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Exposures to Respirable, Airborne *Penicillium* from a Contaminated Ventilation System: Clinical, Environmental and Epidemiological Aspects

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Symptoms compatible with hypersensitivity pneumonitis (HP) in two of fourteen employees in a clerical office prompted an investigation of their work environment. Forced-air heater-cooler units which had not been properly maintained were implicated when they were found to be grossly contaminated with predominantly *Penicillium* molds. Air-sampling for viable, respirable-size particulates in the affected office and an unaffected office in the same building demonstrated a 50- to 80-fold excess in the number of colony-forming-units per cubic meter of air in the affected office. Persistent alveolitis was documented by repeated bronchoalveolar lavage, gallium scan, and other studies in one affected worker whose peripheral lymphocytes underwent blast transformation in response to *Penicillium* antigens obtained by air-sampling in the work environment. The other affected worker had asthma, presumably exacerbated by exposures to a variety of inhaled environmental irritants and antigens. Despite a documented reduction of airborne fungi to background exposure levels after clean-up of the forced-air units, the worker with persistent alveolitis has had occasional recurrences of symptoms consistent with HP. Further research is needed to establish health guidelines for control of occupational and non-occupational exposures to respirable fungal organisms which may contaminate cooling, heating and humidifying systems in these settings. A multidisciplinary method of approach to such research is described.

Introduction

The development of a variety of immunological responses to inhaled organic dusts has been well-described, although the immuno-pathogenic mechanisms by which they occur may be quite complex and are not well-understood at this time.[1-6] Several alternative or interacting host mechanisms may contribute to the development of disease entities such as humidifier fever, extrinsic allergic alveolitis, or hypersensitivity pneumonitis. These include immediate asthmatic (Gell and Coombs' Type 1), immune complex mediated (Type 3), cell mediated (Type 4), cytotoxic, and non-specific complement activation mechanisms.[1-6] The antigens believed to be responsible for initiating granulomatous or chronic interstitial pneumonitis reactions in susceptible individuals have often been associated with specific occupational or avocational exposures. Examples of these include enzymes from *Bacillus subtilis* and organic material from the outer coverings or excrement of plants, insects, animals, birds, and microorganisms such as protozoans and fungal species (especially *Aspergillus, Aureobasidium, Alternaria, Penicillium, Coniosporium, Cryptostroma,* and *Cladosporium*).[2,4-6] However, there are also a number of recent case reports of patients in whom hypersensitivity pneumonitis (HP) is believed to have been caused by hazardous inhalation exposures to antigenic contaminants of cooling, heating, or humidifying systems in offices, factories, private homes, and automobiles.[7-12]

Only recently have there been reported attempts to characterize and quantitate the levels of airborne (viable) antigenic exposures believed to be responsible for an ongoing outbreak of HP; or to conduct follow-up air-sampling to evaluate the efficacy of control measures.[2,13-15] This report represents such an effort.

Background

In the Spring of 1979, two individuals among a group of fourteen workers (14%) in a small clerical office in the Boston area reported recurrent episodes of respiratory illness characterized by cough, wheezing, dyspnea, malaise and fever. Their symptoms tended to increase in severity during the workday; to recur as the workweek progressed; to diminish over the weekend or on holidays; and to begin again on re-exposure to the office in which they worked. Both of them had to work at home periodically because of the nature and severity of their illnesses. A third worker developed bilateral ankle swelling and hilar adenopathy after a prolonged flu-like illness. Hospital-based consultants had made presumptive diagnoses of HP in the first two workers. The third individual was diagnosed as having sarcoidosis.

In November, 1979, the Division of Respiratory Disease Studies of the National Institute for Occupational Safety and Health (NIOSH) was requested by the State Depart-

[D]Present address: Centers for Disease Control, Center for Environmental Health, Chronic Diseases Division, Atlanta, GA 30333.

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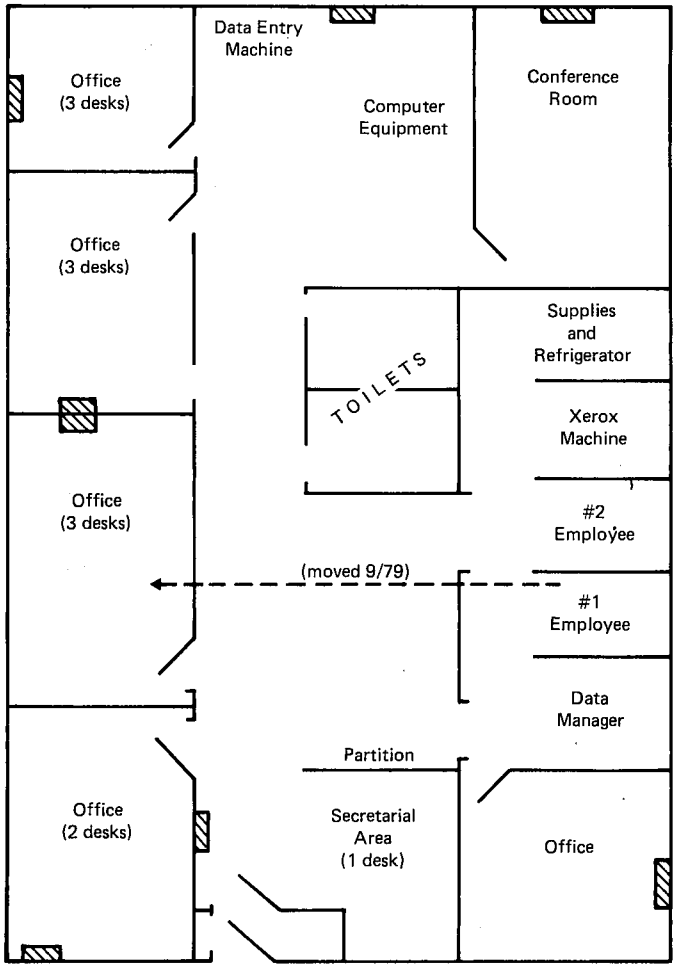

Figure 1 — Sketch of "exposed" office with location of heater-cooler units (lined rectangles) and employees with symptoms of hypersensitivity pneumonitis (#1, #2).

ment of Labor to assist in the evaluation and control of these illnesses. This provided us an opportunity to conduct an industrial hygiene evaluation of the affected office and a comparison office in the same building complex. An epidemiological cross-sectional evaluation of all workers in the affected and comparison offices was also carried out to compare the distribution and occurrence of respiratory complaints in relation to any qualitative or quantitative differences in fungal aerofloral contamination of the two offices.

Case Report

A 48-year-old nonsmoking clerical office worker with a medical history of hypertension, but no previous history of respiratory disease, saw her physician in early August, 1979, because of a non-productive cough which had persisted for two weeks. She noted concurrent fatigue and minimal loss of appetite but denied fever and rash. She also noted dyspnea after climbing one flight of stairs. Her chest roentgenogram was normal and her erythrocyte sedimentation rate (ESR) was 42. Her physician treated her with tetracycline for 20 days without improvement. Although her cough did not resolve and she noted the development of workplace-related chest tightness and malaise, she continued to work in the office building where she had been employed for 11 months. During the last week in August, she went on vacation and noted her symptoms improved. She returned to work on September 4 and later that day developed malaise, mild dyspnea, and a cough productive of small amounts of yellow sputum. Her ESR rose to 84 and she was hospitalized on September 8, 1979 for evaluation.

Physical examination revealed slight wheezing only during coughing. Spirometry revealed a forced vital capacity (FVC) of 2.45 liters (78% of predicted), a forced expiratory volume at one second (FEV_1) of 1.95 liters (71% of predicted), and a mid-maximal expiratory flow rate of 3.40 liters/sec (56% of predicted). The diffusing capacity was 8.9 (67% of predicted). Predicted values are based on observed values for people of the same sex, age, height and race.[16] Changes in arterial pO_2 following exercise were interpreted to indicate a possible abnormality of gas transport at the alveolar level. The chest X-ray remained normal. She was discharged and started on oral cephalexin treatment, and did not return to the office during September.

Her cough, chest pain, and dyspnea on mild exertion persisted and her ESR remained elevated at 82. In late September, she was started on prednisone 40 mg/day which was tapered over 3 weeks and then stopped as her symptoms diminished and her ESR fell to 27.

She returned to work in the third week of October as she was tapering off prednisone. Over the first two weeks in November she developed a non-productive cough, chest tightness and aching, dyspnea with walking on level ground, and malaise. Her ESR rose to 45. Symptoms persisted through December and her sedimentation rate remained elevated. She suffered stress rib fractures and stress urinary incontinence due to her persistent cough. In retrospect, she stated that she felt poorly at the end of each workday and worst by the end of the workweek. However, she usually felt better on Monday morning.

Following an industrial hygiene and medical-epidemiological survey of the office in which she was employed, clinical investigators from NIOSH arranged for her admission to the Clinical Center of the National Institutes of Health (NIH) for evaluation in January, 1980. A ventilation-perfusion

TABLE I
Spectrum of Respirable-size Fungal Organisms Found on Air Sampling in Both Offices in December, 1979 Prior to Clean-up of Ventilation System

Predominant Organisms:	Penicillium[A] (over 80% of all colonies)
	Aspergillus[A]
	Cladosporium[A]
	Alternaria
	Aureobasidium[A]
Other Organisms Present:	Rhizopus
	Mucor
	Helminthosporium

[A]Organisms which have been implicated in previous case reports of hypersensitivity pneumonitis.

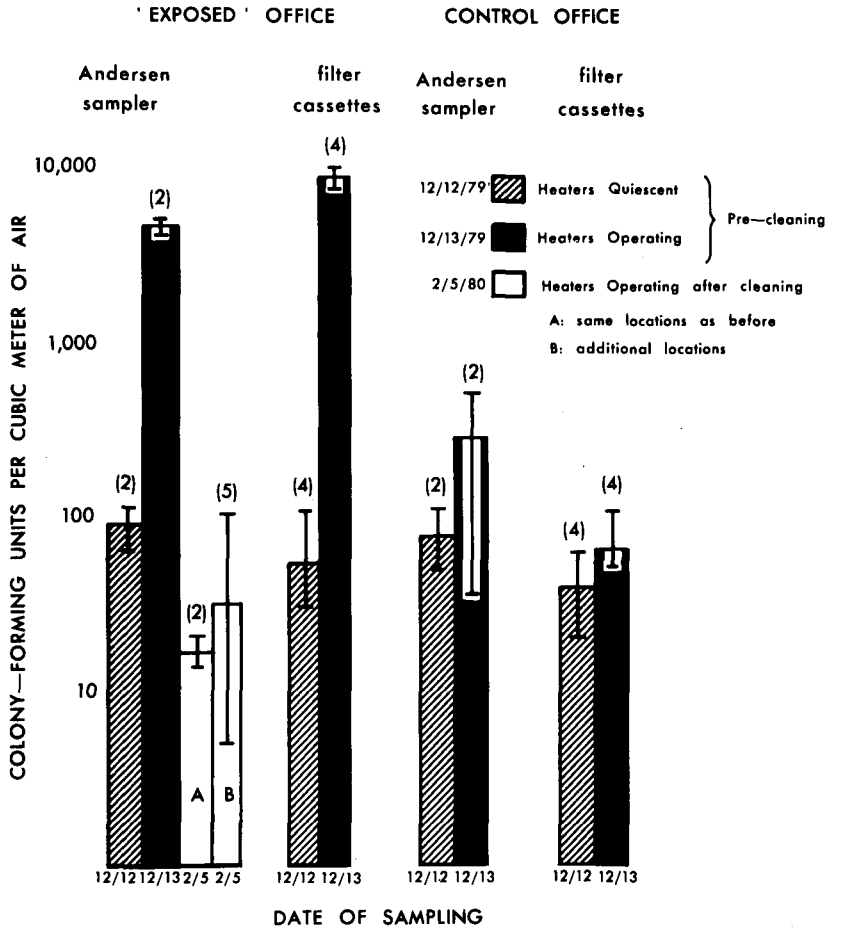

Figure 2 — Results (mean and range of values, number of samples in parentheses) of air-sampling for respirable-size fungal organisms in "exposed" and "control" offices before and after clean-up of forced-air units.

lung study, chest roentgenogram, and lung spirometric studies were normal, except for a marginally abnormal mid-maximal expiratory flow rate. However, she had ESR's between 60-90, a marginally abnormal gallium scan, and an abnormally high percentage of T-cell-predominant lymphocytes were noted on bronchoalveolar lavage. In addition, lymphocytes in her peripheral blood underwent blast-transformation in response to stimulation by antigens prepared from *Penicillium* species which had been collected by air-sampling techniques from her office environment. Although a lung biopsy was not obtained, she was discharged with a presumptive diagnosis of hypersensitivity pneumonitis and treated with prednisone, 50 mg every morning.

The ventilation system at her office, the source of aerosolized *Penicillium* organisms, was thoroughly cleaned with ammonia and chlorine bleach and then maintained regularly. After two months of prednisone treatment, she was re-evaluated at NIH in March, 1980. Her cough had disappeared but some fatigue remained and she complained of occasional dyspnea on climbing two flights of stairs, generally worse on Friday than on Monday in most weeks. A ventilation-perfusion lung study, chest roentgenogram, and lung spirometric studies were normal. Her gallium scan was normal; however, bronchoalveolar lavage still yielded an abnormally elevated percentage of T-cell-predominant lymphocytes (28% observed; less than 10% expected).[17] Because her lung function remained normal, and the treatment of her pre-existing high blood pressure with propranalol might be complicated by further steroid therapy, the prednisone was discontinued and she was discharged with a diagnosis of persistent alveolitis and probable HP.

TABLE II
Demographic Characteristics of the Office Populations

Characteristic	"Exposed" Office	"Control" Office
Sex of Participants		
Male, no.	3	2
Female, no.	11	9
Total, no.	14	11
Age of Participants		
Range, yr.	22-49	20-37
Mean, yr.	31	27
Work Experience in Office		
Range, mo.	1-38	0.5-36
Mean, mo.	15	11
Cigarette Smoking History		
Presently non-smoker, %	64	55
Presently smoker, %	36	45
Mean pack-years, yr.	11.0	10.4

During the next 6 months, she underwent one more course of steroid therapy for symptomatic deterioration which she felt was similar to previous episodes, except that she was the only one in her work environment with symptoms. In December, 1980, she was readmitted to NIH for a follow-up and was found to have some evidence of persistent alveolitis with a marginally abnormal gallium scan and 12% lymphocytes on bronchoalveolar lavage. She was discharged with a recommendation that cessation of exposure rather than steroid therapy be used for treatment and that her pulmonary physiology be monitored at 6-month intervals for early signs of objective deterioration.

Methods

Environmental

The patient worked in an office suite ("exposed" office) on the ground floor of a large building complex where an industrial hygiene survey was conducted on December 12, 1980.[18] After noting the absence of sources of hazardous levels of exposures to chemical fumes which might explain the reported symptoms, sedimentation samples of viable particulates were taken by causing dust from the filters of the forced-air ventilation units to settle onto open Petri dishes placed beneath the units. The plates contained Rose-Bengal-Streptomycin agar (RBS) or modified Sabouraud agar (MSAB), the latter containing 100 units of pencillin per mL and 100 μg Streptomycin G per mL.

In addition to sedimentation samples, we decided to collect air samples to determine whether abnormal levels of airborne, respirable-size fungal organisms were present. For this purpose a comparison office in an adjacent part of the building complex was chosen for a "control" environment. Unlike the "exposed" office, the ventilation system of the control office is in common with that of the rest of the building complex in which both offices and a number of residential apartments and other commercial suites are located.

Sampling for airborne microbes was accomplished using an Andersen (viable) sampler.[19] Airborne microorganisms were thus collected and distributed into six aerodynamic sizes. The Andersen samplers were autoclaved prior to going into the field. On site, their internal surfaces were wiped with 70% ethanol during the loading and unloading of the stages with plastic Petri dishes, each containing 45 mL of RBS agar.[20] The Andersen sampler pumps were calibrated to 1 cubic foot per minute and operated for 15 minutes per sample collection in order to collect particles from about 420 liters of air.

Two types of pumps were used with the second type of direct sampling device, 37 mm filter cassettes. After aseptically loading the sterilized cassettes with previously autoclaved 37 mm Millipore filters and pads, the cassettes were attached to either low-volume (DuPont P4000) or high-volume (General Electric) pumps. These were operated at 4.0 liters/minute for 60 minutes (240 liters) and at 9.8 liters/minute for 45 minutes (422 liters) respectively. After returning to the laboratory, the filters were transferred individually with sterile forceps to sterile 50 mL beakers in which they were rinsed five times with 1 mL aliquots of sterile water. Each rinse was transferred to a sterile tube from

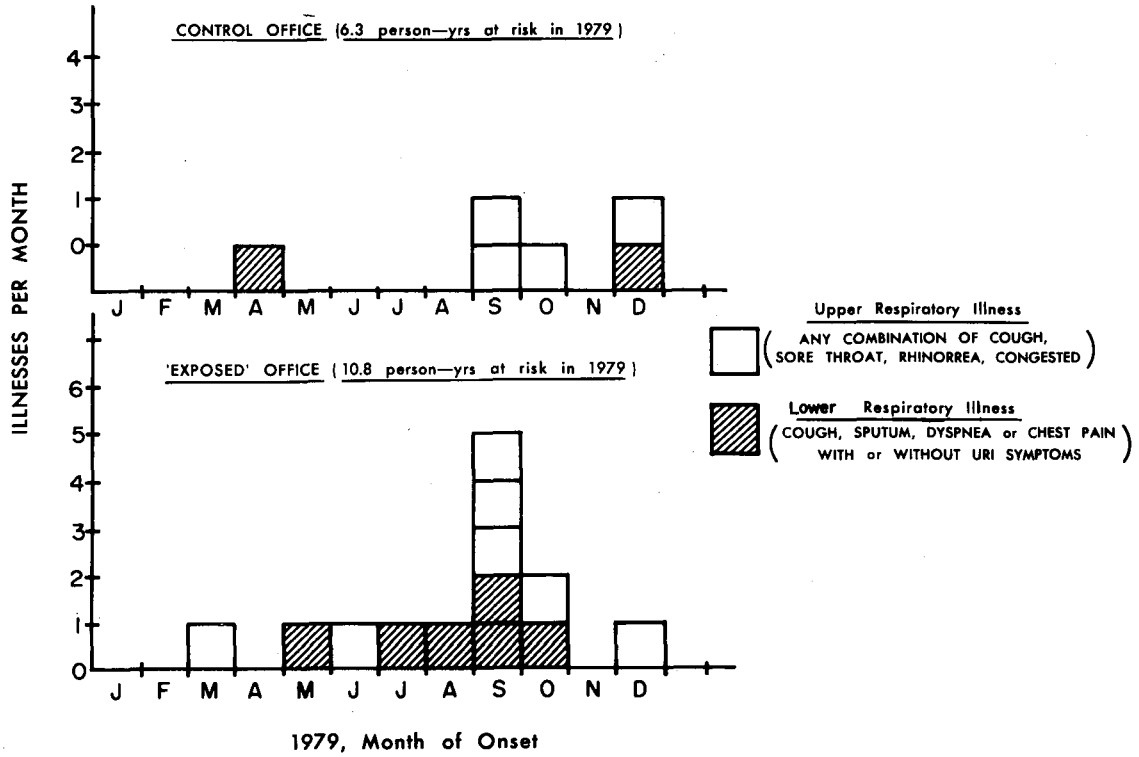

Figure 3 — Epidemic curves for initial onset of non-specific respiratory illness in employees of the "exposed" and "control" offices, 1979. URI = upper respiratory tract illness.

TABLE III
Medical Findings for the Two Index Cases Suspected of Having Developed Hypersensitivity Pneumonitis[A]

Findings	Atopic Smoker Employee #1	Non-atopic, Non-smoker Employee #2
Pattern of Illness:	Recurrent symptoms	Recurrent symptoms
	Rapid onset at work	Delayed onset at work
	Worse at work	Worse at end of day & end of week
	Better at home	Better on weekend, holiday, at home
Nature of Illness:		
Symptoms:	Productive cough	Dry cough
	Chest tightness	Chest tightness
	Malaise	Myalgia, chills, malaise
	Dyspnea	Dyspnea
Signs:	Fever to 100 °F	Fever to 101 °F
	Wheezing, rales	Wheezing
Lab:	Chest X-Ray: Normal	Chest X-Ray: Normal
	ESR: Normal	ESR: Elevated
	PFT: Mild obstruction	PFT: Mild obstruction
	Gallium Scan: Not done	Gallium Scan: Abnormal
	Broncho-alveolar Lavage: Normal for smoker	Broncho-alveolar Lavage: Abnormal increased number of lymphocytes, T-cell predominant
Response to Treatment:	Improved on steroids	Improved on steroids
	Improved at home	Improved at home
Final Diagnosis:	Bronchial asthma	Probable hypersensitivity pneumonitis

[A]ESR = erythrocyte sedimentation rate; PFT = pulmonary function tests; clinical criteria for normal or abnormal values were based on comparisons with expected values by attending physicians.[16,17]

which duplicate aliquots (0.1 and 0.2 mL) of the combined rinses for each filter sample were applied to RBS and MSAB agar plates.

All plates and filters were protected from bright light and maintained at ambient or room temperatures for 12 to 36 hours until transported back to the laboratory where they were incubated at 25 °C for 3 to 5 days. An incubator suitable for incubating and transporting samples at temperatures which would support the growth of thermophilic organisms was not available at the time of this investigation.

Air samples were collected on the afternoon of December 12 and on the following morning at 2 sites near the desks of the affected employees in the "exposed" office and at 4 sites in the "control" office. Mild weather conditions prevailed prior to December 12 but during that night a snow storm came into the area and the heater units were operating continuously by the next morning.

Based on recommendations made at the time of our first survey in December, the units were cleaned and the filters replaced prior to a return visit in February, 1980. At that time the management of the "control" office refused to allow resampling of their office and the additional samplers were placed at other locations in the "exposed" office near heater-cooler units.

Epidemiological

In December, 1979, we investigated the pattern of respiratory complaints among the fourteen employees in the office building where the index cases were employed. A standardized respiratory disease questionnaire containing questions on occupational and medical history, chronic and acute symptomatology, and smoking habits was administered to each employee by an experienced interviewer.[21] A comparison group of the eleven workers from the "control" office described above was interviewed in an identical manner. Interviewers also asked additional questions regarding the characteristic symptomatology and temporal pattern of HP to identify additional cases among the "exposed" and "control" groups.[8,9]

Results

Environmental

Figure 1 is a sketch of the floor plan of the "exposed" office showing the locations of the baseboard-mounted forced-air heater-cooler units and the affected employees (index cases). It was observed that the ventilation system of the "exposed" office is unique to that 2400 square-foot office area which is partitioned into a number of individual work-places. Outside air enters through a vent at the bottom of an exterior

shaft which was noted to be covered with rotting leaves at the time of our visit. The external air passes through filters which are changed every six months and which on visual inspection appeared uncontaminated. The air is then circulated only within the "exposed" office by infiltration and diffusion, and the action of the forced-air units. As evidenced by intact paint seals, the heater-cooler units had not been maintained nor their filters changed since the office was painted 2 years earlier. Sedimentation samples from their filters and working surfaces were grossly contaminated with a spectrum of fungal organisms identical to the organisms which we obtained on air-sampling.

Table I shows the spectrum of organisms found on the ventilation system filters and obtained on air-sampling from both offices. Asterisks indicate those organisms which have been implicated in previously reported cases of HP. Since the sampling, transport, and incubation protocol which we employed would not promote the growth of thermophilic actinomycetes, their presence in the environment cannot be ruled out.

Unlike the "exposed" office, the ventilation system of the comparison office is in common with the rest of the large building complex. There was no evidence of gross contamination of the ventilation system in the comparison office which was otherwise similar to the "exposed" office in design and size. Furthermore, there were no other exposures to hazardous levels of dusts, fumes or exhausts noted in either office.

Figure 2 illustrates the results of air-sampling for fungal organisms. The abscissa contains the dates on which sampling was conducted and the numbers on the Y-axis scale represent the total number of colony-forming units per cubic meter (CFU/M^3) of air sampled. The brackets at the top of each column demonstrate the range of values for 3 or more samples on each occasion. It can be seen that relatively low background levels of fungal aeroflora were obtained by both types of sampling devices (cascade impactor and filter cassette) used in each office on the first day of sampling when the weather was warm and sunny and the heating units were quiescent. However, an increase of 50- to 80-fold in the number of CFU/M^3 of air sampled was observed by both methods only in the "exposed" office on the second day of sampling (December 13) when the weather became freezing cold and wet and the heaters were operating most of the day. The open bars represent resampling in February after the base-board heater-cooler units had been cleaned and the filters changed. Only "background" levels of fungal aeroflora were detected after the units were cleaned, despite the nearly constant operation of the units. Use of the Andersen sampling device enabled us to determine that about 75% of all colony-forming particles in all samples collected were in the respirable-size range.

Epidemiological

Table II shows the demographic characteristics of the "exposed" and comparison office populations. The "exposed" employees were somewhat older and more numerous. Although present smokers in the "exposed" office have smoked longer, on average total pack-years were comparable. There was a greater prevalence of present smokers among the comparison group.

Our interviews with the workers revealed no other individuals in either office group beside the index cases with symptoms consistent with a diagnosis of HP.

Figure 3 illustrates the onset of new complaints of various non-specific respiratory illnesses in both offices in 1979. The case definition used here is not specific for HP. September 1st was the date when the base-board heater-cooler units were changed to the heating mode. The rate ratio for the onset of non-specific respiratory disease symptoms was estimated to be greater in the "exposed" office compared to the "control" during the month of September and the year, 1979.[22] However, statistical significance could not be demonstrated in these estimates. This may have been because of the small size of the study populations, or because a true difference did not exist in the incidence of non-specific respiratory diseases.

Table III compares the clinical data obtained for the two affected individuals, one of whom had several findings suggestive of HP (this is employee #2, described earlier in the case report) and the other had asthma. Unfortunately, the worker diagnosed as having developed symptomatic sarcoidosis decided not to undergo these diagnostic studies. The past history of the latter non-smoking individual was remarkable for alleged episodes of asthma and bronchitis in childhood. It is of interest that HP and sarcoidosis share some immunopathologic features (*e.g.*, granulomatous changes and lymphocyte-predominant alveolitis) except that in occupationally-induced HP the antigenic cause is often identifiable.[17,23]

Discussion

After remedial cleaning and regular maintenance of the ventilation system, the airborne levels of fungal contamination dropped to background levels and presumably stayed there, since the ventilation system has subsequently been routinely cleaned and its filters changed. However, the worker we have described in the case report has had recurrences of probable HP, documented by a persistent alveolitis on lavage. One possible explanation is that this employee is now sensitized to airborne concentrations of *Penicillium* as low as the background levels. It is important to note that without tissue from a lung biopsy, the diagnosis of HP cannot be entirely certain in this individual despite the pattern of symptomatology and the abnormal results on alveolar lavage and gallium scan. Also, this individual's alveolar lymphocytes were not tested for blast transformation with *Penicillium* or other antigens — only her peripheral lymphocytes were used for this test. Therefore, the strength of the association between exposure and disease might also be questioned. While bronchoalveolar lavage is a specific method for the demonstration of an alveolitis, its sensitivity and specificity for HP are not yet clear; but the predictive value of this procedure and its usefulness in conjunction with therapy may be greater than some other more widely used laboratory tests.[17]

The other affected employee was a smoker with a long history of asthma who had no evidence of alveolitis, but may have experienced exacerbations of asthma during intense exposure to fungal antigens. Also, both affected employees were under treatment for high blood pressure with propranalol, a drug with beta-blocking effects which might confound the basis for respiratory (bronchoconstrictive) symptoms assumed to be allergic or atopic in nature.

The epidemiology of HP (extrinsic allergic alveolitis) and humidifier fever are not well described. For example, the relative importance of personal risk factors (susceptibility) versus the importance of the nature, intensity, frequency, and duration of inhalation exposures to respirable organic antigenic material have not been adequately studied in relation to the occurrence and distribution of these potentially disabling diseases. Among the barriers to elucidating the pathogenetic methanisms and controlling these diseases are: the lack of agreement over reliable and precise methods of case definition, case confirmation, and case identification (reporting or surveillance); and a lack of qualitative or quantitative inhalation exposure data where cases have been identified.

The first symptoms of disease may develop between 4 weeks and 3 years from the time of first intense exposure.[24] Symptomatic HP may occur in an acute form characterized by chills, fever, cough, dyspnea, and malaise typically beginning 4 to 8 hours after inhalation of the antigenic dust. The chest roentgenogram may be normal or it may show diffuse nodular infiltrates and hyperinflation.[2,6] Pulmonary function abnormalities occur in a spectrum from restrictive changes in dynamic lung volumes to severely reduced diffusing capacity.[6,9] Another acute form of HP has been described; however, there is some controversy over whether this is a toxic or immunopathogenic form of HP.[25,26]

A more insidious form of the disease may develop when exposure to the organic dust occurs intermittently or continuously at low levels. Acute symptoms may be absent and patients experience progressive dyspnea and chronic cough which may be productive of small amounts of sputum. The diagnosis of HP may be less likely to be entertained in these cases because of the subtlety or absence of acute symptoms in relation to recognized exposure.[27]

Many of the airborne organisms/antigens which are putative causes of HP are ubiquitous in the environment and can be found in up to 65% of homes surveyed in the Milwaukee area, for example.[9,28] Precipitating antibodies to certain common environmental antigens have been demonstrated in 15% of the general population in one survey, while 50% of some exposed, but clinically well, occupational groups may have positive precipitins.[29-32] On the other hand there are reports of individuals with clinical disease (HP) who have no evidence of a humoral antibody response to the suspected causative agent.[29] Thus, measures of humoral immunological response may only represent an indication of exposure and may not be specific for a causative relationship between exposure and disease.[3,17]

Evidence for a causal relationship between exposure to airborne fungal antigens and outbreaks of HP has been supported by the confirmation of the presence in the ventilation system, and/or air of the environment in question, of organisms which have caused HP in occupational settings.[7-12] However, the levels of exposures to such airborne contaminants, necessary and sufficient to cause HP in susceptible individuals, are not known at present. Furthermore, the factors which might make one individual more susceptible than others to the risk of developing HP from equivalent exposures are not known.

The stringency and reliability of criteria for the definition of a case of HP have varied considerably in settings such as physicians' private offices, sophisticated medical centers, and on-site field investigations by industrial hygienists and epidemiologists. The strength and biological plausibility of a causative relationship between documented exposures to respirable airborne antigens and onset of HP would be increased with confirmation of each of the following findings:

(1) A classical presentation of symptoms and signs of HP (see above) which occur consistently several hours after re-exposures to potentially causative, airborne, respirable-size antigens, and which are relieved by removal from exposure;

(2) A greater prevalence of positive humoral and/or cell-mediated immunological responses among cases of HP than among suitably selected controls to antigens collected by air-sampling from the environments occupied by cases and controls;

(3) A greater prevalence of positive objective responses (*e.g.*, abnormal pulmonary function) to environmental or workplace inhalation challenge among informed, consenting volunteer cases than among suitably selected, informed, and consenting volunteer controls;

(4) The demonstration of a T-lymphocyte-predominant alveolitis by bronchoalveolar lavage in affected individuals; and

(5) The use of lung biopsy to demonstrate the presence of granulomatous inflammation of parenchymal, bronchiolar, and alveolar areas in affected individuals in whom these areas of the lung may be positively stained with specific immunofluorescent antibodies directed against suspected airborne antigens.

The literature on sampling for airborne microbial organisms has recently been reviewed.[33] The latter author stated: "There are few standard devices for sampling and virtually no standards for allowable or desirable microbial burden of the air."[33] In fact, occupational health guidelines for allergenic or immunopathogenic exposure to airborne microorganisms and organic dusts are only now in developmental stages of research.[34] Nevertheless, a wide variety of occupational aerogenic exposures to microorganisms, or their toxic products, may be responsible for a spectrum of subclinical, acute, and chronic respiratory diseases.[35,36]

Conclusions

(1) We have demonstrated a useful application of multidisciplinary approaches to the problem of indoor air

pollution, involving epidemiological, clinical, and industrial hygiene techniques of investigation.

(2) In our case report, the absence of infiltrates on chest roentgenograms and the lack of lung biopsy data make the diagnosis of HP somewhat uncertain despite other evidence associating this illness with inhalation exposure to relatively high levels of *Penicillium* antigens which resulted from inadequate maintenance of a common heating and cooling system.

(3) We believe that findings like those described and referred to in this report may have broad implications for public health: what levels of potentially immunopathogenic aerofungi are aerosolized from contaminated ventilation systems in homes, automobiles, and offices; what is the spectrum of illness which normal individuals may develop from various levels of exposure to fungal antigens (from sub-clinical effects to HP); what illnesses may be experienced by atopic or immuno-compromised individuals exposed to the same levels (diseases such as asthma or sarcoidosis); and, for occupations where persistent high levels of these antigen aerosols may occur, what levels of respirable material can be considered non-hazardous?

(4) Finally, in view of the widespread use of these heater-cooler units, it would be important to carry out a well-designed study to assess the nature, frequency, and control of their contamination with immunopathogenic microorganisms.

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