness while the peak flow measurements documented any delayed hyperresponsiveness. The greatest pre and post exposure changes in these two measurements were used in the data analysis.

In those subjects who agreed, bronchoscopy was performed 24 hours after grain dust challenge. Samples were collected and included: 1) bite biopsies from main stem and tertiary airways on the right side, 2) bronchoalveolar lavage (BAL) from right middle lobe and 3) right general cytology brushes.

Results

From the initial survey, 109 non smoking farmers reported respiratory symptoms. Of those participating, the mean age was 45.2, with a mean FEV1 of

3702 and mean FVC of 4872 (table 1). Of the 109 eligible, 91 were contacted, 28 (25.6%) participated and 12 (11%) of these had bronchoscopies performed.

Of those with reported asthma 4/10 (40%) participated, with asthmalike symptoms 18/41 (43 %), chronic bronchitis 5/52 (10%) and 1/4 (25%) with abnormal spirometry. The one person with abnormal spirometry had a phrenic nerve injury, and therefore was excluded from the analysis.

Overall 11% (3/27) had a positive methacholine challenge test (> 20 % fall in post test FEV1 at dose $\leq$ 8mg/ml), and 33% (9/27) had a positive grain dust challenge (> 20% drop in either FEV1 or peak flow measurements). Two individuals had a significant fall in FEV1 readings or developed symptoms after the five minute exposure such that they could not proceed to a thirty minute grain dust exposure. A total of 44% (12/27) had a positive skin test to the agricultural antigens (table 2).

Amongst asthmatics, 25% (1/4) had a positive methacholine challenge test and 50% (2/4) had a positive grain dust challenge. The proportion of those with asthmalike symptoms and a positive methacholine challenge was 11% (2/18) and a positive grain dust challenge was 28% (5/18) (table 2).

In the chronic bronchitis group none (0%) had a positive methacholine challenge test and 2/5 (40%) had a positive grain dust test (table 2).

Although the numbers in each group were small, there did not appear to be any correlation between a positive grain dust test and a positive methacholine test (OR 1.66 p =0.68) (table 3). In asthmatics the odds ratio was 0.50 (p=0.50).

The association between a positive skin test and a positive grain dust challenge was explored. The presence of a positive grain dust challenge and positive skin test had an odds ratio of 7.50 (p=0.06). The correlation was higher in those with asthmalike symptoms (OR= 8.25 p=0.02) and lower in those with chronic bronchitic symptoms (OR=3.00 p=0.58) (t[illegible]

A correlation between skin atopy and a positi[illegible] [illegible]choline challenge test was not seen. Those with asthmalike symptoms had an odds ratio of 1.66 (p=0.73) (table 3).

Conclusions

Persons with demonstrated bronchial reactivity to an aeroallergen who continue to be exposed to that aeroallergen have a greater decline in spirometry measurement[illegible] [illegible]an those not demonstrating bronchial hyperreactivity (58). The decline is [illegible] specific bronchial reactivity (as opposed non specific,i.e. methacholine r[illegible]vity) alone is d[illegible]monstrated. Therefore the identification of individuals who have hyperreactive airways and work in an environment that continually exposes them to an inciting agent can benefit from identification and intervention.

A history alone of either asthma, asthmalike symptoms or chronic bronchitis does not accurately predict those with hyperreactive airways. Knowing whether a person is atopic to the potential offending agents does improve the sensitivity but does not identify all individuals with hyperreactiv[illegible] [illegible]ays. Many of those without a diagnosis of asthma but with asthmalike symptoms do demonstrate airway reactivity similap to asthmatics, in fact they do, by current definitions have asthma.

A positive grain dust challenge test appeared more commonly than a positive methacholine challenge in non-smoking farmers with respiratory symptoms. Therefore, the grain dust challenge test may be more sensitive at identifying hyperreactive airways in farmers than a methacholine challenge testing. This is important to note, because currently methacholine testing is the standard testing procedure to identify airway hyperreactivity.

Atopy was more strongly associated with grain dust challenge than with methacholine challenge, and therefore may indicate that a genetic predisposition is important in the etiology of respiratory symptoms in farmers.

The participation rate of those eligible was low and may affect the interpretation of the results. This could bias the results in either direction, in that those with most respiratory problems related to grain exposure more readily participated in the study therefore tending to falsely elevate the positive response rate to testing or if individuals knew they had a particular respiratory problem related to a specific exposure, may have chosen not to participate and as a result lower the response rate to testing.

The dust levels used were lower than the recommended allowable levels for the grain industry (set by the Canadian Thoracic Society) (2). Since there appears to be a correlation between documented acute hyperreactivity and long term reduction in respiratory function, the results of this study would indicate that allowable dust levels in this range are in fact hazardous to sensitive individuals. It appears that the best way of accurately identifying these individuals in a laboratory setting is to perform a specific challenge test.

It should be noted that the dust used was crude grain dust that contained a variety of allergens and agents. Further study to identify the specific agents or allergens responsible for bronchial hyperreactivity in different individuals would be important in the understanding of the pathogenesis of occupational asthma in these workers.

Using the technique described, no untoward effects in any subjects were noted. This may have been due to careful monitoring of subjects and control of exposure levels. Since the exposure was contained in a closed system there was minimal risk to the technician performing the study.

Table 1: Characteristics of the 27 farmers participating in challenge testing

	Mean	Range	S.D.
Age (years)	45.2	27-64	
Prechallenge FEV1 ml	3702		719
Prechallenge FVC ml	4872		869
Dust concentration mg/m^3	9.13		2.48

Table 2: Frequency of positive response to test and respiratory symptoms

	Total subjects	Atopy to antigens		Methacholine test positive		Grain test positive	
		N	%	N	%	N	%
Asthma	4	4	100	1	25	2	50
Asthmalike symptoms	18	7	39	2	11	5	28
Chronic bronchitis	5	1	20	0	0	2	40
Totals	27	12	44	3	11	9	33

Table 3: Odds ratios (and p values) for associations between various tests (methacholine challenge, grain challenge and skin tests) and respiratory symptom groups

	Methacholine and grain dust	Grain dust and skin test	Methacholine and skin test
Asthma	0.50 (0.50)	all skin test positive	all skin test positive
Asthmalike symptoms	7.00 (0.18)	8.25 (0.02)	1.66 (0.73)
Chronic bronchitis	all methacholine negative	3.00 (0.58)	all methacholine negative
total	1.66 (0.68)	7.50 (0.06)	1.40 (0.76)

CHAPTER VII

OVERALL CONCLUSIONS

Overall Conclusions

From studies performed to date, it was noted that agricultural workers had a greater prevalence of respiratory symptoms, and that amongst grainhandlers, those who reported having asthma, those with the most reactive airways (58) and those who were exposed to the highest dust levels (7) had the greatest longitudinal decline in lung function measurements.

Atopy appears to be one factor that could be important in determining which individuals are at elevated risk for developing respiratory impairment. Therefore, determination of the association between atopy and respiratory health in a group of individuals exposed to aeroallergens known to cause respiratory syndromes is important.

The first paper documented that respiratory symptoms occur in high frequency in farmers and occur even in young farmers. In those who were atopic to any one antigen (20%), the likelihood of being sensitive to any other antigen was high. The greatest correlation was between the grain antigens. Skin atopy is seen commonly in sensitive subjects and many of these subjects have been sensitized to grain antigens.

Certain respiratory symptoms correlate with a positive skin test. These include asthma and asthmalike symptoms (wheeze, attacks of wheeze and chest tightness associated with wheeze), whereas chronic bronchitis (chronic cough and phlegm production) do not correlate with atopy. This would suggest that there is a genetic difference for the development of different respiratory symptoms.

Because those with asthmalike symptoms have a similar pattern of atopy as those with asthma, asthmalike symptoms may represent a reservoir of undiagnosed asthmatics. These individuals are important to identify because of the noted greater longitudinal fall in lung function in asthmatics who remain in the industry and do not take respiratory precautions. Respiratory impairment could potentially be avoided in these individuals.

The second paper compared rates of respiratory symptoms and atopy in farmers and non exposed oil workers.

When adjusted for age and smoking, the farmers did not have an excess of symptoms. This finding is somewhat at variance with other studies of respiratory symptoms in farmers. Most studies indicate that chronic bronchitis symptoms occur more frequently in farmers when compared to unexposed comparison groups (32,33,34,35,36,37). Since these studies were performed several years ago, changes in symptom frequency could be reflective of changes in agricultural practices. Another explanation would be that the comparison workers have exposures to factors that increase the frequency of respiratory symptoms.

Certain respiratory symptoms are associated with atopy, mostly because of their association with asthma. Symptoms of 'wheeze without a cold' or 'wheeze that occurs in attacks' have the greatest association with atopy in both farmers and oil workers. It is possible that some of these symptoms, even in the absence of documented asthma, indicate the presence of asthma. Atopy may be a marker for asthma in those with certain symptoms.

The frequency of atopy to common antigens was significantly less in farmers when compared to oilfield workers. This would suggest that a 'healthy worker effect' may be involved. Individuals that are adversely affected by the work environment remove themselves from that particular work environment. This would partly account for similar frequencies of respiratory symptoms in exposed and non exposed workers. A healthy worker effect has been documented in the grain handlers in Saskatchewan and the port of Vancouver (25,57,58).

The third paper studied respiratory symptoms, atopy and airway reactivity. Asthma can be diagnosed by increased airway reactivity manifested by increased sensitivity to inhaled substances such as methacholine (non-specific challenge) or specific challenge (i.e.grain dust challenge). A positive grain dust challenge test appears more commonly than a positive methacholine challenge test in non-smoking farmers with respiratory symptoms. This would indicate that the grain challenge is a more sensitive test in this population. For the clinician, this would mean that in those farmers reporting respiratory symptoms suggestive of asthma, a negative methacholine test does not rule out the diagnosis of asthma.

Many of those who reported asthmalike symptoms did have a positive grain dust or methacholine challenge test, but less frequently than those with reported asthma. This would suggest that some subjects with asthmalike symptoms do indeed represent undiagnosed asthma.

Atopy is more strongly associated with a positive grain dust challenge than a positive methacholine challenge. This may indicate that genetic predisposition is important in the etiology of respiratory symptoms in farmers.

CHAPTER VI

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CHAPTER VII

APPENDIX

Appendix 1) Questionnaire

I.D. __ __ __ __ __ __ __ __ __ __ Interviewer:__________
Study Site Subject Visit

DO NOT WRITE ABOVE THIS LINE

Today's Date ____ ____ ____
year month day

I. PERSONAL CHARACTERISTICS

The following information will help us to keep in touch with you and will be important to us as we measure your health status. It is confidential and will not be released to another party without your permission.

Full Name:__________________________
LAST FIRST

Address:__________________________

____

Telephone Number:__________________

Social Insurance Number:__________

Name of Family Doctor:__________________

Address of Family Doctor:__________________

Date of Birth:____ ____ ____
year month day

Sex: 1. Male_____ 2. Female_____

Marital Status: 1. Single_____ 3. Widowed_____
(check one) 2. Married_____ 4. Separated/Divorced_____
(married type of arrangement)

Ethnic Origin: specify__________________

Height:_____ feet _____ inches (_____cm.)

Weight:_____ lbs (_____kg.)

Country (Province) of birth:__________________

In what country did you spend the majority of the first 10 years of your life?__________________

In the: - countryside 1._____
(check only one) - town: smaller than 10,000 people 2._____
10,000 - 100,000 people 3._____
larger than 100,000 people 4._____

What is the highest level of education?__________________

II. HEALTH STATUS

These are questions mainly about your health. Please answer yes or no, if in doubt, please answer no.

COUGH

A. Do you usually have a cough? 1. Yes_____ 2. No_____

B. Do you usually cough at all on getting up, or first thing in the morning? 1. Yes_____ 2. No_____

C. Do you usually cough at all during the rest of the day or at night? 1. Yes_____ 2. No_____

If yes to any of above (A, B, or C):

1. Do you usually cough like this most days for 3 consecutive months or more during the year? 1. Yes_____ 2. No_____

2. For how many years have you had this cough? _______________ (Number of years)

3. Does the cough occur more frequently:
   1. in morning only______
   2. at work______________
   3. on return home_______
   4. during sleep_________
   5. no difference________

4. Does the cough improve: on days off? 1. Yes_____ 2. No_____
   on long holidays? 1. Yes_____ 2. No_____

5. Over the past year has the cough become:
   1. worse__________
   2. better_________
   3. the same_______

D. Is there any particular activity or job which makes you cough?

Specify____

PHLEGM

A. Do you usually bring up phlegm from your chest? 1. Yes_____ 2. No_____

B. Do you usually bring up phlegm at all on getting up, or first thing in the morning? 1. Yes_____ 2. No_____

C. Do you usually bring up phlegm at all during the rest of the day or at night? 1. Yes_____ 2. No_____

If YES to any of the above (A, B, or C):

1. Do you bring up phlegm like this on most days for 3 consecutive months or more during the year? 1. Yes_____ 2. No_____

2. For how many years have you had trouble with phlegm? _________ (Number of years)

3. Over the past three years, is the phlegm:
   1. more___________
   2. less___________
   3. the same_______

Phlegm continued:

4. Does the phlegm improve:
   on long holidays 1. Yes_____ 2. No_____
   on days off 1. Yes_____ 2. No_____

D. Is there any particular activity or job which makes you bring up phlegm? Specify__________________ ______________________________
____

BREATHLESSNESS

A. Are you troubled by shortness of breath when hurrying on the level or walking up a slight hill? 1. Yes_____ 2. No_____

B. Do you have to walk slower than people of your age on the level because of breathlessness? 1. Yes_____ 2. No_____

If YES to A or B:

1. Do you ever have to stop for breath when walking at your own pace on the level? 1. Yes_____ 2. No_____

2. For how many years have you suffered from shortness of breath? ___________ years

3. Over the past three years has it become: 1. worse_____________
   2. better____________
   3. the same__________

4. Do you become short of breath when handling:
   grain, fresh 1. Yes_____ 2. No_____
   grain, old 1. Yes_____ 2. No_____

   hay, fresh 1. Yes_____ 2. No_____
   hay, old 1. Yes_____ 2. No_____

   If YES to 4:

   (a) Does this occur: while handling __________
   shortly after handling __________
   some hours after handling__________
   unknown __________

WHEEZING

Does your chest ever sound wheezy or whistling:

A. When you have a cold? 1. Yes_____ 2. No_____

B. Occasionally apart from colds? 1. Yes_____ 2. No_____

C. Most days or nights? 1. Yes_____ 2. No_____

If YES to B or C:

1. Is the wheeze associated with chest tightness or difficulty in breathing? 1. Yes_____ 2. No_____

2. For how many years has this wheeze been present? __________ (years)

Wheezing continued:

3. Over the past three years has it been (check one)	1. worse______________ 2. better_____________ 3. the same___________
4. Does the wheeze occur mostly (check one)	1. at work____________ 2. during sleep_______ 3. no difference______
5. Do these symptoms improve: on long holidays	1. Yes_____ 2. No_____
on days off	1. Yes_____ 2. No_____
6. Is it worse when handling: grain, fresh	1. Yes_____ 2. No_____
grain, old	1. Yes_____ 2. No_____
hay, fresh	1. Yes_____ 2. No_____
hay, old	1. Yes_____ 2. No_____

CHEST TIGHTNESS

A. Does your chest ever feel tight? 1. Yes_____ 2. No_____

If YES to A:

1. Does this come in attacks?	1. Yes_____ 2. No_____
2. Is this associated with difficulty in breathing?	1. Yes_____ 2. No_____
3. How old were you when you had your first chest tightness?	_____ age in years
4. Have you ever required medicine or treatment for these?	1. Yes_____ 2. No_____

ATTACKS OF WHEEZING

A. Have you ever had an attack of wheezing that has made you feel short of breath? 1. Yes_____ 2. No_____

If YES to A:

1. How old were you when you had your first such attack?	_____ age in years
2. Have you had 2 or more such episodes?	1. Yes_____ 2. No_____
3. Have you ever required medicine or treatment for the(se) attack(s)?	1. Yes_____ 2. No_____
4. During the past year, how many attacks did you have?	1. a few(1-3)_________ 2. several(4-12)______ 3. many(13 or more)___ 4. almost every day___
5. Over the past three years has the the wheezing been: (check one)	1. worse______________ 2. better_____________ 3. the same___________ 4. no difference______
6. Does it improve on long holidays?	1. Yes_____ 2. No_____
on days off?	1. Yes_____ 2. No_____

Attacks of wheezing continued:

7. Is the wheezing worse when handling:

grain, fresh	1. Yes_____	2. No_____
grain, old	1. Yes_____	2. No_____
hay, fresh	1. Yes_____	2. No_____
hay, old	1. Yes_____	2. No_____

III. PAST ILLNESSES

A. During the past three years have you had any chest illness that kept you from your usual activities for as much as a week? 1. Yes_____ 2. No_____

<u>If YES to A:</u>
1. How many illnesses like this have you had in the past three years? _____ number

B. Did you have any lung trouble before the age of 16? 1. Yes_____ 2. No_____

C. Have you ever had any of the following:

1. Attacks of <u>bronchitis</u>? 1. Yes_____ 2. No_____

   If **YES**, at what age was your first attack? ______ years

   Was it confirmed by a doctor? 1. Yes_____ 2. No_____

2. <u>Pneumonia</u> (including bronchopneumonia)? 1. Yes_____ 2. No_____

   If **YES**, at what age was your first attack? _____ years

   Was it confirmed by a doctor? 1. Yes_____ 2. No_____

3. <u>Asthma</u>? 1. Yes_____ 2. No_____

<u>If YES to 3</u>:
a. Do you still have it? 1. Yes_____ 2. No_____

b. Was it confirmed by a doctor? 1. Yes_____ 2. No_____

c. At what age did it start? _____ years

d. If you no longer have it, at what age did it stop? _____ years

e. If you still have it,

   i. During the past year have you seen a doctor for it? 1. Yes_____ 2. No_____

   ii. Have you taken medication for it? 1. Yes_____ 2. No_____

D. Have you ever had any other chest illnesses? 1. Yes_____ 2. No_____

If **YES**, specify ______________________________

Past illnesses continued:

E. Chest injury 1. Yes_____ 2. No_____

If **YES**, specify ______________________________

F. Chest operation 1. Yes_____ 2. No_____

If **YES**, specify ______________________________

G. Have you ever had:

hay fever? 1. Yes_____ 2. No_____

eczema? 1. Yes_____ 2. No_____

hives? 1. Yes_____ 2. No_____

H. Has a doctor ever told you that you had heart trouble? 1. Yes_____ 2. No_____

<u>If YES to H</u>:

1. Have you ever had treatment for heart trouble in the past 10 years? 1. Yes_____ 2. No_____

I. Have you had a cold within the last week? 1. Yes_____ 2. No_____

<u>If YES to I</u>:

1. Do you have a cough now? 1. Yes_____ 2. No_____

J. Do you have other health problems? 1. Yes_____ 2. No_____

If **YES**, specify ______________________________

K. Are you currently taking any medication? 1. Yes_____ 2. No_____

If **YES**, specify ______________________________

IV. GENERAL SYMPTOMS

The following questions are about general symptoms associated with your work.

A. Have you had chills, fever or flu-like symptoms during or after work? 1 Yes_____ 2. No_____

1. If **YES** are these associated with any of the following:

dry cough	1. Yes_____	2. No_____
cough with phlegm	1. Yes_____	2. No_____
shortness of breath	1. Yes_____	2. No_____
wheezing	1. Yes_____	2. No_____
chest tightness	1. Yes_____	2. No_____
joint pains	1. Yes_____	2. No_____
muscle pains	1. Yes_____	2. No_____
headache	1. Yes_____	2. No_____
fatigue or tiredness	1. Yes_____	2. No_____
nausea	1. Yes_____	2. No_____

2. How long after work does this occur? ________________ hours

3. How long does it last? ________________ hours

4. How often have you had it:
   - in the past year? ________________ number
   - in the past 3 years? ________________ number
   - ever? ________________ number

5. When did you first have it? ________________ date

6. When did you last have it? ________________ date

7. What time of the year is it most common? (CHOOSE ONE)
   - spring __________
   - summer __________
   - fall __________
   - winter __________
   - no difference ____
   - don't know _______

8. During the worst episode, did you: (CHOOSE ONE)
   - continue to work __________
   - stop work because of symptoms __________
   - see the doctor for symptoms __________

9. Were the symptoms associated with dust exposure? 1. Yes_____ 2. No_____

   9.a. If **YES**, how much dust was in the air: (CHOOSE ONE)
   - a lot of dust __________
   - a small amount of dust __________

10. Were the symptoms associated with a particular job or work activity such as:

handling grain?	1. Yes_____	2. No_____	3. N/A_____
handling hay?	1. Yes_____	2. No_____	3. N/A_____
handling animal feed?	1. Yes_____	2. No_____	3. N/A_____
cleaning manure?	1. Yes_____	2. No_____	3. N/A_____

other (specify) ________________________________

Chills, fever or flu-like symptoms continued:

11. Were the symptoms associated with any of the following:
    - runny nose? 1. Yes_____ 2. No_____
    - sore throat? 1. Yes_____ 2. No_____
    - other family members affected? 1. Yes_____ 2. No_____

12. Did you lose weight following these symptoms? 1. Yes_____ 2. No_____

    12.a. If **YES**, how much? __________ kg. or __________ lbs.

B. The following questions are about symptoms affecting your eyes, ears, nose and throat.

1. Have you ever had any of the following eye symptoms?
    - burning? 1. Yes_____ 2. No_____
    - itching? 1. Yes_____ 2. No_____
    - runny eyes? 1. Yes_____ 2. No_____

1.a. If **YES**, what year was the last episode?__________ year
how often per year? __________ number
how long did it last? __________ hours

If 1.a. occurred within the last 5 years, answer 1.b.

1.b. Do any of the following bring it on?

handling grain?	1. Yes_____	2. No_____	3. N/A_____
handling hay?	1. Yes_____	2. No_____	3. N/A_____
cleaning manure?	1. Yes_____	2. No_____	3. N/A_____
handling silage?	1. Yes_____	2. No_____	3. N/A_____

other (specify) ____________________

2. Have you had any of the following ear symptoms?
    - ear ache? 1. Yes_____ 2. No_____
    - temporary reduced hearing in one ear? 1. Yes_____ 2. No_____
    - burst ear drum? 1. Yes_____ 2. No_____

2.a. If **YES**, what year was the last episode?__________ year
how often per year? __________ number
how long does it last? __________ hours

If 2.a. occurred within the last 5 years, answer 2.b.

2.b. Do any of the following bring the ear symptoms on?

handling grain?	1. Yes_____	2. No_____	3. N/A_____
handling hay?	1. Yes_____	2. No_____	3. N/A_____
cleaning manure?	1. Yes_____	2. No_____	3. N/A_____
handling silage?	1. Yes_____	2. No_____	3. N/A_____

other (specify) ____________________

3. Have you had any of the following nose symptoms (apart from colds):
    - runny nose? 1. Yes_____ 2. No_____
    - stuffy nose? 1. Yes_____ 2. No_____
    - loss of smell? 1. Yes_____ 2. No_____
    - drip at the back of the throat? 1. Yes_____ 2. No_____

Nose symptoms continued:

3.a. If **YES**, what year was the last episode?____________ year
how often per year? _______________ number
how long did it last? ________________ hours

If 3.a. occurred within the last 5 years, answer 3.b.

3.b. Do any of the following bring the nose symptoms on:

handling grain?	1. Yes_____	2. No_____	3. N/A_____
handling hay?	1. Yes_____	2. No_____	3. N/A_____
cleaning manure?	1. Yes_____	2. No_____	3. N/A_____
handling silage?	1. Yes_____	2. No_____	3. N/A_____

other (specify) ____________________________________

4. Have you had any of the following throat symptoms (apart from colds):

scratchy throat?	1. Yes_____	2. No_____
sore throat?	1. Yes_____	2. No_____

4.a. If **YES**, what year was the last episode?____________ year
how often per year? _______________ number
how long does it last? ________________ hours

If 4.a. occurred within the last 5 years, answer 4.b.

4.b. Do any of the following bring on the throat symptoms:

handling grain?	1. Yes_____	2. No_____	3. N/A_____
handling hay?	1. Yes_____	2. No_____	3. N/A_____
cleaning manure?	1. Yes_____	2. No_____	3. N/A_____
handling silage?	1. Yes_____	2. No_____	3. N/A_____

other (specify) ____________________________________

V. FAMILY HISTORY

As some illnesses run in families, we would like to ask you about your family members.

A. Was your father ever told by a doctor that he had:

	1. YES	2. No	3. Don't know
1. Chronic bronchitis	____	____	____
2. Emphysema	____	____	____
3. Lung cancer	____	____	____
4. Asthma	____	____	____
5. Hayfever	____	____	____
6. Other allergic conditions	____	____	____
7. Tuberculosis	____	____	____

B. Is you father alive? 1. Yes_____ 2. No_____

1. Age if living _____ years
2. Age at death ______ years
3. Don't know ________
4. Cause of death ____

C. Was your mother ever told by a doctor that she had:

1. Chronic bronchitis	____	____	____
2. Emphysema	____	____	____
3. Lung cancer	____	____	____
4. Asthma	____	____	____
5. Hayfever	____	____	____
6. Other allergic conditions	____	____	____
7. Tuberculosis	____	____	____

D. Is your mother alive? 1. Yes_____ 2. No_____

1. Age if living _____ years
2. Age at death ______ years
3. Don't know ________
4. Cause of death ____

VI. PERSONAL HABITS

The following questions are about some habits which are important to us in evaluating your health. Please answer to the best of your memory.

TOBACCO SMOKING

A. Did your father smoke? 1. Yes_____ 2. No_____
B. Did your mother smoke? 1. Yes_____ 2. No_____
C. If married, does your spouse smoke? 1. Yes_____ 2. No_____
D. Does anyone else in your house smoke? 1. Yes_____ 2. No_____
E. Have you ever smoked cigarettes regularly? 1. Yes_____ 2. No_____

If YES to E:

1. How old were you when you first started regular cigarette smoking? _____ years
2. On the average of the entire time you smoked, how many cigarettes did you smoke per day? _____ cigarettes per day
3. Do you or did you inhale the cigarette smoke? 1. Yes_____ 2. No_____

   If YES to 3: 1. slightly __________ 2. Moderately_________ 3. Deeply_____________

4. Do you smoke cigarettes now? (as of one month ago) 1. Yes_____ 2. No_____

   a. If NO to 4, how old were you when you stopped? _____ years

   b. If YES to 4, how may cigarettes do you smoke per day now? _____ cigarettes per day

F. Have you ever smoked a pipe regularly? 1. Yes_____ 2. No_____

If YES to F:

1. How old were you when you first started to smoke a pipe regularly? _____ years
2. On the average over the entire time you smoked a pipe, how much pipe tobacco did you smoke per week? (2 oz. per pouch) _____ oz per week
3. Do you or did you inhale the pipe smoke? 1. Yes_____ 2. No_____

   If YES to 3: 1. Slightly_________ 2. Moderately_______ 3. Deeply___________

4. Do you smoke a pipe now? 1. Yes_____ 2. No_____

   a. If **NO** to 4, how old were you when you stopped completely? _____ years

   b. If **YES** to 4, how much pipe tobacco are you smoking now? (pouch = 2 oz.) _____ oz per week

G. Have you ever smoked cigars regularly: 1. Yes_____ 2. No_____

If YES to G:

1. How old were you when you started smoking cigars regularly? _____ years

2. On the average, over the entire time you smoked cigars, how many did you smoke per week? _____ cigars per week

3. Do you or did you inhale the cigar smoke? 1. Yes_____ 2. No_____

   If YES to 3:
   1. Slightly_________
   2. Moderately_______
   3. Deeply___________

4. Do you smoke cigars now? 1. Yes_____ 2. No_____

   a. If NO to 4, how old were you when you stopped completely? _____ years
   b. If **YES** to 4, how many cigars are you smoking per week now? _____ cigars per week

DIET

A. How often do you eat fresh or fresh frozen vegetables?
   1. every day__________________
   2. at least twice a week______
   3. less than twice a week_____

B. How often do you eat fresh fruit?
   1. every day__________________
   2. at least twice a week______
   3. less than twice a week_____

VII. OCCUPATION

The following questions are about your job.

OCCUPATIONAL HISTORY

A. Have you ever worked full time (30 hours per week or more) for 6 months or more? 1. Yes_____ 2. No_____

> If YES to A:
>
> 1.a. Have you ever worked for a year or more in any dusty job? 1. Yes_____ 2. No_____
>
> If YES to 1.a:
>
> b. Specify job/industry ______________________________
>
> c. Total years worked ______________ years
>
> d. Was the dust exposure: mild 1. Yes_____ 2. No_____
> moderate 1. Yes_____ 2. No_____
> severe 1. Yes_____ 2. No_____

2.a. Have you ever been exposed to gas or chemical fumes in you work? 1. Yes_____ 2. No_____

> If YES to 2.a:
>
> b. Specify job/industry ______________________________
>
> c. Total years worked ______________ years
>
> d. Was the exposure mild 1. Yes_____ 2. No_____
> moderate 1. Yes_____ 2. No_____
> severe 1. Yes_____ 2. No_____

3. What has been your usual occupation or job-the one you have worked at the longest?

   a. Job-occupation ______________________________
   b. Number of years employed in this occupation ______________ years
   c. Position-job title ______________________________
   d. Business, field or industry ______________________________

FARMING

B. Have you ever worked on a farm? 1. Yes_____ 2. No_____

If no to B, the questionnaire is complete.

> If YES to B:
>
> 1. Was this a full time occupation? 1. Yes_____ 2. No_____
>
> 2. Do you still farm: 1. Yes_____ 2. No_____
>
> 3. What age did you start farming __________ years

Answer this page only if YES to B:

4. During your farming years, were you ever away from farming longer than one year? 1. Yes_____ 2. No_____

5. How many years has farming been at least 80% of your occupation? __________ years

Nature of your farming:

6. Did you ever grow grain crops? 1. Yes_____ 2. No_____

If YES to 6:

a. Do you grow grain crops now (current year)? 1. Yes_____ 2. No_____

b. How many years? __________ years

c. How many acres (average)? __________ acres

d. What grains have you usually handled (on the average)?

Wheat _________ %
Barley _________ %
Oats _________ %
Canola _________ %
Other (specify) _________ %

e. How many weeks/year did or do you spend seeding grain? ____________ weeks

i. While seeding do/did you ever wear a mask? 1. Yes_____ 2. No_____

ii. Do/did you always use a cab on your tractor? 1. Yes_____ 2. No_____

f. How many weeks/year did you spend combining grain? __________ weeks

i. While combining do/did you ever wear a mask? 1. Yes_____ 2. No_____

ii. Do/did you always use a cab on your combine? 1. Yes_____ 2. No_____

7. Have you ever kept livestock or poultry? 1. Yes_____ 2. No_____

If NO to 7, proceed to 8.

If YES to 7:

7.a. Did you ever have dairy cattle? 1. Yes_____ 2. No_____

If YES to 7.a:

i. Do you have dairy cattle now (current year)? 1. Yes_____ 2. No_____

Answer this page only if YES to B and YES to 7:

ii. How many dairy cattle do/did you average? ________ number

iii. How many years raising dairy cattle? ________ years

7.b. Did you ever raise hogs? 1. Yes_____ 2. No_____

If YES to 7.b:

i. Do you have hogs now? 1. Yes_____ 2. No_____

ii. How many hogs do/did you average? ________ number

iii. How many years raising hogs? ________ years

iv. How many weeks/per year raising hogs? ________ weeks

v. Confined housing? 1. Yes_____ 2. No_____

7.c. Did you ever raise beef cattle? 1. Yes_____ 2. No_____

If YES to 7.c:

i. Do you have beef cattle now (current year)? 1. Yes_____ 2. No_____

ii. How many beef cattle do/did you average? range________ number
feedlot________ number

iii. How many years raising beef cattle? ________ years

iv. How many weeks/year raising beef cattle? ________ weeks

7.d. Did you ever have chickens? 1. Yes_____ 2. No_____

If YES to 7.d:

i. Do you raise chickens now (current year)? 1. Yes_____ 2. No_____

ii. How many chickens do/did you average? ________ number

iii. How many years raising chickens? ________ years

iv. How many weeks/year raising chickens? ________ weeks

v. Confined housing? 1. Yes_____ 2. No_____

7.e. Did you ever raise turkeys? 1. Yes_____ 2. No_____

If YES to 7.e:

i. Do you raise turkeys now (current year)? 1. Yes_____ 2. No_____

Answer this page only if YES to B and YES to 7:

ii. How many turkeys do/did you average? ______ number

iii. How many years raising turkeys? ______ years

iv. How many weeks/year raising turkeys? ______ weeks

v. Confined housing? 1. Yes_____ 2. No_____

7.f. Did you ever raise sheep? 1. Yes_____ 2. No_____

If YES to 7.f:

i. Do you raise sheep now (current year)? 1. Yes_____ 2. No_____

ii. How many sheep do/did you average? ______ number

iii. How many years raising sheep? ______ years

iv. How many weeks/year raising sheep? ______ weeks

v. Confined housing? 1. Yes_____ 2. No_____

7.g. Have you ever raised horses? 1. Yes_____ 2. No_____

If YES to 7.g:

i. Do you raise horses now (current year)? 1. Yes_____ 2. No_____

ii. How many horses do/did you average? ______ number

iii. How many years raising horses? ______ years

iv. How many weeks/year raising horses? ______ weeks

v. Confined housing? 1. Yes_____ 2. No_____

7.h. Have you kept any other livestock? 1. Yes_____ 2. No_____

If YES to 7.h, specify which______________________________

i. Do you keep any other livestock now (current year)? 1. Yes_____ 2. No_____

ii. How many do/did you have? ______ number

iii. How many years do/did you have them? ______ years

iv. How many weeks/years? ______ weeks

8. Did you ever grow hay crops? 1. Yes_____ 2. No_____

If YES to 8:

a. Do you grow hay crops now (current year)? 1. Yes_____ 2. No_____

Answer this page only if YES to B and yes to 8:

b. Are the bales: (check one) a. round ________
b. square ________
c. loose ________

c. How many years spent growing hay crops? ________ years

d. How many acres were hay crops? ________ number

e. How many weeks/year spent with hay crops? ________ weeks

9. Did you ever feed hay crops? 1. Yes_____ 2. No_____

If YES to 9:

a. Do you feed hay crops now (current year)? 1. Yes_____ 2. No_____

b. How many weeks per/year feeding? ________ weeks

c. Do you feed (check one) a. round bales ________
b. square bales ________
c. loose ________

10. Did you ever make silage? 1. Yes_____ 2. No_____

If YES to 10:

a. Do you make silage now? 1. Yes_____ 2. No_____

b. How many weeks per/year spent in making silage? ________ weeks

11. Did you ever feed silage? 1. Yes_____ 2. No_____

If YES to 11:

a. Do you feed silage now? 1. Yes_____ 2. No_____

b. How many weeks per/year spent in feeding silage? ______ weeks

12. Did you ever grind grain for feed? 1. Yes_____ 2. No_____

If YES to 12:

a. Do you grind grain for feed now? 1. Yes_____ 2. No_____

b. How many weeks/year spent in grinding grain? __________ weeks

c. What type of grains ground? 1. Wheat ____________
2. Barley ____________
3. Oats ____________
4. Other ____________

d. Specify other grains ground ______________________________

TEST RESULTS

ALLERGY SKIN TESTS

1. Wheat ________ mm
2. Rye ________ mm
3. Birch ________ mm
4. Alternairia ________ mm
5. Cat ________ mm
6. House dust ________ mm

SPIROMETRY

Observed FEV_1 ________
FVC ________
FEF_{25-75} ________