Causes of atypical pneumonia: results of a 1-year prospective study

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In a protocol study of cases of atypical pneumonia over a 1-year period an etiologic agent was established in 16 cases: *Legionella pneumophila* in 8, *Coxiella burnetii* in 3, *Chlamydia trachomatis* in 2, *Mycoplasma pneumoniae* in 1, parainfluenza 3 virus in 1 and cytomegalovirus in 1. In the remaining 11 cases no agent was identified; the illnesses in these cases tended to be less severe. The pneumonia took much longer to resolve in the patients with Legionnaires' disease than in all the other patients (mean interval from onset of symptoms to clearing of the chest roentgenogram: 69 days v. an average of 16 days). However, the length of stay in hospital was similar for the three groups: those with Legionnaires' disease, those with atypical pneumonia of unknown cause and those with atypical pneumonia of various other established causes. *L. pneumophila* infection may explain a proportion of atypical pneumonias that previously could not be diagnosed, although in this series the cause of 41% of the pneumonias remained unexplained.

Dans une étude des cas de pneumonies atypiques observés au cours d'une période d'un an l'agent étiologique a pu être établi dans 16 cas: il s'agissait de *Legionella pneumophila* dans 8, de *Coxiella burnetii* dans 3, de *Chlamydia trachomatis* dans 2, de *Mycoplasma pneumoniae* dans 1, du virus parainfluenza 3 dans 1 et du cytomegalovirus dans 1. Dans les 11 autres cas aucun agent n'a pu être identifié; dans ces derniers cas la maladie avait tendance à être moins grave. La pneumonie a pris beaucoup plus de temps à guérir chez les patients souffrant de la maladie du Légionnaire que chez tout autre patient (l'intervalle moyen entre l'apparition des symptômes et le nettoyage de l'image pulmonaire a été de 69 jours en comparaison de 16 jours). Toutefois, la durée d'hospitalisation fut la même pour les trois groupes de patients suivants: ceux qui souffraient de la maladie du Légionnaire, ceux qui avaient une pneumonie atypique d'origine inconnue et ceux qui étaient atteints de pneumonie atypique de diverses autres causes identifiées. L'infection à *L. pneumophila* peut expliquer un certain nombre de pneumonies atypiques qui ne pouvaient auparavant être diagnostiquées; toutefois, dans cette série la cause de 41% des pneumonies demeure inexpliquée.

The outbreak of pneumonia that followed the American Legion Convention in Philadelphia in late July 1976, called Legionnaires' disease,[1] focused the attention of investigators on undiagnosed pneumonias. Subsequent investigations revealed that *Legionella pneumophila*, the etiologic agent of Legionnaires' disease,[2] had caused 15 outbreaks of the pneumonic form (Legionnaires' disease) and 2 of the nonpneumonic form (Pontiac fever).[3] Sporadic cases of Legionnaires' disease have been recorded in Canada,[4] and during the summer of 1979 an outbreak of 20 cases occurred in Toronto.[5]

In July 1979 we instituted a protocol approach to all cases of "atypical pneumonia" in patients admitted to our hospital. Our objectives were to determine the causes of atypical pneumonia and to determine whether the clinical characteristics of Legionnaires' disease were different from those of other atypical pneumonias. In this paper we report the results of 1 year's experience with this protocol.

Materials and methods

Patient selection

Patients who had a pulmonary infiltrate but were producing only mucoid sputum or none at all, and in whom no predominant organism was identified in Gram-stained specimens, were admitted to the study. If the initial cultures of blood, pleural fluid or sputum revealed a conventional bacterial cause for their pneumonia they were excluded.

Specimens

Blood samples, sputum (if possible), throat washings and, when clinically indicated, specimens of pleural fluid or lung tissue were collected for culture. The blood samples (10 ml) were collected at the time of admission and once weekly for 6 weeks; the blood was allowed to clot, then the serum was separated and stored at −26°C until tested.

Cultures

Blood and sputum were cultured according to standard techniques. Throat washings were cultured for influenza A and B and parainfluenza 1, 2 and 3 viruses, adenovirus, *Chlamydia trachomatis* and *Mycoplasma pneumoniae*.[6]

Virus isolation

A 0.5-ml aliquot of throat washing fluid was in-

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oculated onto African green monkey kidney cells, primary human amnion cells and a human diploid cell line. After incubation for 1 hour 1 ml of maintenance medium appropriate to the cell line was added and the specimens were incubated at 37°C for a minimum of 14 days. At least one blind passage was carried out during this period.

For the detection of hemadsorption viruses, on day 7 of the incubation period the maintenance medium was removed from one tube of the African green monkey kidney cells and 1 ml of a 0.1% suspension of guinea pig erythrocytes in phosphate-buffered saline was added. After 30 minutes at 4°C the culture was read for the presence of erythrocytes adherent to the tissue culture cells by means of a light microscope with a 10× objective. The specimen was rechecked after 30 minutes at room temperature. At least two passages were performed before a negative report was issued. Viruses in positive specimens were identified with the use of specific antisera in hemadsorption inhibition tests.

Chlamydia isolation

A 2-ml aliquot of throat washing fluid was transferred to an equal volume of *Chlamydia* transport medium and frozen at −85°C. Within 6 days the specimen was thawed and diluted with *Chlamydia* growth medium to a final volume of 5 ml; duplicate 1.5-ml aliquots were then inoculated onto coverglass cultures of McCoy cells (in scintillation vials) that had been treated with cycloheximide. The inoculated cultures were centrifuged at 3000 × *g* for 1 hour at room temperature and then incubated at 37°C for a further 2 hours. The fluid was removed, the cell layer washed once with phosphate-buffered saline of pH 7.2 to 7.4 and fresh *Chlamydia* growth medium added. After 3 days' incubation at 37°C the cells were fixed in absolute methanol and stained with a dilute solution of Lugol's iodine. The coverglasses were removed from the scintillation vials, inverted on glass slides and examined under bright-field illumination with a Zeiss microscope. A positive finding consisted of a typical iodine-stained inclusion.

Serologic testing

Each serum specimen was tested for antibodies to the following antigens: *L. pneumophila* 1, 2, 3 and 4; adenovirus; *Chlamydia* group; influenza A and B; parainfluenza 1, 2 and 3; *M. pneumoniae*; *Coxiella burnetii* and respiratory syncytial virus.

An indirect immunofluorescence test was used to detect antibodies against *L. pneumophila*.[1] All the reagents for this test were kindly supplied by the Center (now Centers) for Disease Control, Atlanta. The *Legionella* antigens were ether-killed suspensions or organisms grown on artificial medium and suspended in normal yolk sac suspended in phosphate-buffered saline. All specimens were screened at dilutions of 1:64 and 1:128. If fluorescence was present at the 1:128 dilution, further dilutions of this sample were prepared. A single titre of 1:256 or a fourfold rise in titre was considered positive.[3] All positive results were confirmed by the Center for Disease Control, as were the negative results we obtained for eight patients.

Testing for antibodies to the remaining antigens was done by a standard complement-fixation technique in microtitre plates. The adenovirus and respiratory syncytial virus antigens were purchased from Flow Laboratories (Rockville, Maryland). All the other antigens were obtained from the Laboratory Centre for Disease Control, Ottawa.

Dr. Sang Ping Wang, department of pathobiology, University of Seattle, kindly confirmed our two cases of *C. trachomatis* pneumonia with the use of a microimmunofluorescence test.

Microagglutination test for Q fever

Some of the serum samples were also tested for antibodies to the phase I and phase II antigens of *C. burnetii*, the rickettsia that causes Q fever, by a microagglutination technique. The serum was inactivated by being kept at a temperature of 56°C for 30 minutes, then duplicate 0.025-ml aliquots of a 1:8 dilution were pipetted into microtitre plates, and serial twofold dilutions were prepared with a Tris buffer; 0.025 ml of phase I antigen was added to one row of dilutions and 0.025 ml of phase II antigen was added to the other row. Positive and negative controls were included with each run. After being mixed the serum and antigen preparation was incubated at room temperature (≃ 21°C) for 24 hours in a moist environment. Antigens and control sera were kindly supplied by Dr. Robert Philip, Rocky Mountain Laboratory, Hamilton, Montana.

Statistical analysis

All tests of statistical significance were carried out by a *t*-test and analysis of variance with the use of a program on a 2001 Commodore computer (Commodore Business Machines Inc., Santa Clara, California).

Results

Etiologic findings

Twenty-seven patients with atypical pneumonia were studied over the 1-year period. Twenty-six of the pneumonias had been acquired in the community. In the remaining case respiratory distress necessitating assisted ventilation developed immediately after an elective cholecystectomy. The patient had been admitted to hospital 24 hours before the operation. On the fifth hospital day pulmonary infiltration was evident; it progressed to involve four lobes and was diagnosed serologically and histologically as Legionnaires' disease.

The seasonal occurrence of the 27 cases is shown in Fig. 1. Cases of Legionnaires' disease occurred during the winter months (December to March) as well as during June and July; there was no clustering of these cases.

An etiologic diagnosis was made, mostly serologically, in 16 (59%) of the cases (Table I). *L. pneumophila* was demonstrated in lung tissue from two patients, and cytomegalovirus was visualized as inclusions in the lung tissue of another patient. *C. trachomatis*

was isolated from the pleural fluid and throat washings of one patient. *M. pneumoniae* was isolated from the tracheal secretions of the only patient in whom infection with this organism was diagnosed. Herpes simplex virus was isolated from the throat washings of six patients, all of whom had herpes labialis that had preceded the pneumonia; three of the isolates were from patients with Legionnaires' disease and one isolate each was from patients with pneumonia of unknown cause, Q fever and cytomegalovirus pneumonia. The labial lesions were considered to be the source of the herpesvirus.

Clinical and laboratory features

To compare the clinical and laboratory features of the 27 cases we divided the patients into three groups on an etiologic basis: group 1, the 8 patients with Legionnaires' disease; group 2, the 11 patients with atypical pneumonia of unknown cause; and group 3, the 8 patients with atypical pneumonia of various other established causes.

Males predominated in groups 1 and 2 (Table II), but there were equal numbers of males and females in group 3. The mean ages of the patients in the three groups were similar, as were the numbers of days of symptoms prior to admission to hospital. The group 2 patients seemed to have less severe disease than the other two groups, as evidenced by a shorter stay in hospital and fewer days of fever after antibiotic therapy was begun. These differences, however, were not statistically significant. One of the patients with Legionnaires' disease died from her pneumonia, and the only patient with cytomegalovirus pneumonia died from complications of a secondary bacterial infection. None of the group 2 patients required ventilatory support, but two patients in each of the other two groups did. The signs and symptoms were similar in the three groups.

There were no statistically significant differences between the three groups in the various laboratory findings shown in Table III.

The roentgenographic findings in the three groups of patients are shown in Table IV. The pneumonia of patients with Legionnaires' disease took significantly longer ($P < 0.05$) to resolve than the pneumonia of the other two groups and it often progressed: the infiltrates involved 1.5 lobes per patient in this group at the time of admission but 2.75 lobes per patient when the disease had progressed to its maximum. The pneumonia did not progress after admission in any of the group 2 patients but did progress among the group 3 patients, who had 1.87 lobes involved per patient at the time of admission, compared with 2.37

Table I—Causes of atypical pneumonia in 27 patients

Cause	No. of patients
Unknown	11
Legionella pneumophila	8
Coxiella burnetii	3
Chlamydia trachomatis	2
Mycoplasma pneumoniae	1
Parainfluenza 3 virus	1
Cytomegalovirus	1

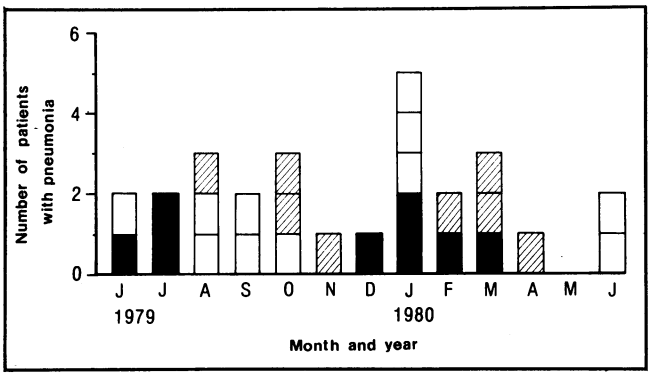

FIG. 1—Distribution of 27 cases of atypical pneumonia according to month of onset. Black areas of bars represent cases of Legionnaires' disease, white areas cases of atypical pneumonia of unknown cause and hatched areas cases of atypical pneumonia of various established causes other than Legionnaires' disease. Note that five of the cases of Legionnaire's disease occurred during the winter months.

Table II—Clinical features of the three groups of patients

Feature	Group 1* (n = 8)	Group 2† (n = 11)	Group 3‡ (n = 8)
Male: female ratio	6:2	7:4	4:4
Mean age (yr)	46	42	56
Mean no. of days of symptoms prior to admission to hospital	7.5	8.5	8
Mean temperature at time of admission (°C)	38.9	38	38.9
Mean no. of days until afebrile	6	2.3	4.3
Mean respiratory rate at time of admission (per min)	29.5	29	28
Mean no. of days in hospital	25	12.3	21
No. of patients with			
Fever	7	7	8
Chills	5	6	5
Rigors	2	2	1
Cough	5	9	7
Pleuritic pain	4	8	0
Headache	1	3	5
Confusion	3	1	0
Nausea	2	2	3
Vomiting	2	2	2
Diarrhea	1	0	4
Pulmonary consolidation	7	5	3
Rales	7	11	8
Rhonchi	3	3	2
Pleural friction rub	0	1	2
No. of patients requiring assisted ventilation	2	0	2
No. of deaths	1	0	1§

*Patients with Legionnaires' disease.
†Patients with atypical pneumonia of unknown cause.
‡Three patients with Q fever, two with *C. trachomatis* infection and one each with *M. pneumoniae*, parainfluenza 3 virus and cytomegalovirus infections.
§Died from complications of a secondary bacterial infection.

lobes per patient when the disease had reached its maximum.

Antibiotic therapy

The antibiotics used to treat the patients are shown in Table V. Since many patients were seriously ill the antibiotics initially administered were broad spectrum. Generally within 24 hours, when the results of the blood and sputum cultures were available, the regimen was changed to one antibiotic. One patient with Legionnaires' disease received no antibiotic therapy. He had a nonresolving pneumonia in a sequestered lobe of his lung and was afebrile. Another patient with Legionnaires' disease was treated with erythromycin only, as were two of the group 2 and four of the group 3 patients.

Serologic findings

Group 1: Seven of the eight patients with Legionnaires' disease had titres of antibodies against *L. pneumophila* of 1:1024 or greater detected by the indirect immunofluorescence test in serum obtained during convalescence. Two of the seven had titres of 1:32 000 and 1:64 000. In all seven a fourfold rise in the titre occurred within 2 weeks of admission, and the peak occurred by 1 month. The only patient with a stable titre was admitted on the eighth day of her illness. Two days later her titre of antibodies against *L. pneumophila* serogroup 4 was 1:256, and it was still at this level on three other occasions up to 126 days after the onset of her illness. She also demonstrated a fourfold rise in the titre of complement-fixing antibodies to *Chlamydia* group antigen and to adenovirus antigen between days 23 and 32 of her illness. When the same serum samples were tested for antibodies against *C. trachomatis* by microimmunofluorescence, antibodies to immunotype J were detected in a titre of 1:64 in the IgM and IgG fractions on days 23 and 32. No antibodies against any of the immunotypes of *C. trachomatis* were present on day 10 or on day 104. The serum of another group 1 patient showed a fourfold rise in the titre of complement-fixing antibodies against *C. burnetii* (from less than 1:4 to 1:64) and parainfluenza 1 (from 1:8 to 1:64), but with a microagglutination technique antibodies against *C. burnetii* were not detected.

Group 2: None of the patients in this group showed a fourfold rise in the serum titre of antibodies to any of the test antigens or a titre of antibodies against *L. pneumophila* that was any higher than 1:128.

Group 3: In this group as well the patients' serum either lacked antibodies against *L. pneumophila* or the titre was 1:128 or less.

Three patients were considered to have Q fever on the basis of a fourfold rise in the titre of antibodies against *C. burnetii* in their serum. Complement fixation and microagglutination demonstrated the rise in two patients; antibodies to phase II antigen were detected by microagglutination only in the other patient's serum.

Two patients showed a fourfold drop in the serum titre of complement-fixing antibodies to the *Chlamydia* group antigen; in both cases a microimmunofluorescence test confirmed that the antibodies were against *C. trachomatis* — immunotype J in one patient (*C. trachomatis* was isolated from this patient's throat

Table III—Laboratory findings in the three groups of patients

Finding (and normal values)	Group; mean value* 1	2	3
Blood levels			
Hemoglobin, g/dl (11–16)	12.8	14.1	13.6
Leukocytes, $\times 10^9$/l (5–10)	13.0	11.6	11.4
Serum levels			
Sodium, mmol/l (138–145)	133	134	137
Inorganic phosphate, mmol/l (0.7–1.3)	0.84	0.97	0.9
Aspartate aminotransferase, IU/l (8–29)	74	55	31
Alanine aminotransferase, IU/l (1–41)	61	45	38
Alkaline phosphatase, IU/l (30–104)	102	130	131
Total bilirubin, μmol/l (0–16)	18.9	12.0	6.8

*Differences between the groups were not statistically significant by a group *t*-test.

Table IV—Findings in the patients' chest roentgenograms

Finding	Group; no. of patients 1	2	3
No. of lobes involved at time of admission			
One	5	9	2
Two	2	2	5
Three	1	0	1
Maximum no. of lobes involved			
One	3	8	2
Two	1	3	3
Three	3	0	1
Four	2	0	2
Lobe(s) involved at time of admission			
Right upper	5	1	2
Right middle	1		2
Right lower	2	5	5
Left upper	2	3	1
Left lower	2	5	5
Mean no. of days from onset of symptoms to clearing of pulmonary infiltration	69*	14	19

*Significantly greater ($P < 0.05$) than the numbers for groups 2 and 3.

Table V—Antibiotic therapy in the three groups of patients

Antibiotic	Group; no. of patients 1	2	3
Erythromycin	7	8	8
Ampicillin	0	4	2
Penicillin G	2	3	3
Cloxacillin	3	5	1
Cephalothin	2	1	0
Gentamicin	3	4	2
Erythromycin alone	1	2	4
None	1	0	0

washing and pleural fluid specimens, but the isolate was not typed) and immunotype B in the other. Both had IgM antibody against the particular immunotype.

One patient had stable serum titres of antibodies against *M. pneumoniae* of 1:2048 or greater, and this organism was isolated from her tracheal secretions. She had diffuse pulmonary infiltrates and required assisted ventilation for 5 days.

A fourfold rise in the titre of complement-fixing antibodies against parainfluenza 3 virus antigen was demonstrated in the serum of only one patient.

Discussion

In this study we have used the term atypical pneumonia in the same context as Cunha and Quintiliani,[7] to include Legionnaires' disease. Traditionally *M. pneumoniae* pneumonia is referred to as atypical pneumonia[8] — and, indeed, it is the most common atypical pneumonia in young adults.[9] It is both endemic and epidemic, with epidemics occurring every 4 years or so.[9] These facts are consistent with the low incidence of *M. pneumoniae* found in this study: only 1 of our 27 patients had this type of atypical pneumonia.

One of the most important findings in our study was the high proportion (41%) of cases of atypical pneumonia in which the cause could not be established despite extensive cultures and serologic testing. Recently several agents have been described as causing pneumonias indistinguishable from Legionnaires' disease;[10] fortunately, pneumonia due to these agents seems to respond to erythromycin, the drug used for treating Legionnaires' disease. These agents — *L. micdadei*, *L. bozemanii*, *L. gormanii* and *L. dumofii* — all require a special medium for growth: charcoal–yeast extract agar. We did not test the serum of our 11 patients with pneumonia of unknown cause for antibodies to these agents, but we treated 9 of them with erythromycin. Overall this group had a milder disease than the other two groups of patients.

The clinical features of the atypical pneumonias in our patients were such that a clinical diagnosis of the exact cause could not be made with a high degree of accuracy.

L. pneumophila was the most common etiologic agent, accounting for 30% of the cases. The spectrum of effects resulting from infection with this agent ranges from asymptomatic seroconversion, through a mild, self-limited febrile illness characterized by headache, chills and myalgia, to the severe, potentially fatal illness known as Legionnaires' disease, characterized by progressive pneumonia.[11] Seven of our eight patients who were infected with *L. pneumophila* fit the Legionnaires' disease category. The other patient was mildly ill when admitted because of a pneumonia that had failed to resolve. A sequestered lobe of the lung was discovered and removed. When it was found that his serum titre of indirect immunofluorescent antibodies against *L. pneumophila* had risen from 1:64 to more than 1:1024 during his 15-day hospital stay his lung tissue was examined by direct immunofluorescence and found to be positive for *L. pneumophila*.

The clinical features of our seven patients with typical Legionnaires' disease were similar to those described in a recent review of 305 cases reported in the literature.[11] This survey found that cough and fever were most common, occurring in 87% and 90% of patients respectively. Chills occurred in 73%. Other symptoms, including diarrhea, dyspnea, chest pain, headache, sweats, nausea, vomiting. myalgia, arthralgia and abdominal pain, were present in 24% to 56% of patients.

The laboratory findings in our patients with Legionnaires' disease were not specific enough to suggest the diagnosis. Hyponatremia due to inappropriate secretion of antidiuretic hormone was reported in 54% of the 65 patients in one series,[11] and 2 of our 8 patients had a serum sodium level below 130 mmol/l; however, the mean serum sodium level was similar in our three groups. Hypophosphatemia was a frequent finding in Kirby and colleagues' study of patients with Legionnaires' disease,[11] and two (25%) of our patients with this disease had a serum inorganic phosphate level below 0.7 mmol/l; however, hypophosphatemia was also occasionally found in our other two groups of patients and the means were not significantly different. In all the hypophosphatemic patients the serum phosphate level had generally returned to normal by the third hospital day. The serum transaminase and bilirubin levels tended to be higher, but not significantly so, in the patients with Legionnaires' disease.

Two of our eight patients with Legionnaires' disease had fourfold rises in the serum titres of antibodies to other antigens. In one patient these antigens were those of *Chlamydia* and adenovirus, and in the other they were antigens of *C. burnetii* and parainfluenza 1. Ormsbee and associates[12] demonstrated an antigenic relation between *L. pneumophila* and the 6 BC strain of *C. psittaci*, and Taylor and coworkers[13] found that some patients with adenovirus infections had high stable titres of antibodies to the antigen of ether-killed *L. pneumophila* prepared by the Center for Disease Control. This raises the question whether one of our patients, the only one of the eight with a stable titre of antibodies against *L. pneumophila*, had adenovirus pneumonia or Legionnaires' disease. She became afebrile within 24 hours of the start of erythromycin therapy, and prior to this she had been ill for 8 days with fever, cough and intermittent delusions. Since we did not isolate either agent we will never be certain whether she was infected with one or both agents. We did not find any cross-reactions between *M. pneumoniae* and *L. pneumophila*, unlike Grady and Gilfillan.[14]

We were surprised to find our three cases of pneumonia due to *C. burnetii*. The American dog tick (*Dermacentor variabilis*) is present in great numbers in southwestern Nova Scotia, and studies at Acadia University, Wolfville, NS have demonstrated that the tick front is advancing about 1.5 km per year (Dr. Thomas Herman: personal communication, 1980). This tick is known to be one of the reservoirs of *C. burnetii*,[15] the etiologic agent of Q fever. Humans are usually infected by inhaling infected material. To date this organism has not been isolated from ticks in Nova Scotia.

A serologic survey carried out in southwestern Nova Scotia during 1978 revealed that 8.4% of 1646 serum samples tested contained complement-fixing antibodies against *C. burnetii* (Dr. Alan Thompson: personal communication), but in 90% of positive samples the titre was 1:64 or less, and all the individuals whose serum was tested were asymptomatic. Our three patients with antibodies against *C. burnetii* had very high titres by complement fixation or microagglutination, or both, and had an illness clinically consistent with Q fever. Tetracycline is the drug of choice for the treatment of Q fever, but recently a favourable response has been reported with the use of erythromycin.[16] Such was the case in two of our patients. The third had a nonproductive cough that persisted for 2 months after his chest cleared clinically and roentgenographically.

Pneumonia due to *C. trachomatis* was first described in infants 4 to 24 weeks of age who had had a cough, pulmonary congestion and diffuse pulmonary infiltrates for a month or more.[17] Recently *C. trachomatis* was isolated from the lower respiratory tract of six adults with a pulmonary infection;[18] four were immunosuppressed and three had a concomitant cytomegalovirus infection. The four who were studied serologically did not show an immune response to *Chlamydia*. Both of our patients with pneumonia due to *C. trachomatis* had high titres of antibodies to *Chlamydia* group antigen demonstrated by complement fixation and high titres of IgM and IgG antibodies to *C. trachomatis* demonstrated by microimmunofluorescence. A fourfold drop in antibody titre was demonstrated by both techniques. One patient was infected with immunotype J and the other with immunotype B. We isolated *C. trachomatis* from the throat washings and pleural fluid of the former.

Conclusion

In this study we have demonstrated the diverse causes of endemic atypical pneumonia. We have also shown that, despite considerable effort, many of these pneumonias remain etiologically unidentified.

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