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Sporadic Cases of Legionnaires' Disease in the Netherlands

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Sera of 24 patients with an unexplained pneumonia were tested for the presence of antibodies against the Legionnaires' disease bacterium. Fifteen patients had positive serology. The series comprised 12 male and three female patients ranging in age from 17 to 66 years (mean, 51.1 years). All of the patients had a high fever, little or no sputum production, and radiographic evidence of pneumonia. The radiographic abnormalities ranged from a patchy infiltrate to extensive consolidation. In eight patients with confirmed Legionnaires' disease, severe confusion was one of the most striking signs. A variety of antibiotics had no clear effect on the duration of the illness in these cases, although the severity seemed to be influenced. Two of the patients died, and in three the course was protracted. All cases were sporadic. Eight patients had been infected abroad and seven in the Netherlands, two of whom were on immunosuppressive therapy and were infected in a hospital.

AFTER REPORTS of Legionnaires' disease appeared (1, 2), we suspected this infection in a patient with an unexplained pneumonia and signs and symptoms compatible with the diagnosis of Legionnaires' disease. The sera of this patient were sent for analysis to the Center for Disease Control (CDC), Atlanta, Georgia. After the serologic confirmation of Legionnaires' disease in the first Dutch patient (3), we made a survey of the occurrence and clinical picture of the disease in the past and present in the Netherlands. The prevalence of antibodies against the Legionnaires' disease (LD) bacterium was assessed in a control group.

Materials and Methods

SELECTION OF PATIENTS

We began with a search, going back to 1974, of the records of the Leiden University Hospital for cases of pneumonia that had remained unexplained in spite of extensive microbiologic testing. Starting in January 1978, efforts were made to obtain conclusive evidence in patients with clinical features compatible with Legionnaires' disease (1) who were admitted to the Leiden University Hospital. In this report we have included patients admitted to other hospitals in the Netherlands in whom Legionnaires' disease was diagnosed. Clinical records and radiographs were obtained, and permission to present their data was given by all attending physicians.

CONTROL GROUP

Fifty sera were randomly selected from 462 deep-frozen sera of men aged 45 to 55 years who had participated between 1975 and 1978 in an open population study (completion rate, 78.3%) (Epidemiological Preventive Organisation Zoetermeer Study [EPOZ], Prof. H. A. Valkenburg). This selection was based on the composition of the patient series under discussion; most of these patients were men in the 45-to-55 age group.

The EPOZ study comprised the entire population of two ar-

eas (rural and urban) of the municipality of Zoetermeer, aged 5 years and older (13 500 persons).

SEROLOGY

The indirect fluorescent antibody test with LD bacterium, Philadelphia 1, as antigen was used (2). Most of the sera were tested in both the CDC and the National Institute of Health of the Netherlands (Bilthoven) until August 1978; since then all tests have been done at the latter institute. The control sera were examined by Dr. R. J. Fallon (Glasgow), using polyvalent antigen from serotypes 1, 2, 3, and 4 of LD bacteria (4), at dilutions of 128, 256, and 512.

MICROSCOPY

In one case lung tissue obtained at autopsy was studied by light microscopy (modified Dieterle silver-impregnation staining and with Gram and Loefflers methylene blue staining) of impression slides, direct immunofluorescence (5), and electron microscopy (Dr. D. J. Ruiter, Dr. C. J. L. M. Meyer, and Dr. H. A. van den Bergen; Department of Pathology, University Hospital; Leiden).

Results

DIAGNOSIS OF LEGIONNAIRES' DISEASE

A fourfold rise in titer to 1:128 or higher was considered to be confirmation for the diagnosis. A single titer of 1:128 or higher was considered positive, because in the control group no titers of 1:128 or higher were found. The titers of the sera tested at the CDC and in Bilthoven were the same or differed by no more than one twofold dilution. Results obtained with sera tested against the ether-treated antigen (Philadelphia 1) and the new polyvalent antigen are comparable (FALLON RJ: Personal communication). Dr. Fallon's serologic results are compatible with those of the CDC (6).

CLINICAL DATA

Sera of 24 patients with an unexplained pneumonia were tested for the presence of antibodies against the LD bacterium; results were positive in 15 of these patients. The data of all cases with a serum titer of 1:128 or higher or a fourfold rise in titer are given in Table 1, arranged according to the time of onset. Seven cases were diagnosed retrospectively, and in eight Legionnaires' disease was suspected during the illness. There is a marked preponderance of male patients in this group; the age range is 17 to 66 years (mean, 51.1 years). Seven of our patients were smokers. Pre-existing diseases are indicated in Table 1. Two patients, both on immunosuppressive therapy, presumably acquired the disease in hospital. For the other patients, the mean duration of the disease before admission was 6.6 ± 4.2 days (range, 1 to 14 days).

Six patients had been treated with antibiotics before admission (three with amoxycillin, two with ampicillin, and one with phenethicillin). Early in the disease all of

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Table 1. Clinical Details of 15 Sporadic Cases of Legionnaires' Disease

Patient	Sex	Age	Time of Onset	Lowest and Highest (or Single) Reciprocal Titer				Main Antibiotic Therapy	Outcome	Remarks
				Titer	Time	Titer	Time			
		<i>yrs</i>								
1	M	50	June 1973	512	1978			tetracycline	Cure	Reference 3
2	M	44	February 1974	256	Day 14	256	Day 26	tetracycline	Cure	
3	M	56	March 1976	128	Day 7	256	Day 45	tetracycline	Cure	
4	M	48	October 1976	64	Day 7	≥1024	Day 30	rifamycin tetracycline	Cure	Reference 3
5	M	51	August 1977	≥1024	Day 12			ampicillin	Cure	
6	M	52	August 1977	≥1024	1978			cephradine	Cure	
7	M	55	August 1977	≥1024	1978			cephalothin	Cure	
8	F	63	November 1977	128	Day 8	512	Day 18	chloramphenicol gentamicin erythromycin tetracycline	Cure	Reference 7
9	M	47	April 1978	<32	Day 7	≥256	4 months	erythromycin tetracycline	Cure	Kidney graft, azathioprine and glucocorticosteroids
10	M	51	May 1978	≤64	Day 14	128	Day 28	rifamycin tetracycline cloxacillin	Cure	Alcohol abuse
11	M	51	May 1978	<32	Day 6	128	Day 32	tetracycline	Cure	
12	M	66	July 1978	128/256	Day 14			ampicillin cloxacillin	Died	Chronic bronchitis, atrial fibrillation, left ventricular hypertrophy
13	F	17	July 1978	<32	Day 13	128	Day 41	ampicillin gentamicin	Cure	
14	M	49	August 1978	<32	Day 8	512	Day 21	erythromycin gentamicin	Died	
15	F	66	August 1978	≥2048	Day 18			erythromycin	Cure	Polymyalgia rheumatica, glucocorticosteroids

the patients had one or more of the following symptoms: malaise, anorexia, headache, myalgia, and the gastrointestinal symptoms listed in Table 2. The history showed that most had developed a dry cough on the second or third day of the illness. Patients 10 and 14 had hemoptysis. All patients had a fever of 38.5 °C or higher, and all had signs of pneumonia found on physical examination that were confirmed by chest radiographs. Serial chest radiographs showed progressive infiltration from patchy localized involvement to multilobar involvement and consolidation. Infiltrate occurred bilaterally in nine of the 15 patients. Extensive pleural effusion was present in one patient (Patient 10). In the two patients on immunosuppressive therapy (Patients 9 and 15) cavitations were seen on the radiographs of the chest. Further details on the clinical features are shown in Table 2. One of the most striking signs seen on admission in most of the patients was severe confusion. In four patients (Patients 4, 11, 13, and 14) a lumbar puncture was done. No abnormalities were found in the cerebrospinal fluid of Patients 4 and 11. There was a mild pleiocytosis (mainly monocytes and lymphocytes) in the cerebrospinal fluid of Patients 13 and 14, who had severe leucopenia, thrombocytopenia, and signs of diffuse intravascular coagulation early in the disease. In Patient 13 the disease was complicated by rhabdomyolysis.

All patients were treated with antibiotics. The antibiotics used are listed in Table 1. Only two patients died, one

(Patient 12) in the third week after the onset of the disease, of irreversible brain damage after an unsuccessful resuscitation attempt to reverse cardiac arrest. At autopsy, gross examination of the lungs showed lobar pneumonia with consolidation and grey hepatization in the right lower lobe. Bacteria structurally identical to the LD bacterium were found electronmicroscopically and by light microscopy with modified Dieterle silver-impregnation staining and Loeffler's methylene blue; no bacteria were seen in the Gram-stained material. Direct fluorescent antibody staining of formalin-fixed lung tissue gave positive results (5). Attempts to culture the LD bacterium from the lung tissue failed. Patient 14 died from the sequelae of long-standing artificial ventilation (septicemia and pneumothorax). In three patients the course was protracted: Patient 7 suffered from cardiac failure and required mechanical ventilation; Patient 10 had a secondary staphylococcal pleural empyema; Patient 13 was ventilated with positive end-expiratory pressure because the adult respiratory distress syndrome was suspected. In the other 10 patients, the mean duration from the onset of the illness until definite clinical improvement and a temperature below 38 °C was 11 days ± 3.8. In 10 patients the radiographic resolution of the lung infiltrate took longer than 6 weeks.

EPIDEMIOLOGY

All of the patients who had contracted the disease in

the Netherlands live in or near Amsterdam and Leiden (see Figure 1); both of these cities are situated in the crowded industrial western part of the country. Two patients (Patients 9 and 15) acquired the disease during a stay in different hospitals in Amsterdam.

Eight patients presumably had acquired the disease abroad (see Figure 1): five of them developed Legionnaires' disease during or after a stay in France; the others probably acquired it in Spain (one), Italy (one), and during a Mediterranean cruise (one). Two patients (Patients 6 and 7) had been traveling together in France and became sick on about the same day. Patients 1 and 4, one of whom acquired Legionnaires' disease in Italy and one of whom acquired it 3 years later in France, are brothers.

Three persons, who presumably were exposed to LD bacteria and did not develop pneumonia, were tested for antibodies against the LD bacterium. The wife of Patient 14, who traveled with him, did not become sick; her antibody titer against the LD bacterium was 1:128. The 2-year-old grandson of Patient 8 (see Reference 7), who was with her in Spain, suffered from diarrhea shortly before his grandmother fell ill. The titer measured in his serum 9 months later was less than 1:32.

About 14 days after doing the autopsy on Patient 12, the pathologist developed malaise, a dry cough, and a subfebrile temperature. Six weeks later, an antibody titer of 1:256 was found in his serum.

Discussion

In this paper the clinical features and relevant epidemiologic data of a series of sporadic cases of Legionnaires' disease in the Netherlands are given. We are not aware of other cases of Legionnaires' disease diagnosed in the Netherlands. This series includes patients without a fourfold rise of titer. In three of them (Patients 2, 3, and 10) the serum specimen was taken after the second week of

Table 2. Clinical Features and Laboratory Findings in 15 Patients with Legionnaires' Disease

	Patients
	no.
Clinical features	
Shaking chills	9
Mental confusion	9
Gastrointestinal symptoms	11
Diarrhea	5
Nausea and vomiting	4
Abdominal pain	2
Pulmonary infiltrates	
Bilateral	8
Right side only	4
Left side only	3
Pleural effusion	1
Laboratory findings	
Erythrocyte sedimentation rate >70 mm	12
Granulocytosis	10
Granulocytopenia	2
Transient renal insufficiency	4
Serum sodium level below 130 mmol/L	7
Glutamic-oxalacetic transaminase elevation	13
Alkaline phosphatase elevation	9
Diffuse intravascular coagulation	2

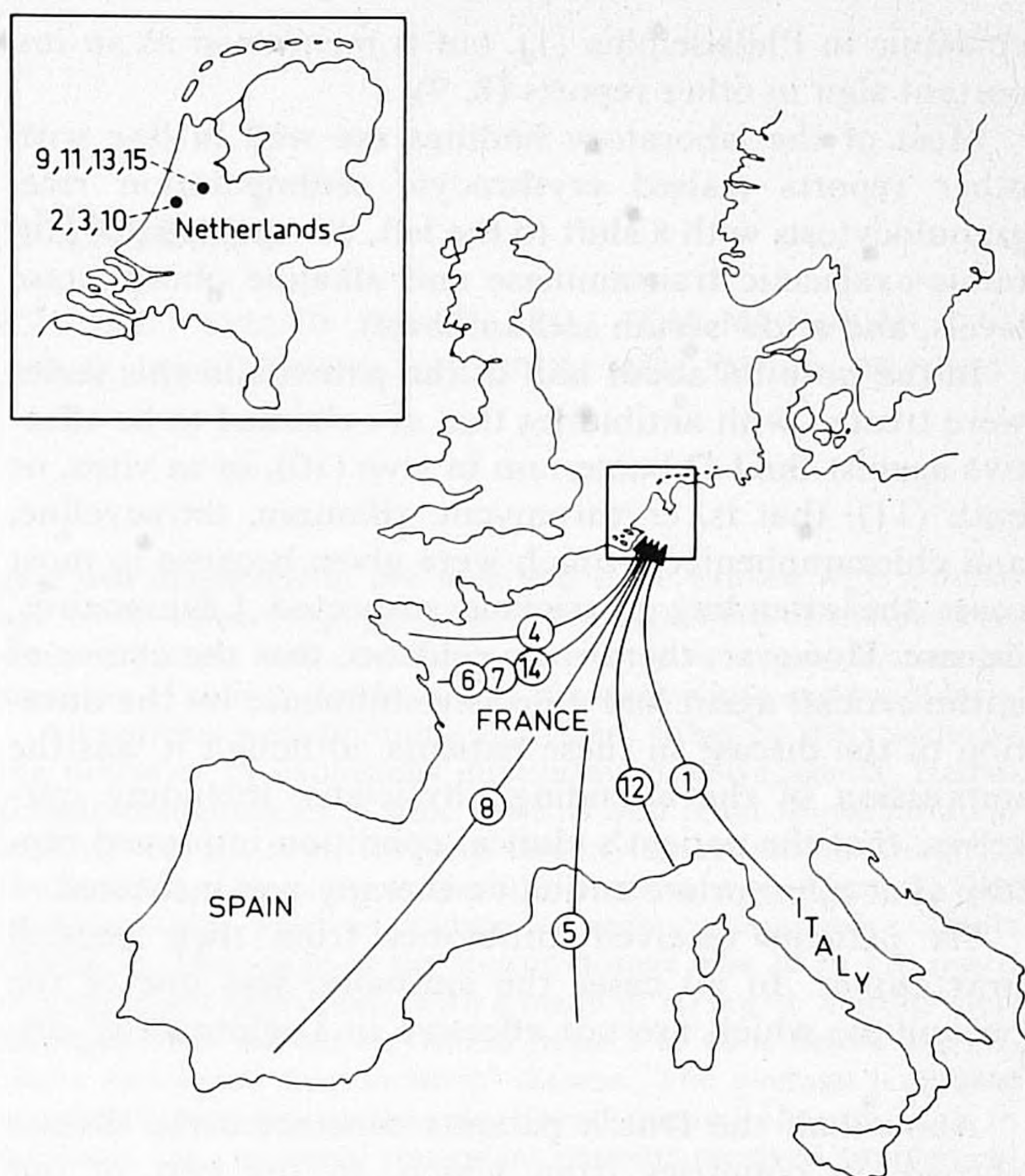


Figure 1. Map showing the countries in which the patients in this series presumably contracted Legionnaires' disease. The numbers indicating the patients correspond with the numbers in Table 1. The insert shows the place of residence of the other patients, who had not been outside the Netherlands shortly before they became ill.

illness. Only one serum specimen was still available for Patient 5; in three cases (Patients 1, 6, and 7) no serum collected during the course of the disease was left, but these patients had a single high titer afterward. In the Dutch population the prevalence of antibodies against the LD bacterium is still unknown. However, in a small randomly selected control group of male subjects with ages in approximately the same range as those of our patients, no titers of 1:128 or higher were found. In the cases where only one serum sample could be tested or no fourfold rise of the titer was found, the diagnosis Legionnaires' disease cannot be definitely established. Nevertheless, in view of the control group results, a (single) titer of 1:128 or higher combined with a clinical picture in accordance with that of proven cases of Legionnaires' disease is a strong argument for a positive diagnosis.

At least six patients with unexplained pneumonia and negative serology for the LD bacterium (Philadelphia 1) had exactly the same clinical picture as patients with proven Legionnaires' disease. It may be that these patients had Legionnaires' disease but had been infected with another serotype of the LD bacterium, and therefore the diagnosis could not be confirmed by the serologic tests used at that time.

The clinical features of the Dutch patients are similar to those in the cases of Legionnaires' disease reported from the epidemics, as well as those of sporadic cases. However, in the present series severe confusion and amnesia were among the most striking signs. This combination was not included in the initial description of the

epidemic in Philadelphia (1), but is mentioned as an important sign in other reports (8, 9).

Most of the laboratory findings are well in line with other reports (raised erythrocyte sedimentation rate, granulocytosis with a shift to the left, elevated serum glutamic-oxalacetic transaminase and alkaline phosphatase levels, and a low serum sodium level).

In the hospital about half of the patients in this series were treated with antibiotics that are claimed to be effective against the LD bacterium in vivo (10), or in vitro, or both (11); that is, erythromycin, rifampin, tetracycline, and chloramphenicol, which were given because in most cases the attending physicians suspected Legionnaires' disease. However, there is no evidence that the choice of antimicrobial agent had a decisive influence on the duration of the disease in these patients, although it was the impression of the attending physicians, including ourselves, that the patient's clinical condition improved rapidly after appropriate antibiotic therapy was instituted.

Six patients received antibiotics from their general practitioner. In all cases the antibiotic was one of the penicillins, which are not effective in Legionnaires' disease.

About half the Dutch patients contracted the disease abroad, in countries from which, to the best of our knowledge, no Legionnaires' disease among inhabitants has been reported. Reports of the disease have not yet appeared from our neighboring countries, but recently two cases were diagnosed in Belgium (BUTZLER JP: Personal communication).

ACKNOWLEDGMENTS: The authors thank Charles S. Shepard, M.D.; Hazel Wilkinson, Ph.D.; John Feeley, M.D. (Center for Disease Control, Atlanta); and R. J. Fallon, M.D. (Ruchill Hospital, Glasgow, Scotland) for their cooperation; and Prof. H. A. Valkenburg (Erasmus University, Rotterdam) for providing the sera of the control group. They also thank the attending physicians Dr. W. J. van Amstel, Leiderdorp (Patient 5); Dr. F. van Kersen, Hilversum (Patient 6); Dr. R. G. Vanderschueren, Utrecht (Patient

7); Dr. R. M. van der Heide, Amsterdam (Patient 8); Dr. J. H. ten Veen, Amsterdam (Patient 9); Prof. J. H. Dijkman, Leiden (Patient 10); Dr. S. P. ten Holt, Amsterdam (Patient 11); Prof. C. van der Meer, Amsterdam (Patient 13); Prof. C. Hilvering, Rotterdam (Patient 14); and Dr. H. Roebbers, Amsterdam (Patient 15) for their cooperation and their permission to use data from their patients.

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Received 15 November 1978; revision accepted 8 January 1979.

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