Sporadic Community-Acquired Legionnaires' Disease in the United States

A Case-Control Study

GREGORY STORCH, M.D.; WILLIAM B. BAINE, M.D.; DAVID W. FRASER, M.D.; CLAIRE V. BROOME, M.D.; HERBERT W. CLEGG II, M.D.; MITCHELL L. COHEN, M.D.; STELLA A. J. GOINGS, M.D.; BRENDA D. POLITI, D.V.M.; WILLIAM A. TERRANOVA, M.D.; THEODORE F. TSAI, M.D.; BRIAN D. PLIKAYTIS, M.Sc.; CHARLES C. SHEPARD, M.D.; and JOHN V. BENNETT, M.D.; Atlanta, Georgia

One hundred patients with sporadic, community-acquired, serologically confirmed Legionnaires' disease were matched with control subjects known by the patients (acquaintance controls) and control subjects chosen from among patients with negative serodiagnostic tests for Legionnaires' disease (clinical controls). Each clinical control subject was also matched with an acquaintance control of his own. Legionnaires' disease patients had smoked more cigarettes, consumed more alcohol, and were more likely to have resided near excavation sites than acquaintance or clinical control subjects. Parallel differences between clinical controls and their acquaintances were not seen. Legionnaires' disease patients had traveled away from home for more time during the 2 weeks before onset of illness than had their acquaintances. The difference was of greater magnitude than that between clinical control subjects and their acquaintances. Legionnaires' disease patients were more likely to have resided near construction sites than clinical controls, and there were more construction workers among patients than among clinical control subjects.

WITH THE DEVELOPMENT of laboratory tests for the diagnosis of Legionnaires' disease, hundreds of sporadic confirmed Legionnaires' disease (LD) cases have been reported to the Center for Disease Control (CDC). To learn more about the epidemiology of these cases, we undertook a case-control study of 100 consecutive sporadic, community-acquired cases in which the diagnosis was confirmed by indirect fluorescent antibody (FA) serologic testing at the CDC. We directed particular attention to factors that might increase susceptibility to Legionnaires' disease and to hypotheses on sources and modes of transmission of the etiologic agent.

Materials and Methods

SELECTION OF RESPONDENTS

The Bureau of Epidemiology maintains a list of sporadic cases of confirmed Legionnaires' disease reported to the CDC from state health departments and other sources. As of 24 October 1977, 169 cases with onset since 1 August 1976 were listed. Laboratory confirmation had met one or more of three diagnostic criteria: fourfold or greater rise in indirect FA titer (stated as the reciprocal of the dilution) to 128 or above (146 cases), visualization of the LD bacterium in lung tissue by direct immunofluorescence (21 cases), or isolation of the LD bacterium from clinical or autopsy specimens (six cases).

One hundred consecutive sporadic, community-acquired cases diagnosed serologically at the CDC (Group I) were selected for study. Patients known to have been hospitalized in the 2 weeks before onset of disease were assumed to have infections that were possibly nosocomially acquired and were excluded from this study. Two control groups, each made up of one person matched with each patient in Group I, were selected. For one set (Group II), acquaintance controls were chosen by asking each respondent in Group I to provide the name of an acquaintance of roughly the same age (usually ± 5 years) and sex who lived in the same community but at least 1 mile away. For the other set (Group III), clinical controls were chosen from a computer listing of all persons from whom specimens had been obtained and submitted to the CDC for LD serodiagnosis. For each patient in Group I, the Group III control selected was the person of the same sex and age (usually ± 5 years) whose specimen was received at the CDC from the same state in closest time to the date of receipt of the diagnostic specimen from the Group I patient. Selection for Group III was limited to persons with LD indirect FA titers to LD bacterium strains Philadelphia 1 and Philadelphia 2 of 64 or less in one or more serum specimens drawn at least 21 days after onset of illness. A third set of controls (Group IV) was chosen by asking each person in Group III to suggest someone of the same age, sex, and community according to the conditions that governed the selection of Group II controls for Group I.

DATA COLLECTION

All respondents were informed of the study's purpose, and those who consented were interviewed by telephone by an investigator using a standardized precoded questionnaire designed to test various hypotheses about Legionnaires' disease. All questions were addressed to the 2-week interval before onset of illness in the relevant LD case (Groups I and II) or clinical control (Groups III and IV). For Groups I and III, interviews were conducted with the person who had been ill unless that person was incompetent or dead, in which case the closest available contact was interviewed. Interviewers were medical or veterinary epidemiologists knowledgeable about Legionnaires' disease. A serum specimen for LD indirect FA testing was requested from each person in Group II. The physician of each person in Group III was asked to supply a hospital discharge summary or other description of the illness for which LD serologic testing had been requested.

DATA ANALYSIS

Legionnaires' disease patients (Group I) were compared separately with their acquaintances (Group II) and with clinical controls (Group III) by matched-pair analysis. Clinical controls (Group III) were also compared with their acquaintances (Group IV). This comparison was analyzed in parallel with the comparison between Groups I and II.

Differences between Groups I and II might represent specific risk factors for Legionnaires' disease, nonspecific risk factors for pneumonia or similar illness, or factors erroneously thought to be risk factors for Legionnaires' disease (misdirections) that had stimulated physicians to request LD indirect FA testing of their patients' serum specimens. Differences between Groups III and IV might represent specific risk factors for whatever diseases were responsible for illness in patients in Group III, nonspecific risk factors for pneumonia or similar illness, or misdirections. Differences between Groups I and III might represent specific

► From the Bacterial Diseases Division, Bureau of Epidemiology, and the Leprosy and Rickettsia Branch, Virology Division, Bureau of Laboratories, Center for Disease Control, Public Health Service, U.S. Department of Health, Education, and Welfare; Atlanta, Georgia.

risk factors for Legionnaires' disease, specific risk factors for whatever diseases were responsible for illness in patients in Group III, or differences in the populations of patients seen by physicians who were either relatively astute or relatively poor at deciding from whom to submit specimens for serodiagnosis. Parallel differences in the comparisons of Groups I and II and of Groups III and IV might represent nonspecific risk factors or misdirections. Differences in the comparison of Groups I and II that were not found in comparing Groups III and IV might be most likely to represent specific risk factors for Legionnaires' disease.

Differences were tested for statistical significance using McNemar's test for correlated proportions (1), except where otherwise specified. A linear logistic model (2; HALVORSEN KT: "Estimation of Simple and Multiple Relative Risk Functions in Matched Case-Control Studies," Master of Science Thesis, University of Washington, Seattle, 1978) was used to assess interactions among variables.

Results

CHARACTERISTICS OF RESPONDENTS

One hundred LD patients were considered for inclusion in the study. Seven were found to have possibly nosocomial acquisition of disease, and substitutes were chosen to maintain a final target population of 100 community-acquired cases. Of these 100, one was subsequently linked to a large cluster of cases and four patients could not be interviewed for various reasons, leaving 95 patients with sporadic community-acquired Legionnaires' disease about whom data were collected for the study. Thus, seven patients (6.9%) of 102 sporadic cases of Legionnaires' disease had possibly nosocomial infection.

The 95 patients included nine (9.5%) who had died of Legionnaires' disease. At the time of their illnesses these 95 had ranged in age from 24 to 83 years (median, 55 years). Sixty-nine were men and 26 were women, a sex ratio of 2.7. There were 75 whites, 17 blacks, one American Indian, one Asiatic, and one Hispanic. The ratio of whites to blacks was 4.4:1, substantially lower than the 7.5:1 ratio in the general population of the United States (3). Legionnaires' disease patients had various occupations: Seven had been in construction work, four in jobs involving soil exposure, three in health-related jobs, two in building maintenance, and one in air-conditioning maintenance. None had been hotel workers. Eighteen patients had been retired. Twelve had been housewives. Thirty-nine percent had not completed high school, whereas 17% had graduated from college. Sixty-eight percent had been cigarette smokers at the time of illness. Sixty-seven percent had occasionally or frequently consumed alcohol, including 22% who had averaged more than three drinks or beers per day. Only three had been taking immunosuppressive medications.

Serum specimens were received from 35 respondents in Group II. One person had an indirect FA titer of 1024 or greater to the Philadelphia 2 strain of the LD bacterium and titers of 64, 128, and 64 to the Wadsworth, Togus, and Bloomington creek strains, respectively. Indirect FA titers to these four antigens in the other 34 serum specimens were low—Philadelphia 2, 25 at less than 64 and nine at 64; Wadsworth, 32 at less than 64 and two at 64; and Bloomington creek, 34 at less than 64.

Hospital discharge summaries or other medical records were available for 59 of the subjects in Group III. Forty-five (76%) had had pneumonia as part of the illness for which serologic testing was requested. An etiologic diagnosis had been microbiologically confirmed for only one—a case of blastomycosis. Two cases of pneumonia had been tentatively ascribed to *Acinetobacter* and one to *Haemophilus parainfluenzae* infection on the basis of sputum cultures. *Mycoplasma* had been an etiologic agent suspected in three cases but had not been confirmed by serologic testing or isolation. Diagnoses other than pneumonia had included pericarditis (three cases), bronchitis (two), sepsis (two), influenzal syndrome, lung abscess, pleurisy with effusion, respiratory failure, metastatic adenocarcinoma of the lung, viral meningoencephalitis, and upper respiratory infection (one each).

MATCHED-PAIR ANALYSES

The comparison of patients (Group I) with their acquaintances (Group II) was based on completed interviews with 87 matched pairs (I-II comparison). The comparison between clinical control subjects in Group III and their acquaintances was based on interviews with 72 matched pairs (III-IV comparison). The comparison of patients with clinical control subjects was based on interviews with 88 matched pairs (I-III comparison).

There was an unexpected and striking racial difference in the matched pairs for the I-III comparison, with 16 blacks in Group I and one in Group III ($P < 0.001$). The educational level of persons in Group I was lower than that of persons in Group III, but not significantly so ($P = 0.09$, Wilcoxon signed rank test [4]).

HOST SUSCEPTIBILITY FACTORS

The major differences between patients and control subjects involved cigarette smoking and alcohol consumption. There was a highly significant excess of cigarette smoking among patients, both in the I-II comparison ($P < 0.0001$, Wilcoxon signed rank test) and in the I-III comparison ($P = 0.008$, Wilcoxon signed rank test). The smoking difference between clinical control subjects and their acquaintances (III-IV comparison) was much smaller and not statistically significant. Alcohol consumption was also significantly greater for patients in both the I-II and the I-III comparisons ($P = 0.03$ and $P = 0.04$, respectively, Wilcoxon signed rank test). The relative risk associated with alcohol consumption rose with increasing intake; there was no excess relative risk with alcohol consumption overall in comparison to abstinence, but the relative risk for persons consuming more than three drinks per day in comparison with respondents with lesser alcohol intakes was 4.0 ($P < 0.05$) in the I-II comparison and 2.4 ($0.05 < P < 0.10$) in the I-III comparison. There was no difference in alcohol consumption between Groups III and IV.

We sought evidence of underlying chronic disease by inquiring about a history of renal disease (other than urinary tract infection), diabetes mellitus, and chronic bronchitis and about treatment with glucocorticoids, other immunosuppressive drugs, cardiac medications, diuret-

ics, antihypertensives, and bronchodilators or other pulmonary medications. There was a significant excess of patients with evidence of chronic disease relative to the Group II controls (relative risk = 2.4, $P < 0.05$); the clinical control subjects (Group III) also had more apparent chronic disease than their acquaintances (Group IV), but the excess was not statistically significant (relative risk = 1.7, $P > 0.2$). The excess of apparent chronic disease in Group I subjects over that found in Group III was not significant (relative risk = 1.4, $P > 0.2$).

Patients were significantly more likely to have taken diuretics than were Group II control subjects (relative risk = 4.7, $P < 0.05$), whereas there had been no difference in diuretic use between respondents in Groups III and IV (relative risk = 1.0). These differences were only partly explained by differences in the number of people reporting hypertension. The excess of diuretic use in patients in the I-III comparison was not statistically significant (relative risk = 2.1, $0.10 < P < 0.20$).

ENVIRONMENTAL EXPOSURE FACTORS

Legionnaires' disease patients were significantly more likely to have lived near excavation sites than were respondents in either control group (II, III) (relative risk = 3.0, $P < 0.05$, for I-II comparison; relative risk = 2.3, $P < 0.05$, for I-III comparison). Significantly more patients than Group III control subjects had lived near construction sites (relative risk = 2.7, $P < 0.05$). In the I-II comparison, patients had had more construction sites near their homes, but the difference was not significant (relative risk = 1.7, $P > 0.2$). There were no differences in excavation or construction exposure near home in the III-IV comparison. The only significant occupational difference noted in the study was the finding of seven construction workers among the Legionnaires' disease patients and none in Group III ($P < 0.05$). There were essentially no differences in exposure to soil or wind-blown dust in any comparison.

There were no differences in any comparison with regard to exposure to air-conditioning, heating, humidifying, or dehumidifying systems or exhaust fans, nor were there any differences in the number of persons who had done maintenance or repair work on such climate-control systems or on other home appliances. More patients (six) than respondents in Groups II (two) or III (one) had been exposed to malfunctioning air-conditioning systems, but these differences were not statistically significant.

As previously noted, 6.9% of patients with sporadic cases of Legionnaires' disease about whom information was available were excluded from this study because of hospitalization during all or part of the 2 weeks before onset of illness. The proportion of potential respondents in Group III similarly excluded was three of 92 (3.3%) (chi-square = 0.65, $P > 0.2$, for I-III comparison). Twenty-one (22%) of the 95 patients in the study had had some sort of exposure to a hospital, but not as inpatients, in the 2 weeks before onset of disease. No significant differences in such hospital exposure were seen in the I-II, III-IV, and I-III comparisons. In general, patients had had less exposure than respondents in Group II to 12 kinds of public buildings that were neither hospitals nor buildings associated with travel. A similar pattern was seen in the III-IV comparison. No consistent pattern regarding exposure to public buildings emerged from the I-III comparison.

Legionnaires' disease patients had traveled away from home for more time during the 2 weeks before onset of their illnesses than had their acquaintances ($P = 0.02$, Wilcoxon signed rank test). No similar significant differences in time spent on trips away from home were seen in the I-III or III-IV comparisons.

There were no differences in any of the comparisons in exposure to insects, birds or bird roosts, other animals, or fish aquariums.

INTERACTIONS AMONG RISK FACTORS

We attempted to calculate the relative risk for Legionnaires' disease associated with certain variables in the presence of other potentially interacting ones by using a linear logistic model. The variables were potential risk factors chosen from the univariate analysis: cigarette smoking, heavy drinking (more than three drinks or beers per day), educational level, use of diuretics, presence of an underlying illness, excavation near home, construction near home, overnight travel during the 2 weeks before onset, race, and occupation as a construction worker. Smoking, heavy drinking, travel, and presence of an underlying disease were associated with the relative risks in the I-II comparison most significantly different from unity, whereas there were no risk factors with relative risks significantly greater than unity in the III-IV comparison. In the I-III comparison the variables of greatest significance were smoking, heavy drinking, race, and construction near home. The sequential elimination of the remaining variables from the I-II and I-III comparisons did not have a significant effect on the ability of the model to distinguish patients from control subjects. The significant or borderline significant variables were then used in the final linear logistic model (Table 1).

Discussion

Interpretations of the results of this study on possible risk factors in Legionnaires' disease should be made with caution. A large number of tests for possible associations were explicitly or implicitly done. The impact of an association shown to exist at a given level of statistical significance is diminished in proportion to the number of comparisons carried out to find that association.

Sporadic confirmed cases of Legionnaires' disease reported to the CDC have included an excess of cases in middle-aged men, both in relation to the general population and to the age and sex composition of persons from whom serum specimens are submitted to the CDC for serologic testing (STORCH G, SHEPARD CC: Unpublished data, 1978). This study clearly adds cigarette smoking to advanced age and male sex as a risk factor for Legionnaires' disease and strongly suggests that heavy alcohol consumption is an additional independent risk factor. Cigarette smoking, but not alcohol consumption, was

Table 1. Relative Risks (95% Confidence Limits) for Factors Associated with Legionnaires' Disease in the Linear Logistic Model

Risk Factor	Comparison		
	I-II	III-IV	I-III
Smoking			
Less than one-half pack per day versus none	1.6 (1.2-2.3)	1.1 (0.8-1.7)	1.6 (1.1-2.3)
One-half to one pack per day versus none	2.6 (1.3-5.1)	1.3 (0.6-2.9)	2.5 (1.3-5.2)
More than one pack per day versus none	4.2 (1.6-11.4)	1.5 (0.4-4.9)	4.1 (1.4-11.8)
Heavy drinking*	3.5 (1.0-13.0)	1.1 (0.2-7.1)	4.8 (1.3-18.0)
Underlying disease	2.0 (0.9-4.7)	2.0 (0.9-4.5)	NA†
Travel‡	2.5 (0.9-6.8)	2.0 (0.7-5.9)	NA
Construction near home	NA	NA	4.4 (1.2-15.7)
Black or other race versus whites	NA	NA	14.0 (1.8-112.0)

* Three drinks or beers per day versus less or no consumption.
† NA = no association, not included in model for this comparison.
‡ Mean number of days (7) spent in travel by Legionnaires' disease patients who were away from home for at least one night versus no travel.

shown to be a risk factor in the epidemic among members of the American Legion in Philadelphia in 1976 (5). Although alcohol consumption has not previously been shown to be a risk factor for Legionnaires' disease, gram-negative bacterial pneumonia, particularly that caused by *Klebsiella pneumoniae,* has been thought to show a predilection for middle-aged and elderly men, especially those who abuse alcohol (6, 7).

Epidemics and sporadic cases have occurred in several instances after the affected persons have traveled. The results of this study support an association between travel and the acquisition of Legionnaires' disease. This association could be due to the stress of travel, to exposure to point sources of the etiologic agent in buildings or other sites frequented by travelers, or to transit of nonimmune residents of areas with low risk of exposure to endemic foci.

Although a high proportion of the Legionnaires and others afflicted in the 1976 Philadelphia epidemic had underlying illnesses (62% of 94 hospitalized patients) (5), in our study the presence of an underlying illness appeared to be a relatively small and nonspecific predisposing factor. Since only three of our 95 patients had been taking immunosuppressive medications and there were few others with diseases that severely affect the immune system, it appears that most community-acquired sporadic cases occur in persons without major defects in system-immunity. Experience from several epidemics (8-10), however, indicates that immunosuppression does predispose to Legionnaires' disease and may be particularly important in nosocomial acquisition of the disease.

The very high relative risk (14.0 in the linear logistic model) for blacks and others in comparison to whites had not previously been suggested by analysis of Legionnaires' disease epidemics. This racial difference is also not apparent in more recent surveillance data on sporadic cases (11), which show that Legionnaires' disease patients approximate the racial distribution of the general population of the United States. Several possible biases may have affected the comparison between patients (Group I) and clinical control subjects (Group III), the only control group not implicitly racially matched and thus the only group used to evaluate the racial factor. If the diagnosis of Legionnaires' disease had been considered more indiscriminately in whites than in blacks or if physicians who were relatively adept at identifying likely cases on clinical grounds were disproportionately involved in the care of black patients, then the proportion of negative specimens submitted would be higher for whites than for blacks. When persons having negative specimens were then selected as clinical controls, whites could be over-represented in the control group, resulting in an apparent excess of Legionnaires' disease cases in blacks. Alternatively, if the diseases in which the diagnosis of Legionnaires' disease is mistakenly considered actually occur more frequently in whites than in blacks, clinical control subjects as chosen in this study could include a disproportionately large number of whites, again resulting in an apparent excess of blacks as cases. Thus, the observed excess relative risk for blacks may be an artifact of this study. The possibility of differing race-specific attack rates should receive further study in future epidemics of Legionnaires' disease and in continuing analysis of sporadic cases.

The presence of a construction site near home emerged in the linear logistic model as significantly associated with Legionnaires' disease, but only in the I-III comparison. The small but statistically significant excess of construction workers in the patient group further supports the hypothesis that exposure to construction sites may be meaningful in transmission of Legionnaires' disease. The association in the univariate analysis of Legionnaires' disease with excavation sites near dwellings may point to a source in soil, as suggested by findings from one epidemic (12).

In addition to the exposure risk factors suggested by our study, many other sources of exposure conceivably exist. In particular, air-conditioning systems have been involved in several epidemics (13-16). Although the study questionnaire dealt extensively with exposure to air-conditioning systems, such exposure was difficult to characterize, and the results of our study should not be taken as evidence that air-conditioning systems play no role in sporadic cases. In epidemics, however, cooling towers or evaporative condensers rather than household units have been contaminated with the LD bacterium. Perhaps when these components of large air-conditioning systems are contaminated, enough people are exposed to cause epidemics rather than sporadic cases.

ACKNOWLEDGMENTS: The authors thank Ms. K. T. Halvorsen for extensive consultation on the application of the linear logistic model; the officers and members of the Association of State and Territorial Epidemiologists for their assistance and cooperation in the design and execution of the study; the many physicians who aided us in contacting their patients and obtaining needed information; Ms. Dianne L. Hill and Ms. Peggy S. Hayes for performing indirect FA serologic testing of serum specimens from respondents in Group II; Ms. Deena A. Koniver for facilitating certain administrative tasks; Ms. Billie Miller and Ms. Burnese Harper for organizing and maintaining the data files for the study; and the respondents in Groups I, II, III, and IV for their helpfulness and patience.

▶ Requests for reprints should be addressed to William B. Baine, M.D., Bureau of Epidemiology, Center for Disease Control; Atlanta, GA 30333.

Received 15 November 1978; revision accepted 22 January 1979.

References

1. McNemar A: Note on the sampling error of the difference between correlated proportions or percentages. *Psychometrika* 12:153-157, 1947
2. Breslow NE, Day NE, Halvorsen KT, Prentice RL, Sobai C: Estimation of multiple relative risk functions in matched case-control studies. *Am J Epidemiol* 108:299-307, 1978
3. U.S. Bureau of the Census: Estimates of the population of the United States, by age, sex, and race: 1970-1977. *Current Population Reports*, Series P-25, No. 721. Washington, D.C., U.S. Government Printing Office, 1978
4. Wilcoxon F: Individual comparisons by ranking methods. *Biom Bull* 1:80-83, 1945
5. Fraser DW, Tsai TR [sic], Orenstein W, Parkin WE, Beecham HJ, Sharrar RG, Harris J, Mallison GF, Martin SM, McDade JE, Shepard CC, Brachman PS, Field Investigation Team: Legionnaires' disease. Description of an epidemic of pneumonia. *N Engl J Med* 297:1189-1197, 1977
6. Pierce AK, Sanford JP: Aerobic gram-negative bacillary pneumonias. *Am Rev Respir Dis* 110:647-658, 1974
7. Tillotson JR, Lerner AM: Pneumonias caused by Gram negative bacilli. *Medicine (Baltimore)* 45:65-76, 1966
8. Marks JS, Tsai TF, Martone WJ, Baron RC, Kennicott J, Holtzhauer FJ, Baird I, Fay D, Feeley JC, Mallison GF, Fraser DW, Halpin TJ: Nosocomial Legionnaires' disease in Columbus, Ohio. *Ann Intern Med* 90:565-569, 1979
9. Beaty HN, Miller AA, Broome CV, Goings S, Phillips CA: Legionnaires' disease in Vermont, May to October 1977. *JAMA* 240:127-131, 1978
10. Kirby BD, Snyder KM, Meyer RD, Finegold SM: Legionnaires' disease: clinical features of 24 cases. *Ann Intern Med* 89:297-309, 197
11. Center for Disease Control: Legionnaires' disease—United States. *Morbid Mortal Weekly Rep* 27:439-441, 1978
12. Thacker SB, Bennett JV, Tsai TF, Fraser DW, McDade JE, Shepard CC, Williams KH Jr, Stuart WH, Dull HB, Eickhoff TC: An outbreak in 1965 of severe respiratory illness caused by the Legionnaires' disease bacterium. *J Infect Dis* 138:512-519, 1978
13. Glick TH, Gregg MB, Berman B, Mallison G, Rhodes WW Jr, Kassanoff I: Pontiac fever. An epidemic of unknown etiology in a health department. I. Clinical and epidemiologic aspects. *Am J Epidemiol* 107:149-160, 1978
14. Politi BD, Fraser DW, Mallison GF, Mohatt JV, Morris GK, Patton CM, Feeley JC, Tetu RD, Bennett JV: A major focus of Legionnaires' disease in Bloomington, Indiana. *Ann Intern Med* 90:587-591, 1979
15. Center for Disease Control: Isolation of organisms resembling Legionnaires' disease bacterium—Tennessee. *Morbid Mortal Weekly Rep* 27:368-369, 1978
16. Center for Disease Control: Isolation of organisms resembling Legionnaires' disease bacterium—Georgia. *Morbid Mortal Weekly Rep* 27:415-416, 1978