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Chlamydia/Mycoplasma
Do They Cause New-Onset Asthma in Adults?

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I. Introduction

The origins of adult-onset asthma are obscure. Five to six decades ago, some clinicians believed that asthma was primarily related to infection and that allergy, while important, played a secondary role (1,2). A decade ago, expert opinion held that asthma was a noninfectious allergic disease whose root cause was inflammation (3). Since then a growing body of evidence, reviewed in this book, has emerged to suggest again a significant role for viral and atypical infections in the pathogenesis of asthma.

Regarding the atypical organism *Chlamydia pneumoniae* (*Cpn*), Chapter 23 reviews the evidence that acute *Cpn* infection is associated with asthma exacerbations and Chapter 24 presents evidence relevant to a potential role for chronic *Cpn* infection as an asthma promoter. The focus of this chapter is on a third question about atypical infections and asthma: can these infections cause (initiate) new-onset asthma in adulthood?

II. Definitions of New-Onset Asthma

What is meant by new-onset asthma in adults? In the context of infection as a possible cause for asthma, it must be stated at the outset that many are exposed (infected)

but only some get asthma. This is particularly germane for *Cpn*, to which the majority of people worldwide are exposed one or more times during life (4). Thus, host reponse must be assumed to play a major role in this complex multifactorial syndrome. In defining new-onset asthma, therefore, pre-existing characteristics such as asymptomatic bronchial hyperreactivity, atopy, or other covariates may be contributing factors but are insufficient to define new-onset asthma. A reasonable working definition of new-onset asthma ideally includes the history of a first attack of characteristic symptoms (e.g., wheeze, shortness of breath, chest tightness, or cough) accompanied by objective evidence of reversible airway obstruction either spontaneously or after treatment. A weakness of this definition in the clinical setting is the retrospective nature of the history, with the possibility of unremembered or unrecognized previous symptomatic episodes. This weakness also applies to any prospective epidemiological study that does not begin at birth. This limitation notwithstanding, careful history-taking from reliable informants reporting new-onset asthma can produce consistent correlations with microbiological findings (5).

For purposes of this discussion, it is worthwhile to differentiate between new-onset asthma in adulthood (adult-onset asthma; AOA) and childhood-onset asthma that persists into adulthood (COA). AOA and COA have characteristically distinct clinical and epidemiological features, although there appear to be major overlaps between these syndromes for asthma appearing during the middle years (roughly ages 20–40). Compared to COA, AOA is associated with fewer markers of atopy (6), more likely to affect women (7), more clinically severe (8,9), less likely to remit (10,11), and associated with more fixed obstruction (12–14). It is unclear, however, whether COA and AOA are different diseases with different underlying causes or different clinical presentations of the same underlying cause. Nor do we know what factors determine whether a child with asthma will go into remission, reactivate asthma later, or persist with symptoms into adulthood.

AOA is a clinical entity that, unlike classic COA, does not fit cleanly into the rubric of asthma as a noninfectious atopic disease. From the perspective of the primary care clinician, patients with AOA often deny previous respiratory problems, do not have a history of clinical allergy, and are skin test negative. Furthermore, patients developing AOA often recall that their asthma symptoms started after an acute respiratory illness such as acute bronchitis, pneumonia, or an influenza-like illness (15). This description applies most clearly to AOA beginning after age 40. Clinical observations (l6,17) and prospective epidemiological studies (18-20) also support an association between bronchitis/pneumonia and subsequent adult asthma. While these observations have often been interpreted to suggest that the preceding illnesses were actually misdiagnosed asthma symptoms or merely viral exacerbations of previously unrecognized asthma, a third possibility is that acute infectious illnesses might actually play a role in asthma initiation. Of additional interest are the facts that epidemiological associations of respiratory illness and subsequent asthma also pertain to children (21) and adolescents (22) and that the association of atopy with asthma in both children and adults is not as great as previously believed (23).

III. Illness Burden Due to Various Forms of Asthma

The economic burden (direct and indirect costs) of asthma illness in adults is equivalent to the economic burden in children (24,25). What proportion of the economic burden of adult asthma is borne by those with AOA, compared to those with COA persisting into adulthood, is an open question. In adults with active asthma, AOA may account for a greater proportion of active disease than COA (26). It is likely that the morbidity and economic burden due to AOA are disproportionately greater than that of persistent COA since, as mentioned earlier, AOA tends to be more severe and more associated with fixed obstruction (i.e., chronic obstructive pulmonary disease; COPD), the consequences of which (disability and premature death) have not been accounted for in current economic analyses of asthma (24,25,27). An example of the long-term consequences of severe AOA is given in the following clinical case report.

IV. Asthma or COPD?

A. Asthma

On July 15, 1981, a previously healthy 55-year-old nonsmoking man was seen for complaints of nasal congestion, sore throat, and cough lasting 2 weeks. He was diagnosed with acute bronchitis and treated with antihistamines, decongestants, and a 1-week course of erythromycin. Respiratory symptoms improved temporarily and then relapsed to include wheezing, shortness of breath, and nocturnal awakening with respiratory trouble. On September 21 his pulmonary function was normal (forced expiratory volume in 1 s [FEV_1] 87% predicted) with no significant bronchodilator response. On October 19 he presented with a severe exacerbation of asthma symptoms and had decreased pulmonary function (FEV_1 25%) that responded to a burst of oral prednisone (postprednisone FEV_1 119% predicted). He later continued to experience severe exacerbations of asthma requiring steroid pulses and was hospitalized in late 1981. This description of a patient I encountered is characteristic of the so-called infectious asthma syndrome (15) and also typifies the often rapid deterioration in lung function noted in AOA in older adults (28).

B. COPD

On December 18, 1997, I again encountered this patient, now 71 and retired. He was being treated with theophylline 300 mg three times daily, inhaled albuterol 2 puffs four times daily, terbutaline sulfate 5 mg orally three times daily, and prednisone 10 mg alternating with 5 mg orally each day. His FEV_1 while taking steroids was 50% predicted and his FEV_1/forced vital capacity (FVC) ratio was 48%. His medications controlled, but did not eliminate, persistent cough, wheezing, shortness of breath, and chronic sputum production. He appeared emaciated, older than his stated age, and was unable to engage in vigorous physical activity. He suffered from multiple lumbar compression fractures due to osteoporosis. He met diagnostic

criteria for chronic bronchitis. His *Chlamydia pneumoniae* IgG titer was 1:64, without an IgM response. On May 24 1998, he died unexpectedly in cardiac arrest with documented ventricular fibrillation, presumably from an acute myocardial infarction. Postmortem examination was not performed.

This case illustrates the shortcomings of cross-sectional diagnostic thinking that does not acknowledge the natural history of disease. Morbidity attributable to AOA should include long-term complications including loss of lung function, decreased quality of life, complications of anti-inflammatory therapy, and decreased life expectancy. This patient's story also highlights known epidemiological associations among asthma, chronic bronchitis, and heart disease (29-32) that remain unexplained.

V. Asthma Temporal Trends

A key factor motivating publication of this book is the observed increase in asthma in westernized countries. Indeed, a consensus has emerged that asthma prevalence in both children and adults has increased worldwide in recent decades (33). This increase cannot be satisfactorily explained by changes in traditional asthma risk factors (34). Since one purpose of this book is to stimulate research into interactions between infectious agents and increasing asthma, it is worthwhile noting an association between the increasing population burden of *Cpn* infection and increases in asthma, in both adults and children of both genders (Fig. 1). While these ecological data (from different study groups in the same place and times) cannot prove causality, the data presented in Figure 1 do support the suggestion that research into the current asthma epidemic should include a search for infectious agents as a cause.

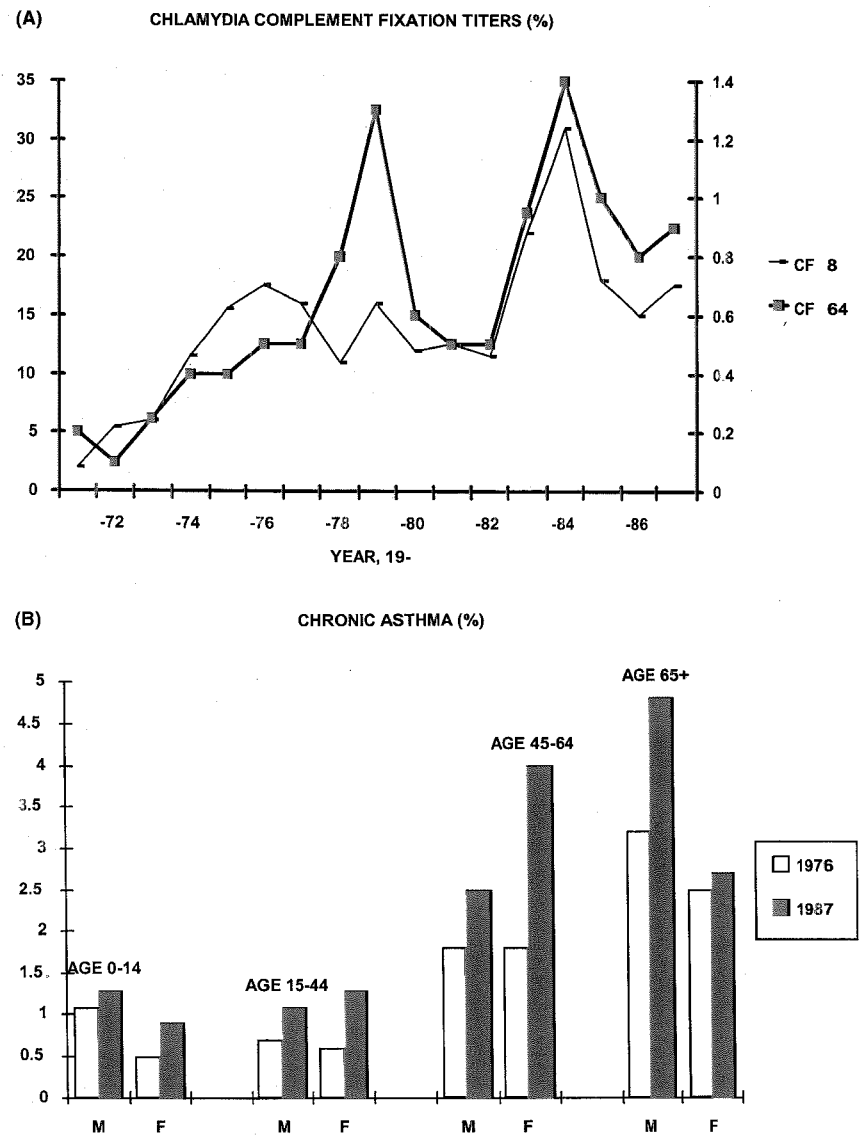

Figure 1 Temporal trends in *Chlamydia* antibodies and asthma in Finland over two decades. (A) *Chlamydia* complement fixation titers in sera sent for virus serological screening 1971–1987 (5000–14,000 patients annually, total number of sera studied: 162,401). These data almost certainly represent *Cpn* infection, as *Chlamydia trachomatis* and *C. psittaci* infections are rare in Finland and another epidemic of CF titer in Denmark was *Cpn*. [Mordhorst CH, Wang SP, Grayston JT. Epidemic "ornithosis" and TWAR infection, Denmark, 1976-85. In Oriel D and Ridgeway G (eds). Chlamydial Infections: Proceedings of the Sixth International Symposium on Human Chlamydial Infections. Cambridge, Cambridge University Press, 1986, pp 325-328]. (From Puolakkainen M, Ukkonen P, Saikku P. The seroepidemiology of Chlamydiae in Finland over the period 1971 to 1987. Epidemiol Infect 1989; 102: 287–295.) (B) The self-reported prevalence of chronic asthma in the Finnish population, by age and gender, in 1976 and 1987. The samples were representative of the Finnish noninstitutionalized population and the number of interviewed adults was 16,413 in 1976 and 13,138 in 1987. (Adapted from Klaukka T, Peura S, Martikainen J. Why has the utilization of antiasthmatics increased in Finland? J Clin Epidemiol 1991; 44:859-863.)

VI. *Chlamydia/Mycoplasma* and Asthma Initiation in Adults

The amount of available information on whether *Cpn/Mpn* can intiate asthma is much smaller than the body of evidence for chronic atypical infection in asthma (35). Factors contributing to the paucity of available data include the facts that initial episodes are relatively rare compared to prevalent disease episodes, patients do not always seek medical attention for them, and if an initial encounter does occur, it is usually in a primary care setting where research does not often occur. Initiating events may be obscured or undetectable years later when chronic asthma presents to academic medical centers, where most asthma research is currently performed. Thus, current published evidence for an infectious initiation for AOA is limited to case reports and case series from primary care settings (Table 1).

Table 1 Evidence That *Chlamydia/Mycoplasma* Can Cause New-Onset Asthma in Adults

Reference	Type of study	Findings
Mpn		
(36)	Case series	*Mpn* infection in eight adults admitted with wheezing, four had no prior hx of asthma. No long-term follow-up.
(37)	Case report	Association of *Mpn* antigen with initial onset of bronchial asthma and with *Mpn*-specific IgE antibodies
Mpn/Cpn		
(38)	Case report	A case having initial onset of bronchial asthma, probably induced by prolonged *Mpn* infection, accompanied by concurrent highly suspicious chlamydial infection (in Japanese)
Cpn		
(39)	Case report	Serological proven acute *Cpn* infection initiated severe chronic asthmatic bronchitis in an adult
(40)	Case series	Nine patients wheezed during serologically acute *Cpn* infection: of these, four had newly diagnosed asthma after illness
(41)	Case report	38-year old previously nonasthmatic physician developed prolonged asthmatic bronchitis following culture and serologically proven acute primary *Cpn* infection; positive culture persisted despite prolonged doxycycline treatment
(42)	Case report	An adult with persistent symptoms of new-onset reactive airways disease following a culture and serologically proven acute primary *Cpn* infection
(5)	Case series	10 adults with new-onset wheezing had serological proven acute primary (8) or secondary (2) infection: of these, 5 developed chronic asthma and 1 chronic bronchitis along with serological profiles compatible with chronic infection.

A. Case Reports and Case Series

Mycoplasma pneumoniae

While ample evidence exists for acute *Mpn* infection exacerbating established asthma (43,44) only a few reports suggest that *Mpn* can initiate asthma in adults (36-38). Buckmaster et al. (36), described eight adults with wheezing and *Mpn* infection, four of whom had no prior history of asthma, but no long-term follow-up was available. Yano et al. 1994 (37) presented a meticulously detailed case report of a previously nonasthmatic 37-year-old man with community-acquired pneumonia and hemolytic anemia who had serologically diagnosed acute *Mpn* infection. One month after macrolide treatment and resolution of pneumonia, the patient developed asthma symptoms and reversible airways obstruction. Two months later, and then again 1 year after initial onset of asthma, bronchial hyperresponsiveness to methacholine was demonstrated. IgE antibody against *Mpn* was detected 1 and 7 months after illness onset and a skin prick test to *Mpn* was positive 2 years after onset. Further evidence for direct involvement of *Mpn* in the patient's asthma symptoms was demonstration of bronchial hyperreactivity to inhaled *Mpn* antigen but lack of response to inhaled *Mycoplasma salivarium* antigen. Lastly, IgE antibodies to *Mpn* were demonstrated in an additional 7 of 13 patients with pneumonia (not asthma) compared to none of 10 controls, suggesting that IgE antibody can be generated also in *Mpn*-infected nonasthmatic patients. The authors also made the interesting observation that, in total, six of the eight patients with detectable *Mpn*-specific IgE had persistent cough lasting 3 months, although only the one case patient had symptoms or signs of asthma. This case report could not answer the question of whether the case patient's atopic state (ability to produce IgE) preceded or followed the acute *Mpn* infection. This report also suggests that prescence of *Mpn*-specific IgE was not always sufficient to cause asthma, since other infected patients with *Mpn*-specific IgE did not develop asthma after pneumonia.

In another report, the same authors (38) described a case of new-onset asthma that appeared to be associated with *Mpn* and chlamydial coinfection. This observation has potential significance since coinfections with *Cpn* and other respiratory pathogens are common (45) and it has been speculated that *Cpn* may serve as a cofactor to enhance pathogenicity of these other agents (46).

Chlamydia pneumoniae

Evidence that *Cpn* can intiate asthma is more common than for *Mpn* but it is unclear whether this is due to a true difference in incidence or to the fact that *Cpn* has been more often studied. Several case reports (39,41,42) have documented new-onset reactive airways disease, sometimes called asthmatic bronchitis, in patients with serological, culture, and/or polymerase chain reaction (PCR) test-proven acute infection. As part of a prospective study into the role of *Cpn* and *Mpn* in community-acquired respiratory illnesses (bronchitis and pneumonia), Hahn et al. (40) described nine patients with serologically proven acute *Cpn* infection who wheezed: four of

these patients were newly diagnosed with chronic asthma after the reported infection episode. No comparable associations were found for acute *Mpn* infection, however. The diagnostic accuracy of these findings was obscured, however, by the fact that pulmonary function testing was not routinely performed as part of the study. Furthermore, serological criteria for acute infection used in the study included both a fourfold titer rise (universally accepted as valid) and a single high titer of 1:512 or greater (not universally accepted as valid, since it might indicate previous exposure or ongoing chronic infection). In a follow-up analysis of the significance of the two different titer categories in asthma, Hahn et al. (5) reported that incident wheezing and prevalent asthma, confirmed by pulmonary function testing, demonstrated different serological patterns of so-called acute *Cpn* antibodies in adults. Of 20 adults meeting serological criteria for acute infection (both titer categories) 10 adults had a first ever (incident) wheezing episode and 10 others had chronic (prevalent) asthma. Notable was that none of the chronic asthmatics had evidence of a fourfold titer rise whereas all 10 of the first ever wheezers had a fourfold rise in titer, of whom 8 also had detectable IgM antibody indicating an acute primary infection. The other two had no detectable IgM, indicating an acute secondary (re)infection. Another significant finding was the prospective observation that 6 of these 10 patients with incident wheezing subsequently developed chronic asthma (n = 5) or chronic bronchitis (n = 1) along with a serological profile that resembled that of the 10 patients who already had chronic asthma. This report provides the strongest available evidence that acute *Cpn* infection can lead to new-onset chronic asthma in adults. The likelihood of a causal association between the acute infection and development of chronic asthma is further strengthened by the additional observation that prolonged courses of antichlamydial antibiotics administered to those who developed new-onset asthma resulted in disappearance of asthma symptoms and return of normal pulmonary function (47).

B. Epidemiological Data

The available epidemiological evidence suggests that the population-based proportion of asthma cases attributable to atopy is usually less than 50% (23). The (more limited) seroepidemiological data for *Cpn* in asthma suggest that half of adult asthma cases could be attributable to this infection (48).

What proportion of AOA is attributable to *Cpn* or *Mpn* infection is unknown and can only be answered conclusively by large prospective studies. In the absence of such studies it is worthwhile examining some indirect evidence. Melbye et al. (49) performed a prospective microbiological and clinical study in over 500 adult general practice patients without known asthma or COPD to determine the occurrence of airflow limitation and the frequency of significant reversibility during acute upper and lower respiratory illnesses. They measured spirometry (before and after bronchodilator) during illness and at follow-up after the acute phase (4–5 weeks later). They compared results of pulmonary function testing with microbiological testing for five respiratory viruses (influenza A and B, RSV, parainfluenza 3, and adenovirus), *Mpn*, and *Cpn*. Patient Groups with detectable viral or *Mpn* infections

showed improvement in pulmonary function at follow-up. Only patients with evidence for *Cpn* infection had worse pulmonary function at follow-up than during acute illness, suggesting a unique ability for *Cpn* to produce long-lasting obstruction after acute infection. Furthermore, *Cpn*-infected patients had the lowest rate of clinical recovery at follow-up (71% for *Cpn*, 84% for viral infection, and 92% for *Mpn*).

Additional unpublished epidemiological evidence relating to the topic of this chapter is presented here for the first time. In a retrospective study, I have investigated relationships between asthma duration and the quantities of IgG and IgA antibodies against *Cpn* in seroreactive adults with asthma to determine any associations that might support or reject the hypothesis that asthma began after acute *Cpn* infection that had occurred sometime in the past.

Methods

Adult outpatients (104) (mean age 42 years) with acute asthmatic bronchitis (AAB, 24 patients) or chronic asthma (CA, 80 patients) were selected from a community-based primary care clinic. AAB was defined as acute bronchitis with wheezing in a patient without a previous diagnosis of asthma. CA was diagnosed based on persistent asthma symptoms and results of pulmonary function testing. The date of first reported wheezing symptoms was used to calculate asthma duration. *Cpn*-specific IgG and IgA antibodies were measured using the microimmunofluorescence (MIF) test (50). IgG was adsorbed prior to IgA testing (51).

Patients who were seroreactive against *Cpn*-specific IgA (titer of 1:16 or greater in the MIF test) were categorized by asthma duration (<1 year, 1 to <3 years, 3 to <10 years, and 10+ years). Geometric mean antibody titers (GMT) were calculated separately for these patient groups. The correlation between asthma duration and antibody titer level (after ordinal transformation) was calculated, and analysis of covariance (ANOCOVA) was used to control for potential confounders such as age of asthma onset and smoking. P values less than 0.05 are reported as significant.

Results

Fifty-five patients (53%) with reactive airways disease were IgA seropositive. All 55 patients who were IgA seropositive were also IgG seropositive (1:16 or greater). There was no significant correlation between asthma duration and IgA titer levels. However, these was a significant inverse correlation of asthma duration and IgG titer levels ($r = -0.34$, $p < 0.001$) that persisted after controlling for IgA titer magnitude, age of asthma onset, and smoking by ANOCOVA. The relationship between asthma duration and IgG titer was not strictly linear, however (see Fig. 2). Patients with asthma duration between 1 and 3 years had the highest IgG GMT titer level, and patients with asthma more than 10 years had the lowest titers. As previously noted, IgA titer levels were similar for all categories of asthma duration, even for patients with asthma for more than 10 years. These data suggest that asthma duration is, along with age, gender, and smoking, an additional confounder of the association between *Cpn* IgG antibodies and asthma. This confounding is a possible

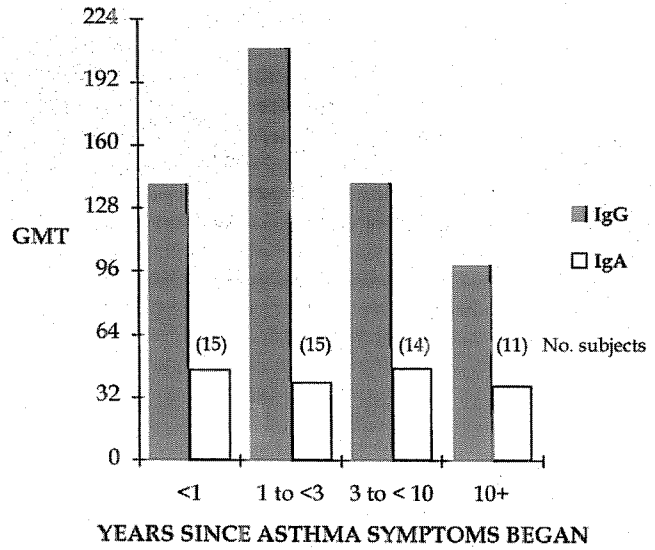

Figure 2 *Chlamydia pneumoniae* antibodies (GMT, y axis) and asthma duration (x axis) in 55 adult patients with asthma encountered in a family practice outpatient setting. All subjects were IgG and IgA seroreactive (titers ≥ 1:16) against *Cpn*. Figures in parentheses are the number of asthma patients in each group.

explanation for the observation that when both IgA and IgG antibodies against Cpn are measured in case–control studies of asthma, significant associations are more often reported for IgA than for IgG (35,52).

Had these data been obtained prospectively on the same cohort over time, it would be proper to conclude that IgG titers initially increased over the first to third year after symptom onset, then declined significantly over the remainder of the 10 year period, whereas IgA titers remained constant. Since IgA titers have a relatively short half-life (7 days) and reflect mucosal antigen stimulation, it would also have been reasonable to conclude that persistent detection of Cpn-specific IgA was evidence for persistent infection. It would also be reasonable to suggest that the initial rise and subsequent fall in IgG titer provided evidence that acute infection might have occurred around the time that asthma symptoms first began. These interpretations cannot be made, however, since the data were actually collected retrospectively on different patient groups. The data are, however, suggestive and illustrate the importance of performing prospective microbiological and clinical studies.

A recent prospective study (the Caerphilly Prospective Heart Disease Study) followed a cohort of 2512 middle-aged Welshmen for almost 14 years, but did not collect information on chronic respiratory symptoms or diagnoses (53). Nevertheless, *Cpn* IgG and IgA antibodies were measured on stored sera obtained at entry

from a subgroup of subjects, and titers were analyzed in relation to self-reported use of a broad range of medications that might have been prescribed for respiratory symptoms (beta-adrenergic or antimuscarinic bronchodilators, theophyllines, inhaled steroids, cromoglycate, or oxygen). Death certificate information on deaths from respiratory illnesses and lung function decline between entry and the 5 year visit (no further lung function testing was available) were also analyzed. Positive quantitative associations were found between *Cpn*-specific IgA titer magnitude and medication use at baseline ("prevalent") and new medication use during follow-up ("incident") but neither trend attained statistical significance. Using IgA seronegative (<1:8) patients as the reference group, the odds ratio (95% confidence interval) associating IgA titers ≥ 1:16 with "incident" cases was 1.7 (0.83–3.48). No comparable trends were noted for IgG antibodies nor were any antibody associations found for respiratory deaths or lung function decline. Given the nonspecific nature of medication use as a proxy for asthma or COPD, the short (5 year) interval over which lung function decline was measured and the small number of respiratory deaths, these results are hard to interpret. They do not conclusively exclude a role for *Cpn* infection as a cause for "incident" respiratory disease in adults, and they do illustrate the need for further prospective studies.

VII. Future Prospects

A. Prospective Studies

Two types of prospective studies could help to answer the question of whether *Cpn*/*Mpn* can cause new-onset asthma in adults. The first type of study is the classic population-based prospective study, resembling the Tucson Epidemiologic Study that has provided insight into the natural history (28,54) and immunopathology (6) of asthma. A prospective study should include (in addition to detailed clinical information, pulmonary function testing, and measures of atopy) microbiological testing for *Cpn* and *Mpn* including serial serology and PCR on respiratory secretions and on peripheral blood mononuclear cells (PBMCs) (55). Since the incidence of AOA is about 1:1000 per year (56), this study will need to follow 10,000 adults over a decade to accrue approximately 100 cases of new-onset adult asthma. This study would therefore be expensive.

An alternative strategy that might yield comparable information at a reduced cost would be to enroll-high risk patients via a large geographically dispersed practice-based research network (PBRN). This strategy might decrease the required sample size and, possibly, the follow-up interval needed to accrue 100 new cases of AOA. Although PBRN populations are not random samples of the general population, the study sample can nevertheless be representative of a random sample of the adult primary care population, as long as the sample is large (57,58). Since AOA often begins after an acute respiratory illness that persists (15), it is reasonable to suggest that one recruitment strategy would be to enroll as high risk those patients encountered with acute bronchitis or pneumonia who deny a prior history of asthma symptoms. The risk of being diagnosed with asthma within 3–4 years after acute

bronchitis was 3.7% per year in a primary care study (16) and 4–6% in a prospective cohort study (20). Risk of asthma diagnosed after pneumonia, at least in children and teenagers, may be even greater (59). An advantage of this strategy is the ability to study relationships between these acute lower respiratory tract illnesses and other chronic sequelae such as chronic bronchitis and chronic sinusitis. A disadvantage is the possibility that clinical interventions might confound the results. This problem can also occur in classic epidemiological studies that, unlike PBRN studies, do not have comparable access to treatment details.

This type of PBRN study might not have been feasible (at least in North America) one or two decades ago. Currently, however, a growing number of North American PBRNs have a track record of performing quality research on a variety of primary care topics, including asthma (60). European centers have a successful track record of collaboration between general practitioners and specialists in the study of respiratory illnesses (61) and asthma (62). Prospective studies on infectious causes for asthma in adults would be an ideal framework for international collaboration between PBRNs.

Previously published prospective epidemiological studies that have investigated a role for *Cpn* in asthma onset or in airflow limitation have been limited by lack of any clinical respiratory diagnoses (53) or by dependence on a history of a physician diagnosis of asthma without any supporting pulmonary function evidence (63). A properly conducted PBRN study can include detailed clinical information (16,40) along with objective evidence for reversible airway obstructions (5,17,49,64,65) to support a diagnosis of asthma, thus increasing both internal and external validity.

B. Animal Studies

Another approach to the question of whether *Cpn* infection initiates asthma is to explore the effects of *Cpn* infection in existing animal models of asthma. This approach requires choosing an animal model in which both asthma and infection can be established. For example, Hsiue et al. (66) recently isolated *Cpn* from lung homogenate and from alveolar macrophages obtained by bronchoalveolar lavage after intranasal inoculation of *Cpn* in guinea pigs. Further studies of infection and bronchial hyperresponsiveness are planned. Mouse and rabbit models have been commonly used to study *Cpn* lung infection (67,68). Animal models for asthma are also available. To my knowledge, however, there are as yet no published studies on the effects of *Cpn* acute primary, secondary, or chronic infections on bronchial hyperreactivity or airway obstruction in animal models.

VIII. In Vitro and In Vivo Observations Relating to Pathogenesis

A growing body of in vitro experimental evidence demonstrates that *Cpn* infection of relevant human cell lines is capable of inducing inflammatory mediators that are

Table 2 *Chlamydia pneumoniae*: Potential Mechanisms in Asthma Pathogenesis

Observations(s)	Potential role in asthma
Cpn induces pulmonary epithelial ciliary stasis (69)	Mucociliary clearance is impaired in adult asthma (70)
Cpn-specific IgE antibodies are associated with culture-positive childhood asthma (71)	IgE incites acute bronchospasm and may lead to chronic inflammation
Cpn-specific IgE antibody is associated with adult-onset asthma (65)	IgE, but not skin test positivity, is associated with adult-onset asthma: the "missing antigen"? (6)
Cpn infects human monocytes and induces TNFa, IL1-b and IL-6 in vitro (72)	Pulmonary inflammation is the hallmark of asthma
Cpn infects human alveolar macrophages in vivo and in vitro and induces reactive oxygen species, TNF α, IL-1β, and IL-8 in vitro (73)	Inflammation and free radical production; upregulation of IgE reponses by dysregulation of alveolar macrophage function? (74)
Cpn infects human smooth muscle cells in vivo (75)	Demonstrated in vascular smooth muscle; effect on bronchial smooth muscle hyperreactivity?
Cpn infects human bronchial smooth muscle cells in vitro, to produce IL-6 and basic fibroblast growth factor (76)	Inflammation and airway remodeling
Cpn heat shock protein 60 (hsp60) antibodies are associated with adult asthma (65,77,78)	Chlamydial hsp60 has been implicated in other chronic inflammatory chlamydial diseases (pelvic inflammatory disease, tubal infertility, trachoma)
Cpn contains a chlamydial lipopolysaccharide (LPS) related to gram negative endotoxin	Bacterial LPS augments IgE response to allergen in an animal model (79) and induces bronchial hyperresponsiveness in humans correlated with release of IL-6 and IL-8 from alveolar macrophages and monocytes in vitro (80)

thought to play a key role in asthma pathogenesis (Table 2). Less is known about the ability of *Mpn* in this regard, but the lack of evidence is related more to the difficulty in studying this slow growing organism than to an established body of negative evidence. Regarding asthma initiation specifically, several mechanisms could be important. As well as generating an inflammatory response, acute *Cpn* infection can damage bronchial epithelium and impair mucociliary clearance by producing ciliary stasis (69). It has been hypothesized that bronchial epithelial disruption could produce hyperreactivity and enhance penetration of allergens after viral infection (81), a hypothesis that applies also to acute atypical infections. As described elsewhere in this book, a growing body of evidence suggests significant interactions between viral infections and the atopic immune response (82). Preliminary studies suggest that a similar interaction may be operative for *Cpn* lung infection (65,71,79). Of potential importance are observations that *Cpn* infection of hu-

man bronchial smooth muscle cells can induce basic fibroblast growth factor (76) and that heat shock protein 60 is associated with asthma (65,77,78). Both observations may be relevant to production of airway remodeling and accelerated decline of lung function in asthma. Thus, current in vitro evidence is consistent with a role for *Cpn* not only in asthma initiation but also over the long course.

IX. Conclusions

Prospective clinical observations drawn mainly from primary care settings show that acute *Cpn* (and to a lesser extent *Mpn*) infections are associated with de novo wheezing that, in some patients, becomes persistent and leads to a diagnosis of asthma with all the typical clinical and spirometric characteristics to support that diagnosis. Of considerable additional interest are a limited number of examples of induction of complete remissions (at least for a year or two) in some of these patients following prolonged courses of antibiotics with activity against atypical infections. Some of these reports have even documented microbial eradication associated with asthma remission. Thus, the available evidence strongly supports a role for acute atypical infections in asthma initiation, at least in a small subset of patients, and this possibility is supported by a limited number of in vitro pathogenesis studies, outlined above.

A role for initiation cannot be considered proven, however, because none of the clinical observations summarized above can rule out the possibility of low-grade so-called asymptomatic asthma that was exacerbated but not initiated by atypical infection. Thus, long-term prospective studies of nonasthmatic subjects are necessary to determine the quantitative role of *Cpn/Mpn* infection as a cause of new-onset asthma in adults.

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