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AN OUTBREAK OF RECURRENT ACUTE AND CHRONIC HYPERSENSITIVITY PNEUMONITIS IN OFFICE WORKERS

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Three episodes of an acute, flu-like illness, one studied in detail, were associated with manipulations on the central air handling system of an office building in Tennessee in the summer and early fall of 1981. Symptoms were compatible with acute hypersensitivity pneumonitis, although the time of onset revealed a biphasic epidemic curve. Breathing air not supplied through the central air handling system protected against disease. Ill persons had significantly more precipitins to agents cultured from the building than did controls. Symptoms suggestive of chronic hypersensitivity pneumonitis were also found. Chronic disease was associated with the presence of humidifiers at home, asthma, and longer work in the building. Acute disease occurred less frequently in smokers and persons who had previously worked in the building before 1976. Persons with acute disease were more likely to have chronic disease. No single etiologic agent could be identified. Because of difficulties with demonstrating safety for reoccupancy, the building was vacated and remains empty at this time.

alveolitis, extrinsic allergic; antibodies; hypersensitivity pneumonitis

Outbreaks of respiratory illness associated with ventilation systems in buildings have been described with increasing frequency since the first report by Pestalozzi in 1959 (1). The spectrum of disease has ranged from irreversible fibrosis (2) to asthma (3). Most outbreaks have been associated with use of water sprays or the presence of stagnant water in building air handling systems (4, 5). Although recognition of such outbreaks usually presents no problem, the epidemiology, prognosis, risk factors, and interrelationship of the acute and chronic forms of hypersensitivity pneumonitis have not been well described. This report presents the epidemiology of a large

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outbreak of both acute and chronic disease from the same source, including risk factors and the interrelationship of the two forms.

History of the outbreak

The outbreak occurred in a seven-story office building constructed during the 1930s and leased by the Tennessee Valley Authority. Its air handling system, described in detail elsewhere (5, 6), contained two open water spray systems for summer cooling and was similar to the kind associated with hypersensitivity pneumonitis in the past (7, 8). The building had been occupied by the Tennessee Valley Authority until 1975. It then stood vacant for five years until April 1981, when it was reoccupied by the same group, consisting of many of the same employees who had worked there prior to 1976. Between April and September 1981, a number of employees developed fatigue, malaise, and other nonspecific symptoms. Table 1 lists the temporal sequence of the acute outbreaks of disease, the manipulation of the air handling system, and the conduct of the investigation.

On Wednesday, September 16, 1981, the Tennessee Valley Authority local medical office treated two employees who had become ill while at work in the building on the previous Monday. A third employee was reported to have gone home with the same symptoms. The Industrial Hygiene Branch was requested to investigate for chemical or physical agents which might have caused the illnesses.

With cooler weather expected, the air cooling system was shut off for the first time since building occupancy on Friday evening, September 18, 1981, with the circulating fans remaining on. However, by Monday morning the temperature in the building had exceeded 80 F (26.7 C), and the water spray was turned back on. During that day and evening a flu-like illness occurred in approximately two-thirds of the building occupants. The Special Health Services Branch of the Tennessee Valley Authority's Division of Medical Services conducted an investigation that implicated the air handling system. The air cooling system was immediately turned off. The sumps were drained, and the system was scrubbed with detergents and cleaned with high-pressure steam. The sumps were then refilled with fresh water and treated with a quarternary ammonium antimicrobial. The antimicrobial treatment was repeated twice weekly thereafter. One of the two units was repaired over the next two weeks.

TABLE 1

Temporal sequence of the epidemic and steps in the investigation. hypersensitivity pneumonitis in office workers, Tennessee, 1981

Date	Event
1940–1975	Tennessee Valley Authority (TVA) occupies the building.
1975–1981	Building is empty.
1981	
April	The TVA reoccupies the building.
September 18	Air cooling system turned off for the first time since April.
September 21	Air cooling system turned on again; the first outbreak occurs
September 22	Knoxville County Health Department and TVA Industrial Hygiene Branch contacted.
September 23	First (TVA) questionnaire survey, air cooling system subsequently turned off.
October 12	Air cooling system turned on again.
October 13	Second outbreak; air handling system turned off.
October 14	Serum for precipitin titers drawn.
October 15	Air handling system turned on again; third outbreak occurs.
October 16	TVA removes employees from the building.
October 25–28	Industrial hygiene survey.
1982	
March 2–4	Second questionnaire survey.

No new illness occurred until October 13 (after the second unit had been turned on), when the second outbreak ensued, whereupon the whole air handling system was turned off with reliance on passive air supply. The third outbreak occurred after the air handling system was inadvertently turned on again two days later. The building was vacated and the National Institute for Occupational Safety and Health invited to assist in an investigation.

Materials and methods

First round: acute disease

A first questionnaire was designed by the Tennessee Valley Authority investigators and distributed to all employees in the building two days after the first outbreak. It elicited information on the type and number of symptoms, the time of onset, location of employees within the building, and their proximity to open windows.

Second round: chronic disease

The second questionnaire, although never formally validated, has been used in two previous cross-sectional investigations (7, 9) and as a screening questionnaire in a plant with endemic hypersensitivity pneumonitis. It elicited the frequency ("usually", "sometimes", "rarely") and temporal pattern of symptoms (chills, myalgias, feverishness, chest-tightness, cough, and wheezing), information on smoking habits, and the presence of possible risk factors (allergies, eczema, asthma, hay fever, air-conditioner at home or in car, humidifier at home, duration of work in the building, and whether persons had worked in the building before 1981). The questionnaire was distributed six months after the outbreak to all employees, who had meanwhile been moved to four different office buildings in Knoxville. It inquired whether these symptoms occurred during the time of building occupancy and whether all symptoms had resolved. Employees from a second Tennessee Valley Authority group who performed the same kind of work but who had not worked in the building under study were selected as controls.

Medical records

Medical records were reviewed on 28 individuals who went to the Tennessee Valley Authority Medical Office after the second outbreak. Serum samples were collected from these cases, from 28 age- (within five years) and sex-matched non-ill individuals from the same building, and from 28 age- and sex-matched Tennessee Valley Authority employees from another office building in Knoxville (controls). Sick and annual leave records for each building occupant were reviewed for their period of occupancy in 1981 and for the corresponding period in 1980.

Industrial hygiene and immunology

Airborne fungi and thermo-tolerant bacteria were collected with six-stage Anderson samplers with the air cooling system either turned off or running. Bulk samples were obtained from the water sumps, baffle plates, and fan room of the air handling system, and from dust, dirt, and debris from the rest of the building. Serum reactivity to agents cultured in the building and to a standard diagnostic panel of hypersensitivity pneumonitis agents were assayed with counterimmune electrophoresis and immune fluorescence. The questionnaires and further details of sampling strategies, industrial hygiene methods, and culture techniques are published elsewhere (6).

Disease definition

In this report, "acute disease" will refer to disease detected by the first questionnaire. The original working disease definition was "any three or more symptoms [on the first questionnaire] that began after 11:00 AM." After plotting symptom frequencies, this definition was considered too restrictive. Persons with only one symptom were arbitrarily excluded from analyses of risk factors to eliminate "noise." "Chronic disease" was defined as "usually" or "some-

times" responses to at least two symptoms on the second questionnaire (7).

Statistical analyses

Standard statistical tests were used. Odds ratios, 95 per cent confidence intervals, and exact probabilities were calculated with a program on the University of Pittsburgh computer system (10).

RESULTS

First round

At the time of the first outbreak, 363 people were employed in the building. Of those, 28 were not in the building on the day of the first outbreak. Eleven persons did not return their questionnaires, for a response rate of 96.7 per cent. Figure 1 plots the time of onset of each individual's first symptom by the number of persons with one, two, and three or more symptoms. By the working disease definition, 45.4 per cent were ill. At least two symptoms were reported by 203 people, for an overall attack rate of 62.6 per cent. Twenty-five of 203 ill persons (12.3 per cent) had onset of their first symptom before 11:00 AM. No differences were observed in sex-specific attack rates within the various symptom frequencies nor in the distribution of symptom-frequency by floors. The median time of onset for the different floors was 2:49 PM (standard deviation (SD), 32 minutes), seven to eight hours after turning on the ventilation system. No temporal pattern of spread by floors was observed.

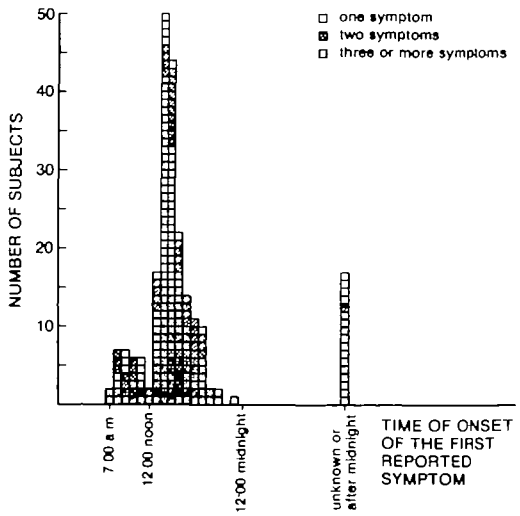

FIGURE 1. Epidemic curve from first questionnaire: hypersensitivity pneumonitis in office workers, Tennessee, 1981.

On floors 3–7, the outside windows could be opened. Among workers sitting within 8 ft (2.4 m) of a window that could be opened, having this window open for at least one hour between 7:00 AM and noon protected against disease by the working definition (odds ratio, 2.36; 95 per cent confidence interval, 1.03–5.41) but not after including persons who had onset of their symptoms before 11:00 AM. Eight persons occupied the computer room, which had a totally separate air supply system. None of these eight persons was ill ($p < 0.001$). Table 2 lists the frequency distribution of each symptom. Constitutional complaints were much more frequent than respiratory complaints. Respiratory complaints consistently did not occur more frequently before 11:00 AM than afterwards. No consistent change in the percentage distribution was observed among persons with various symptom frequencies.

Second round

Fifty eight per cent of the original respondents responded to the second questionnaire. There was no indication of bias among respondents; men and women were

TABLE 2

Frequency distribution of symptoms· hypersensitivity pneumonitis in office workers, Tennessee, 1981

Symptom	% of persons with 2+ symptoms who had symptom
Myalgias	84.9
Fever	69.8
Headache	66.6
Chills	61.0
Cough	47.2
Fatigue	37.7
Nausea	37.1
Wheezing	22.6
Chest tightness	17.0
Chest congestion	12.6
Shortness of breath	4.4

TABLE 3

Risk factors for acute and chronic disease by persons with two or more symptoms, showing odds ratios (OR) and 95 per cent confidence intervals (CI): hypersensitivity pneumonitis in office workers, Tennessee, 1981

Risk factor	Acute disease			Chronic disease		
	No	OR	95% CI	No	OR	95% CI
Current cigarette smoking	44	0.64	0.47–0.91	12	0.92	0.51–1.43
Humidifier at home	24	1.34	0.67–2.97	10	2.23	1.04–4.14
Asthma	7	2 42	0.68–10.58	7	4.15	1.40–11.18
Building-exposure before 1976	26	0.54	0.34–0.87	5	0 53	0.19–1.19

equally likely to respond to the second questionnaire as were persons in the four symptom classes. Chronic complaints were significantly more frequent among building occupants than among controls ($p < 0.045$ for the most conservative comparison). Also, persons who reported two or more symptoms on the first questionnaire were significantly more likely to report two or more symptoms on the second questionnaire ($p < 0.025$). Table 3 lists the risk factors for the development of acute and chronic disease, the associated odds ratios, and the 95 per cent confidence intervals for those risk factors that were statistically significantly different among ill than among non-ill individuals for either acute or chronic disease.

Environmental investigation

Review of the weather data provided by the National Oceanic and Atmospheric Administration showed no unusual weather conditions during the three outbreaks of mass illness. Review of building operations showed that the outbreaks could not be related to environmental changes or variables such as new construction, renovation, use of new cleaning agents, or pesticide application. The geometric mean level of airborne respirable dust in several office locations was 46 $\mu g/m^3$ (SD = 37 $\mu g/m^3$), comparable to that found in other office buildings (5, 6). Airborne fungi and bacteria were collected via Andersen samplers at several locations on October 25, ten days after the third acute outbreak. Water spray sumps, which had been drained and cleaned between October 15 and 20, were refilled on October 25, several hours prior to the initiation of microbial sampling. Airborne levels of fungi and bacteria recorded on October 25 approached but never exceeded 1,000 colony-forming units per m^3. A wide variety of micro-organisms (table 4), in-

TABLE 4

Organisms isolated from the Study Building to which precipitins were measured hypersensitivity pneumonitis in office workers, Tennessee, 1981

Category of organism	Specific organism
Fungi	*Aspergillus flavus* (1)*, *versicolor* (1), *fumigatus* (1), *niger* (1), and one unidentified species
	Cephalosporium spp. (1)
	Cladosporium spp. (1)
	Cryptococcus spp (1)
	Dermatiaceus spp. (2)
	Epicoccum nigrum (1)
	Fusarium spp. (1)
	Harposporium spp. (1)
	Mucor spp. (1)
	Oidiodendrum spp (1)
	Penicillium spp (3)
	Phoma spp. (1)
	Pithomyces spp. (1)
	Rhodotorula spp (1)
	Stachybotrys spp (1)
	Trichoderma spp. (1)
	Verticillium spp. (1)
Actinomycetes (5)	
Bacteria	*Achromobacter* spp. (1)
	Alcaligenes spp (4)
	Bacillus spp. (2)
	Corynebacterium spp. (1)
	Flavobacterium spp. (4)
	Pseudomonas spp. (4)
	Xanthomonas spp (1)

* Numbers in parentheses indicate the numbers of different strains isolated.

cluding several that have been implicated as agents causing hypersensitivity pneumonitis, were recovered from air-samples as well as from dust and slime present in the air handling system (5, 6).

Immunology

Ill employees had precipitins to significantly more fungal agents than either the building occupants who were not ill or the control group (table 5). In addition, ill persons were more likely to have at least one precipitin to an agent isolated from the building than were either the non-ill occupants ($p < 0.01$) or the control group ($p < 0.025$). Still, there were no differences in the frequency distribution of precipitins to individual fungal and bacterial agents great enough to explain the occurrence of disease, although two of the 56 distributions were significant at the 0.05 level (nonsignificant after Bonferroni adjustment (11)). Also, no differences in the distribution of antibodies to *Acanthamoeba castellanii*, *Acanthamoeba polyphaga*, *Naegleria gruberi*, *Naegleria lovaanensis*, and to a standard panel of organisms associated with hypersensitivity pneumonitis (*Aspergillus fumigatus*, *Candida albicans*, *Penicillium notatum*, *Saccharomonospora viridis*, *Thermoactinomyces vulgaris*, and *Thermoactinomyces candidus*) were seen. As the illness of several subjects was at least compatible with the diagnosis of legionellosis, sera were tested for immunofluorescent antibodies to *Legionella pneumophila*, serogroups 1–6, *Legionella bozemanii*, and *Legionella micdadei*. Only one person had a titer of greater than 1:128. Immunofluorescent antibodies to four legionella strains were positive in the water sump itself at low titers.

No differences in the distribution of combined annual and sick leave were noted between ill and non-ill building occupants from the preceding to the current year.

TABLE 5

Mean number of fungal precipitins per group: hypersensitivity pneumonitis in office workers, Tennessee, 1981

Group	Mean no. of precipitins	No
Study building		
Ill (I)	3.2 ± 3.1	26
Non-ill (II)	1.8 ± 2.4	28
Control building		
(III)	1.4 ± 2.4	28
$t_{I\text{-}II} = 2.30$,	$p < 0.01$	
$t_{I\text{-}III} = 2.96$,	$p < 0.005$	
$t_{II\text{-}III} = 0.88$,	$p > 0.20$	

DISCUSSION

This outbreak does not fit the pattern of mass hysteria, classical criteria for which include "transmission by sight or sound", sex-specific attack rate differential, an index case with social power, and nonspecific symptoms. The median time of symptom onset was similar from floor to floor, and the problem was noted only the day after occurrence, making the first point—"transmission by sight or sound"—unlikely. Sex-specific attack rates were not different for either acute or chronic disease, addressing the second point, sex-specific attack rate differential. There was no index case as a source of transmission. Last, the symptoms were not dizziness, fainting, and weakness, as have been described in mass hysteria (4).

The disease was clearly associated with the air handling system. No one in the computer room, with a separate supply of air, was ill. There was a temporal relationship three times with manipulating the air cooling system. Other diseases with similar symptoms possibly related to ventilation systems include simple viral illness ("flu") and Pontiac Fever. The former was unlikely here because of the recurrent nature, the shape of the epidemic curve, and the association with the air conditioning unit. Pontiac Fever was unlikely because of its longer incubation period (12–48 hours) and longer duration of symptoms (2–5 days). Symptoms and course were therefore suggestive of humidifier fever or hypersensitivity pneumonitis.

Some authors have attempted to distinguish hypersensitivity pneumonitis from humidifier fever on the basis of negative

chest x-rays present in the latter (12, 13). Although outbreaks of humidifier fever are characterized by negative chest x-rays, case reports and case series of humidifier fever have demonstrated clearly abnormal chest x-rays (4). In addition, even in hypersensitivity pneumonitis, normal chest x-rays are regularly described. Both are restrictive, infiltrative lung disease, with similar lung function abnormalities, and both have been described from the same kinds of sources. In Great Britain, some authors feel humidifier fever is characterized by "Monday miseries" (13), a finding not demonstrated in the United States. We are unable to distinguish the two diseases in this case.

Over ten per cent of the cases seemed to have onset of their disease before the 3–4 hours minimum "incubation period" (14) usually assumed necessary. The epidemic curve showed a symmetric distribution around two points in time. Although hypersensitivity pneumonitis and humidifier fever have been thought to have some obstructive component (15, 16), an early onset of hypersensitivity pneumonitis such as is found in acute-onset asthma has not been described. Although asthma has been described from contaminated humidifiers (17), asthma alone is not associated with fever, chills, and myalgias. However, in the absence of concurrent clinical studies, we cannot with certainty exclude asthma as a component of this outbreak. Similarly, in the absence of chest x-rays and pulmonary function studies performed while individuals complained of chronic symptoms, the presence of chronic hypersensitivity pneumonitis is based on questionnaire responses alone. These questionnaire responses have been associated with decreased single-breath carbon-monoxide diffusing capacity (9) and forced vital capacity changes (7) in similar outbreaks. Despite lack of clinical studies, there is no reason to doubt the existence of chronic disease in this building.

Precipitins are considered an indication of exposure to an agent rather than of the presence of disease (18). Although antibodies to two agents occurred significantly more often in the case group, and in the expected direction, after adjustment for "multiple comparisons" this was no longer true. In addition, they occurred in only five and six persons, respectively. Neither of the two agents have been associated with hypersensitivity pneumonitis in the past. Precipitins to no single agent were frequent enough to attribute the outbreak to a single organism. Some authors (19, 20) have implicated not organisms themselves but endotoxin. At least one investigator (21) has shown that persons without precipitins will react to a specific challenge. The above results indicate the disease may not be a reaction to one organism alone but a cumulative reaction to a number of organisms in the air. Conversely, persons who develop illness may be immunologically different from those who do not.

Acute disease occurred less frequently in persons who had worked in the building before 1976 and in those who smoked than in those who did not. Smoking has been associated with lower rates of infiltrative lung diseases and sarcoidosis (22). In addition, ill persons in outbreaks of building-associated hypersensitivity pneumonitis have more often than not been nonsmokers. All of four ill persons (23) and all of seven ill persons (24) in early reports were nonsmokers. In the two outbreaks of disease in office workers where smoking information was given, three of 26 ill persons versus eight of 22 controls (25) and four of 20 ill persons versus 14 of 20 controls (19) were smokers (Mantel-Haenszel chi-square $= 13.204$, $p < 0.001$). Nonsmoking seems to be consistently associated with slightly higher rates of disease. Two explanations for the protective effect of previous work in the building: persons who had been ill earlier in 1975 may have selectively left the building or previous work may have desensitized workers in some way. Which explanation is more likely is unclear.

Chronic disease was associated with the presence of humidifiers at home and with asthma. The chronic symptoms had disappeared by the winter months, when humid-

ifiers are more likely to be in use, but were present during the summer, when humidity is higher. Disease was therefore unrelated to current humidifier use. More likely is that persons become sensitized to antigens through additional exposure at home, or persons with chronic respiratory complaints use humidifiers at home. Asthma itself involves frequent coughing and wheezing. As the questionnaire did not ascertain whether asthmatics' symptoms increased during building-exposure, the risk factor cannot be distinguished from disease itself, although asthma occurred much less frequently than did coughing and wheezing. The finding warrants further investigation.

The acute and chronic forms of disease are not completely independent, as persons with acute illness were more likely to have some form of chronic disease, although two of the risk factors, smoking and prior work, did not follow the same pattern for the two forms.

It was clear from the outset that an answer to the question "Could the building be safely re-occupied?" might require a large amount of additional laboratory and clinical investigation to determine the etiologic agent. Such identification has allowed others to measure airborne levels of antigen (26). These studies were not performed. In this investigation, we were unable to predict safety for reoccupancy.

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