A New Respiratory Tract Pathogen: Chlamydia pneumoniae Strain TWAR


Chlamydia pneumoniae strain TWAR, the new third species of Chlamydia, is a common cause of pneumonia and other acute respiratory tract infections. About 10% of hospitalized and outpatient pneumonia cases have been associated with TWAR infection. TWAR is among the four or five most commonly identified causes of all pneumonia. Most TWAR infections are mild or asymptomatic, but occasionally severe pneumonia with death has been observed. Laboratory diagnosis is not generally available. Vigorous treatment with tetracycline or erythromycin is recommended. Both epidemic and endemic infections have been described in North America and the Nordic Countries. Population prevalence antibody studies suggest that TWAR infection is widespread throughout the world, that nearly everyone is infected and reinfected during their lifetime, and that infection is common in all ages except those <5 years in temperate zone countries. The infection is transmitted from person to person, apparently with a long incubation period.

We are pleased to participate in honoring Joseph E. Smadel. Joe Smadel was a "triple-threat" infectious disease investigator. He made basic contributions in the laboratory. He did clinical investigations and field epidemiologic studies. While work with psittacosis was not one of Smadel's major areas of interest, he had six publications on the subject and in one predicted Chlamydia pneumoniae.

In 1943, he questioned the source of infection of seven patients who had no known contact with birds [1]. After admitting that it was impossible to rule out "transient indirect exposure to infected pigeons," a popular explanation for cases thought to be psittacosis on the basis of complement fixation antibody but without known bird contact, he went on to say "it appears desirable to search for a humanized strain of virus of this general group which is moderately contagious for man and which is transmitted from man to man by way of the upper respiratory route. A family of viruses, as widely disseminated throughout the avian, mammalian, and human species as is the psittacosis-lymphogranuloma venereum group of agents, might be expected to possess a member with potentialities of this type." It took 40 years for Smadel's prediction of a humanized strain to be shown to be correct.

Here we review information of Chlamydia pneumoniae strain TWAR and its role in human infection.

Microbiology

Table 1 shows some basic characteristics of the three Chlamydia species. Both Chlamydia trachomatis and C. pneumoniae are primarily human pathogens, while humans are infected accidentally from birds by Chlamydia psittaci. The major diseases caused by C. trachomatis are trachoma and genital infections. The other two species cause respiratory infections.

The species name for the TWAR organism is now officially Chlamydia pneumoniae [2]; thus far only one strain or serovar of the new species has been identified. The strain name TWAR came from the laboratory identifying letters of the first two isolates: TW-183 and AR-39. TW-183 was isolated from the eye of a control child in a trachoma vaccine study in Taiwan in 1965. AR-39 came from a throat swab of a University of Washington student with pharyngitis in 1983. There is no evidence that C. pneumoniae plays a significant role as a cause of conjunctivitis.

At first we considered the TWAR organism to be C. psittaci, because it clearly did not belong to the C. trachomatis species [3]. Subsequent studies have identified these organisms as a separate species of Chlamydia [4-7].

Table 2 shows results of quantitative DNA homology studies. C. pneumoniae isolates had ≥94% homology with each other but <10% with C. psittaci and C. trachomatis isolates. C. trachomatis and C. psittaci also showed <10% DNA relatedness with the other species. There was considerable heterogeneity among the C. psittaci strains tested, with homologies of 20%-100% [7].

An electron micrograph (figure 1) shows that the TWAR elementary body is pear-shaped and has a large periplasmic space, different from the typically round elementary bodies of C. trachomatis and C. psittaci [4]. In addition, small electron-dense bodies of undetermined function were seen in the periplasmic space of the TWAR elementary bodies.
Table 1. Some properties of Chlamydia species.

<table>
<thead>
<tr>
<th>Property</th>
<th>C. trachomatis</th>
<th>C. psittaci</th>
<th>C. pneumoniae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural hosts</td>
<td>Humans</td>
<td>Birds, lower mammals</td>
<td>Humans</td>
</tr>
<tr>
<td>Major human diseases</td>
<td>Trachoma, sexually transmitted diseases, lymphogranuloma venereum</td>
<td>Pneumonia, fever of unknown origin</td>
<td>Pneumonia, bronchitis</td>
</tr>
<tr>
<td>No. of serovars</td>
<td>15</td>
<td>Unknown</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 2. Percentage of relatedness (homology) in DNA sequence among Chlamydia species. Three to five strains or isolates of each species were tested (after [7]).

<table>
<thead>
<tr>
<th>Labeled DNA</th>
<th>C. pneumoniae</th>
<th>C. psittaci</th>
<th>C. trachomatis</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. pneumoniae</td>
<td>94–100</td>
<td>≤5–8</td>
<td>≤5</td>
</tr>
<tr>
<td>C. psittaci</td>
<td>≤5–10</td>
<td>21–100</td>
<td>≤5–11</td>
</tr>
<tr>
<td>C. trachomatis</td>
<td>≤5–7</td>
<td>≤5–6</td>
<td>97–100</td>
</tr>
</tbody>
</table>

The DNA homology results and the unique fine structure appearance of the elementary body were essential to the establishment of the new species [2].

Laboratory Diagnosis

Laboratory diagnosis is based on isolation of the organism and serology.

Isolation. C. pneumoniae grows poorly, more so than trachoma biovar strains of C. trachomatis. It likely would have been discovered earlier if it grew more readily. We use HeLa 229 cell culture and the yolk sac of embryonated chicken eggs for its isolation and growth. The techniques used for enhancement of cell culture growth are similar to those used for C. trachomatis [8, 9].

TWAR organisms are susceptible to inactivation from the freeze-thaw cycle. Specimens in transport medium for isolation studies may be kept at 4°C if inoculated within 24 h. Rapid freezing inactivates >50% of the organisms. If specimens are chilled at 4°C for 1–4 h before freezing to below −65°C, viability is preserved [8].

Our ability to isolate the organism was greatly enhanced by the development of a TWAR-specific monoclonal antibody that, when conjugated to fluorescein, allows identification of TWAR organisms. A Chlamydia genus monoclonal antibody will also stain TWAR inclusions but does not identify them as C. pneumoniae. The fluorescent stain is important in finding the inclusions, because often few are seen.

Serology. The serologic test has played a crucial role in our investigations. The microimmunofluorescence test with TWAR antigen is specific for C. pneumoniae. It can distinguish antibodies in the IgM and IgG serum fractions, which is helpful in determining current versus previous infection [10]. Table 3 shows our interpretation of positive results in the serologic tests. Antibody indicating current or recent infection we call "acute." While IgM and complement-fixing antibody usually are lost 2–6 months after infection, the IgG antibody persists. The length of persistence varies, but we have followed six proven cases for 2–3 years and found persistence...
Table 3. Positive results in serologic tests for *Chlamydia pneumoniae*.

<table>
<thead>
<tr>
<th>Test</th>
<th>Positive result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microimmunofluorescence with <em>C. pneumoniae</em> antigen</td>
<td></td>
</tr>
<tr>
<td>Acute antibody</td>
<td>Fourfold titer rise:</td>
</tr>
<tr>
<td></td>
<td>IgM ≥1:16;</td>
</tr>
<tr>
<td></td>
<td>IgG≥1:512</td>
</tr>
<tr>
<td>Preexisting antibody</td>
<td>IgG ≥1:16 and &lt;512</td>
</tr>
<tr>
<td><em>Chlamydia</em> complement fixation*</td>
<td>Fourfold titer rise:</td>
</tr>
<tr>
<td>Acute antibody</td>
<td>≥1:64</td>
</tr>
</tbody>
</table>

* Not specific.

of antibody in three. An IgG antibody titer <512 is considered preexisting antibody, antibody from a previous infection. Population prevalence antibody data are based on preexisting antibody.

The microimmunofluorescence test was devised in 1970 for *C. trachomatis* [11]. It remains the only specific and sensitive serologic test for any of the chlamydiae. When properly done there is no significant cross-reaction between *C. pneumoniae* and *C. trachomatis* [10, 12].

The *Chlamydia* complement-fixation (CF) test is not specific but measures antibodies to all chlamydiae. It had been used for many years for presumptive diagnosis of psittacosis. Since TWAR infections are much more common than psittacosis, it is probable that many infections diagnosed as psittacosis on the basis of the CF test were actually infections with *C. pneumoniae*, including some of Smadel's 1942 cases.

Older patients with *C. pneumoniae* infections often do not show a CF antibody response. In our studies of hospitalized pneumonia patients, fewer than one-third with evidence of TWAR infection had CF antibody.

We found two patterns of antibody response to TWAR infections, which we believe are associated with first or primary infection and with reinfection. In first infection a prompt chlamydia CF antibody response is seen. TWAR microimmunofluorescence antibody in the IgM serum fraction appears ~3 weeks after onset of illness and antibody in the IgG serum fraction not until 6–8 weeks after onset. In reinfection there may be no CF antibody and no IgM antibody. IgG antibodies may show a titer rise within 1–2 weeks and reach a high titer. Understanding these patterns is important in interpreting serologic studies of TWAR infection. In first infection if the second serum sample is obtained <3 weeks after onset, TWAR antibody may be missed. In reinfections, the absence of CF and IgM antibody may make it difficult to differentiate current infection from preexisting antibody.

Unfortunately, laboratory diagnosis is not easy. The methods need to be simplified if they are to become widely used clinically.

Etiologic Association

Our longest study of TWAR infection and the most important in associating the organism etiologically with human disease has been in University of Washington students with acute respiratory disease [2]. Table 4 shows the percentage who were TWAR-positive by year and by three diagnostic categories. The frequency of TWAR infection in 1986–1987 (and also in 1988) has been much less than in earlier years. The data show that there has been a strong tendency for TWAR to be associated with lower respiratory tract disease. During the first 3 years, *C. pneumoniae* infection was associated with 13% of all diagnosed pneumonia and 24% of radiographically proven pneumonia. Those proportions had fallen to 10% and 20% at the end of the 5 years (Thom et al., unpublished data).

Including two 1988 cases (not shown), 22 patients have been identified as having TWAR infection by isolation of the organism or microimmunofluorescence serology. In 1983 and the first half of 1984, the organism was isolated from only 2 of 8 patients who were positive serologically. However, since July 1984 there have been 12 isolates from 14 serologically positive patients. This isolation rate is as good as could be expected with any microorganism. The improved isolation results since mid-1984 coincide with the development of the TWAR monoclonal antibody conjugated to fluorescein for identification of the organism.

The close agreement between isolation and serology adds evidence that the microimmunofluorescence test is both specific and sensitive and allows acceptance of the results from seroepidemiologic studies. The findings also add considerable weight to the presumption that the TWAR organism is etiologically associated with human infections, particularly those of the lower respiratory tract.

Clinical Characteristics

Clinical findings in 20 students shown to have *Chlamydia pneumoniae* infection in 1983–1987 and in those shown serologically to have *Mycoplasma pneumoniae* or viral infection are shown in table 5. As is generally true with respiratory

Table 4. Isolation or serologic evidence of *Chlamydia pneumoniae* infection in University of Washington students by diagnosis.

<table>
<thead>
<tr>
<th>Year</th>
<th>Pneumonia</th>
<th>Bronchitis</th>
<th>Other</th>
<th>Total</th>
<th>With isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td>1983</td>
<td>17 (28)</td>
<td>8 (18)</td>
<td>3 (38)</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>1984</td>
<td>9 (28)</td>
<td>3 (27)</td>
<td>0 (115)</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>1985</td>
<td>14 (30)</td>
<td>6 (39)</td>
<td>0 (118)</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>1986</td>
<td>6 (33)</td>
<td>0 (36)</td>
<td>0 (30)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>1987</td>
<td>0 (21)</td>
<td>5 (21)</td>
<td>0 (68)</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
tract infections, there were no distinctive findings. Pharyngitis often with hoarseness is a common accompaniment of TWAR infection. Fever at the time of examination was less frequent with TWAR. This was influenced by the time from onset of symptoms to examination. The time for Chlamydia pneumoniae cases was 13 days versus 8 and 7 days for the others, suggesting a less acute onset. The tendency of TWAR infections to involve the lower respiratory tract is shown by the high percentage with abnormal breath sounds. Although not all patients had radiologic examinations, pneumonitis was demonstrated in 100% (12/12) of TWAR patients examined compared with 80% (12/15) of those with mycoplasma and 20% (4/20) of those with viruses. Elevated white blood cell counts were uncommon and similar to viral infections.

These TWAR infections caused relatively mild illnesses. No patient was hospitalized or had serious complications. Most required bed rest for several days and some further restriction of activity.

Another study from which we have a series of TWAR isolations provides information on the clinical characteristics of first (primary) infection and reinfection in young adults (Ekman et al., unpublished data). A countrywide epidemic of Chlamydia pneumoniae infection occurred in Finland in 1985–1987. By prospective monitoring of military training battalions, an outbreak was identified in Kajaani in 1987. Pharyngeal swab specimens and paired blood samples were obtained from 86 of the 18- to 20-year-old trainees during the epidemic [13]. Most were obtained from outpatients in an effort to study TWAR's association with disease milder than pneumonia. Table 6 considers only 10 trainees from whom we isolated Chlamydia pneumoniae. We were surprised to find that 5 showed the serologic pattern of first infection and 5 the pattern of reinfection (CF and IgM microimmunofluorescence antibody present in first infection and absent in reinfections). The reinfections all had IgG antibody titer rises to 1024.

Table 7 shows that of those with first infection, three had pneumonia and all five were hospitalized, while none of those with reinfection had pneumonia and only one was hospital-
of 20 patients appeared to have acquired their pneumonia in the hospital. Of the 9, 7 were admitted with multiple injuries from severe trauma, and the other 2 underwent major surgery. The mode of transmission in the hospital was not determined, but on the basis of the sensitivity of Chlamydia organisms to inactivation outside the body and the lack of clustering of the cases (which occurred in two hospitals), it is possible that these infections represent reactivations of the TWAR organism in the lungs of these very sick patients rather than an infection transmitted in the hospital.

Another retrospective serologic study from which we obtained information about clinical diseases associated with TWAR infection is shown in table 9. Sera and clinical information were available from >1100 patients diagnosed as possibly having ornithosis, whose sera had been submitted to the Statens Seruminstitut, Copenhagen, for Chlamydia CF testing in 1975–1987 (Mordhorst et al., unpublished data). Ornithosis, a broader term, is used instead of psittacosis in many European countries. Most of the sera available for study had Chlamydia CF antibody; more than half had evidence of current C. pneumoniae infection.

The frequency of clinical diagnoses in the patients with acute TWAR antibody is shown by three age groups. Half of the patients were diagnosed as pneumonia, with confirmatory radiographic evidence in 87%. Bronchitis was the next most common diagnosis. The older patients had more pneumonia, less bronchitis, and less upper respiratory infection, while those <20 years old had milder illnesses with fewer diagnosed pneumonias, more bronchitis, and many more upper respiratory infections. Only 23% of these patients were hospitalized.

In addition to these primary diagnoses, symptoms of sinusitis occurred frequently in the patients with diagnosed lower respiratory tract symptoms. There was evidence of sinusitis in 12% of the patients with bronchitis and 7% of those with pneumonia.

These results are from a specialized serum bank that cannot be considered representative. A diagnosis of ornithosis is based on clinical findings and/or a history of bird contact. The fact that 50% of the patients has pneumonia may reflect this selection. Nevertheless, in all of our studies of acute respiratory illness, pneumonia has been the most common disease associated with Chlamydia pneumoniae infection.

**Summary of Syndromes Associated with TWAR Infection**

**Pneumonia.** On average, ~10% of both outpatient and hospitalized pneumonia has been associated with evidence of C. pneumoniae infection. TWAR pneumonia is most often mild with a single subsegmental infiltrate. Even asymptomatic persons have had pneumonitis and evidence of C. pneumoniae infection [19]. Severe illness has been seen, especially in older persons and those with chronic diseases. Onset is often prolonged with upper respiratory symptoms, especially pharyngitis with hoarseness. These are followed by increasing cough and other symptoms of lower respiratory disease. Persistent cough and malaise often follow acute illness.

Epidemics have occurred in communities and in closed population groups. While pneumonia has been the most common syndrome associated with TWAR infection, serologic studies during epidemics in military trainee companies at the beginning and end of their training period have suggested that only ~1 in 9 or 10 C. pneumoniae infections resulted in pneumonia [13, 20]. This suggests that many TWAR infections are mild or asymptomatic and are not recognized.

**Bronchitis.** TWAR bronchitis often has an insidious onset. The subacute onset is often preceded or accompanied by pharyngitis. These patients may not come to medical attention for several weeks. Some may have had unrecognized pneumonitis earlier in the course of illness. In young adults ~4% of bronchitis has been shown to be associated with TWAR infection. The symptoms respond to appropriate antibiotic therapy.

**Pharyngitis.** Pharyngitis, often relatively severe with hoarseness, is frequently associated with C. pneumoniae infection. Up to 80% of those with TWAR lower respiratory tract infection have sore throat. However, in our prospective studies <1% of patients with pharyngitis who did not develop lower respiratory tract involvement had evidence of TWAR infection. Studies of pharyngitis could show a higher percentage with C. pneumoniae if subsequent development of lower respiratory tract disease is missed or if early treatment prevents development of pneumonia or bronchitis.

### Table 8. Summary of results from three retrospective TWAR serologic studies of hospitalized pneumonia (from [16–18]).

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
<td>301</td>
<td>359</td>
<td>198</td>
</tr>
<tr>
<td>Acute TWAR antibody</td>
<td>18 (6%)</td>
<td>27* (8%)</td>
<td>20 (10%)</td>
</tr>
<tr>
<td>Mean age (y)</td>
<td>64</td>
<td>66</td>
<td>61/43†</td>
</tr>
<tr>
<td>Died</td>
<td>2</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

* Five had pneumonia of primary origin other than the TWAR organism.
† Community-acquired/hospital-acquired.


<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>0–19 y (n = 113)</th>
<th>20–59 y (n = 424)</th>
<th>≥60 y (n = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>38</td>
<td>51</td>
<td>65</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>36</td>
<td>27</td>
<td>15</td>
</tr>
<tr>
<td>Fever of undetermined origin, pharyngitis</td>
<td>8</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Sinusitis, otitis</td>
<td>4</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>4</td>
<td>2</td>
<td>6</td>
</tr>
</tbody>
</table>

**NOTE.** Most patients had Chlamydia complement-fixation antibody. Data are percentages.
Sinusitis. Sinusitis, both alone and in association with other syndromes, has been consistently found in studies of TWAR infection. About 5% of primary sinusitis in young adults has been associated with TWAR infection, and at least 5% of patients with lower respiratory tract TWAR infection have had evidence of sinusitis. Otitis is less commonly associated with TWAR.

Other syndromes. Fever of undetermined origin and influenza-like illness have been associated with TWAR infection in many of our studies. Fever of undetermined origin is frequent with C. psittaci infection [21]. These syndromes may account for some of the spectrum of milder TWAR syndromes that usually are unrecognized.

Myocarditis and endocarditis have been caused by the other Chlamydia species [21-23]. We have associated these syndromes with C. pneumoniae infection, both alone and with pneumonia [24-26]. Evidence has been presented of a serologic association of C. pneumoniae with coronary artery disease [27]. There also is evidence of association of TWAR infection with sarcoidosis [24-28]. More studies will be needed to establish an etiologic role for C. pneumoniae in these syndromes.

Treatment of C. pneumoniae Infection

There have not been any controlled studies of treatment of C. pneumoniae infection. We have obtained laboratory data in cell culture on antibiotic and sulfa drug sensitivities that support clinical observations [29]. Table 10 shows that tetracycline and erythromycin are the most effective drugs, as they are with other Chlamydia species. Penicillin, while failing to prevent first passage of TWAR in cell culture, does cause aberrant inclusions whose infectivity on second passage is decreased. Unlike its effect on C. trachomatis, sulfa is not effective against TWAR or most C. psittaci strains.

We recommend intensive prolonged therapy, similar to that for psittacosis: 2 g/day of tetracycline or erythromycin for 10 days to 2 weeks. The clinician should not be surprised if the patient requires additional antibiotic therapy even after one of these courses. Unless contraindicated, we recommend tetracycline for the second course of treatment.

Table 10. Antibiotic and sulfa drug sensitivity of Chlamydia pneumoniae in HeLa 229 cell culture (after [29]).

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Viability (first passage)</th>
<th>Infectivity (second passage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetracycline</td>
<td>0.05-0.1</td>
<td>0.05-0.1</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>0.01-0.05</td>
<td>0.01-0.05</td>
</tr>
<tr>
<td>Penicillin</td>
<td>&gt;100</td>
<td>0.1-0.2</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>&gt;100</td>
<td>0.8-1.6</td>
</tr>
<tr>
<td>Sulfisoxazole</td>
<td>&gt;400</td>
<td>&gt;400</td>
</tr>
</tbody>
</table>

NOTE: Data are minimum inhibitory concentrations in micrograms or units per milliliter for eight TWAR isolates.

Epidemiology

We have developed a concept of the epidemiology of C. pneumoniae infection in a relatively short time by use of seroepidemiology. This has been possible because of available serum banks from previous studies of respiratory disease.

Population TWAR antibody prevalence. Early in our studies, we recognized that TWAR antibody indicating previous infection was found in adults 5 to 10 times more frequently than C. trachomatis antibody [10]. This preexisting antibody in the IgG serum fraction was found in ~50% of adults in seven countries. It varied from ~40% in Canada (Nova Scotia) to >60% in Taiwan and Panama. The rates were 10%-25% higher in men.

We had enough sera representing all ages in Denmark and Seattle to study antibody prevalence by age. Figure 2 shows that the antibody rates were low in young children in both countries and increased sharply in teenagers, continued to increase until middle age, and remained high into old age.

In view of the expected decay of antibody after infection, the finding of TWAR antibody in 50% of adults at one time suggests that most people have more than one C. pneumoniae infection during their lifetime.

The age curve of antibody prevalence, with most of the increase after school age, and the higher prevalence in men suggest that the place of infection may more often be outside the household than is customary with many respiratory infections.

Periodicity. While C. pneumoniae infections have been found in all years of our prospective and retrospective studies, there has been wide variation in incidence. Our early studies suggested that it was endemic in the USA and epidemic in Scandinavia and Finland [30]. We were fortunate to have begun our studies in university students in 1983. For three years evidence of TWAR infection was found in 25% of patients with pneumonia confirmed by chest radiography [3]. However, since that time the incidence has been low. The expecta-
tion that we would soon see an increase in TWAR infections has yet to come true.

We have tested several serum banks that give us an idea of the past periodicity of TWAR infections. One was from a 12-year population-based study of *M. pneumoniae* in pneumonia in a large Seattle health maintenance organization [31]. Figure 3 shows results of testing >1100 paired serum specimens, stratified by age, gender, and time, from these mostly outpatient cases of pneumonia. TWAR infections occurred as early as 1963 and continued through 1974. There were no patients <5 years old with TWAR infection. Acute TWAR antibody was present in 3%-15% per year of the cases of pneumonia in persons ≥5 years old. The figure shows a periodicity with a high point every 4 years.

The 13-year Danish ornithosis serum bank shown in Table 9 also provides information on periodicity. Denmark, Norway, and Sweden suffered countrywide outbreaks of *C. pneumoniae* infection in 1981-1983 [25]. In addition, there was an outbreak of TWAR infection in Denmark in 1976-1977. There appears to be a new TWAR epidemic beginning this year. We already have evidence of a high percentage of TWAR-positive ornithosis sera. This would suggest a possible 6-year cycle for outbreaks in Denmark.

No evidence of consistent seasonal periodicity in TWAR infection has emerged from this or our other studies.

Transmission. All evidence suggests that TWAR is a primary human pathogen that is transmitted from human to human without a bird or animal reservoir. However, the mode and place of transmission, the incubation period, and the infectiousness of the organism are unknown.

Four TWAR pneumonia epidemics in Finnish military trainees were identified by retrospective serology [20]. Table 11 shows the length of the four epidemics and the approximate size of the population exposed. All seasons of the year were involved in these epidemics. It took 5–8 months for them to run their course, despite the fact that the population in each garrison was relatively small. These data suggest that TWAR infections spread slowly, even in a closed population (which is known to promote spread of respiratory infections). An influenza epidemic could probably go through one of these garrisons in 2 weeks.

As part of the 1975–1987 Danish ornithosis study, sera were available on household and other contacts related to a *Chlamydia* CF-positive case. Of 111 contact groups, 80 had serologic evidence suggesting TWAR infection. Figure 4 shows case interval times in the TWAR positive groups. The intervals shown are for 7 days, beginning 10 days after the first case. Those with intervals <10 days were considered coprimary cases. In some larger household or contact groups there appeared to be tertiary cases; the time interval shown is from another member of the group rather than from the first case. The mean case interval time was 31 days. The general pattern of interval times was the same for spousal pairs or for parents and children as for nonhousehold contacts. While this provides data on the long time between contact cases, it does not tell us what the true incubation period is, who is infectious, or when during their illness they transmit.

Discussion

A previous presentation to this Society in 1974 [32] was at the time that *C. trachomatis* was beginning to be identified

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### Table 11. *Chlamydia pneumoniae* pneumonia epidemics in military trainees in Finland (after [20]).

<table>
<thead>
<tr>
<th>Location</th>
<th>Date</th>
<th>Duration (mo)</th>
<th>Group size</th>
<th>Pneumonia rate/1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oulu</td>
<td>March–October 1977</td>
<td>8</td>
<td>2500</td>
<td>84</td>
</tr>
<tr>
<td>Kajaani</td>
<td>February–June 1978</td>
<td>5</td>
<td>1500</td>
<td>69</td>
</tr>
<tr>
<td>Tamminsaari</td>
<td>January–June 1985</td>
<td>6</td>
<td>1000</td>
<td>60</td>
</tr>
<tr>
<td>Sodankyla</td>
<td>July–December 1985</td>
<td>6</td>
<td>1200</td>
<td>71</td>
</tr>
</tbody>
</table>

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**Figure 3.** Patients of the Group Health Cooperative of Puget Sound, Seattle, with pneumonia, 1963–1974: percentage of persons ≥5 years with acute *Chlamydia pneumoniae* antibody.

**Figure 4.** Case interval times among persons in households and other contact groups with serologic evidence of *Chlamydia pneumoniae* infection. Case intervals are from first patient in group except for apparent tertiary cases. Onsets <10 days from first case are considered coprimary.
as an important cause of genital tract infection. Since then there has been a virtual explosion of research and development concerning Chlamydia trachomatis as a sexually transmitted organism. We now expect to see greatly increased research activity with Chlamydia pneumoniae. In the past year a number of abstracts of research with Chlamydia pneumoniae from other workers have appeared. Having more investigators working with the TWAR organisms will accelerate the acquisition of new knowledge.

One of the things that our 1974 talk emphasized was the importance of reinfection in the pathogenesis of the disease caused by Chlamydia organisms. We have already shown that infection with Chlamydia pneumoniae is much more common than with other Chlamydia species and that reinfection is common. What we don’t yet understand is the clinical significance of these frequent reinfections.

There remain many unknowns concerning transmission. Why does transmission appear frequently to occur outside the home—at school, in the military, or in other institutions? Who transmits the organism and at what stage of illness? Is there endogenous reinfection?

Other areas that need attention include diagnostic methods and treatment. Easier and more widely available laboratory diagnosis is badly needed. No antibiotic has succeeded with any Chlamydia species in regularly eradicating it from the body. The search for more effective treatment should continue.

References

11. Wang SP, Grayston JT. Immunologic relationship between genital TRIC, lymphogranuloma venereum, and related organisms in a new micro-