Chlamydia pneumoniae and the "Dutch Hypothesis"

David L. Hahn

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exposure to furred pets, since total exclusion of the pet from the home is so simple and effective. For patients with the courage to get rid of their pets, it is important to remind them that the full benefits of their action will be reaped only over many months, since pet allergen, especially cat allergen, can persist for prolonged periods at significant levels in the home.[5]

In summary, all patients with asthma deserve an allergy evaluation to identify sensitization to common inhaled allergens. Avoidance of allergens to which a patient with asthma is sensitized is an integral and effective part of asthma management. Indoor allergens are of particular importance because of the large amount of time spent indoors. The indoor allergens most likely to be relevant are dust mites, cockroaches, and furred pets. Avoidance measures for dust mites[5] and cockroaches[9] are well described and are probably effective at improving asthma control if the measures are strictly adhered to. Air filtration devices are unlikely to be important or effective over and above the more usual measures, given the characteristic distribution of these allergens in the home. Air filtration devices are effective at reducing levels of pet allergen in the home and may improve asthma control when combined with exclusion of the pet from the bedroom. This is likely to be much less effective than ridding the home of the pet completely and is therefore difficult to recommend.

Pierre Ernst, MD
Montreal, PQ, Canada

Dr. Ernst is associated with the Division of Clinical Epidemiology, McGill University Health Centre.
Correspondence to: Pierre Ernst, MD, Division of Clinical Epidemiology, McGill University Health Centre, Hôpital Royal Victoria, 687 Avenue des Pins Ouest, Bureau R4.29, Montréal, PQ, Canada H3A 1A1

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Chlamydia pneumoniae and the "Dutch Hypothesis"

One argument casting doubt on the validity of early epidemiologic studies associating smoking with lung cancer was the nonspecificity of the association. Since smoking also was linked to a variety of other airway diagnoses such as chronic bronchitis and COPD, critics argued initially that the associations with smoking were too nonspecific to be causal. *Chlamydia pneumoniae*, a ubiquitous intracellular human respiratory pathogen with a propensity to produce chronic infection, has likewise been associated with many respiratory and nonrespiratory conditions, from Alzheimer disease to asthma, casting doubt on specificity and, hence, casting doubt on the likelihood of causation. Thus, it is interesting to read an epidemiologic report that finds no association with one class of conditions (the metabolic syndrome) yet confirms and extends a previously reported association with another class (chronic respiratory illness).

In this issue of *CHEST* (see page 1587), Falck et al studied a series of 796 male and female adult outpatients and relatives who were encountered by the primary author during his medical practice at a healthcare center in Kopparberg, Sweden. Blood specimens were obtained from 631 patients who had acute or chronic upper or lower respiratory tract complaints, and the remaining 165 specimens were obtained from healthy family members. Specimens were tested for *C pneumoniae*-specific IgG and IgA antibodies using the microimmunofluorescence (MIF) test. The authors report the results of a nested case-control study of all 100 case patients with specific *C pneumoniae* IgA antibody titers of $> 1:128$ that persisted over at least 6 months, using as control subjects 100 patients who had been matched for age and sex with persistently low titers (*ie*, $< 1:32$) over a comparable time period. Since the majority of patients in the sampling frame (631 of 796 patients) had respiratory complaints and most were potentially eligible to be selected as control subjects,

this study design provides a more rigorous test of an association with respiratory illness than if the control subjects had been chosen from an entirely asymptomatic population. Purists may be concerned about the heterogeneity of the study population, but I will argue later that this characteristic is a strength, not a weakness.

IgA Antibody: Method and Interpretation

Some authors have criticized the MIF test, but the Centers for Disease Control and Prevention and its Canadian counterpart (Laboratory Centre for Disease Control)[1] currently recommend the MIF test as the "gold standard" serologic test for *C pneumoniae*, as long as the test is performed in an experienced laboratory and is interpreted by an experienced serologist, which was the case in this study. Importantly, for other laboratories wishing to replicate this work, the sensitivity of the IgA MIF test was enhanced by the overnight incubation of the serum samples with *C pneumoniae* antigen prior to the application of the detection reagent. Assuming that the test is valid, what is the correct interpretation of persistent IgA seropositivity? Since this study did not systematically test patient tissue for the presence of the organism, it is not possible to conclude from these results alone that the persistent detection of IgA antibodies is diagnostic for chronic infection. In previous work, Falck et al[2] correlated *C pneumoniae* throat tissue infection, specific IgA antibodies, and chronic symptoms in a subset of patients with chronic pharyngitis. This correlation will be difficult to reproduce in primary care patients with chronic lower respiratory tract illnesses, who may be understandably reluctant to undergo lung biopsies. A growing body of indirect evidence supports the conclusion that IgA antibodies may serve as a marker for persistent *C pneumoniae* infection,[3,4] but these epidemiologic data should serve as hypothesis-generating material for further studies, not as proof of diagnosis in individual patients.

With this caveat in mind, what did Falck et al show? Because of previous studies linking chronic *C pneumoniae* infection with atherosclerotic heart disease and with a high-risk atherogenic lipid profile (*ie*, low high-density lipoprotein and high triglyceride levels) that is also suspected to be caused by chronic, low-grade, Gram-negative bacteremia (*C pneumoniae* is derived from Gram-negative ancestors), Falck et al first sought to associate IgA antibodies with the clinical manifestations of the metabolic syndrome and failed to show an association. This failure does not necessarily contradict the previous findings but does suggest that, taken as a group, not all clinical syndromes that are risk factors for atherosclerosis (*ie*, the metabolic syndrome) are associated with persistent *C pneumoniae* infection, as measured by the IgA antibody level. On the other hand, Falck et al did find associations of *C pneumoniae* IgA antibodies with a heterogeneous group of chronic respiratory syndromes and with objective evidence for respiratory obstruction, as measured by peak expiratory flow rates. The chronic respiratory illnesses included clinical diagnoses of upper respiratory tract disorders, asthma, and chronic bronchitis/emphysema. Again, the issue of nonspecificity arises: is it credible that *C pneumoniae* could be causally associated with so many different respiratory syndromes, or is this nonspecificity due to confounding by other unmeasured variables? Evidence now exists that the *C pneumoniae* organism is present in the target tissues of patients with the syndromes associated by Falck et al with the presence of IgA antibodies, as follows: chronic upper respiratory illness[2]; asthma[5]; and chronic bronchitis/emphysema.[6,7] Thus, it is worthwhile to consider the possibility that the serologic associations might, as for smoking, actually be causal.

The Dutch Hypothesis

In the United States, most research into obstructive airways disease assumes a "splitting" approach. Asthma is distinguished from chronic asthmatic bronchitis, which is distinguished from COPD. Lip service may be given to the fact that sometimes these conditions may seem to overlap, but study populations are usually chosen to exclude, rather than to include, heterogeneity. A competing view is that this spectrum of obstructive airways disease syndromes is related to similar etiologic and pathologic processes. This "lumping" approach is more prevalent among European investigators and has become known as *the Dutch hypothesis*.[8] The clinical syndromes of asthma, chronic bronchitis, and emphysema, referred to by the Dutch as *chronic nonspecific lung disease*,[9] are often difficult to distinguish in clinical practice, may respond to similar treatments, and are linked in epidemiologic studies.[10] Having practiced family medicine for >20 years, I have had the opportunity to observe many patients with attacks of wheezing that occurred only during episodes of acute respiratory illness (acute asthmatic bronchitis [AAB]), other patients with "pure" chronic asthma (CA), and yet others with "burnt out" asthma and COPD (asthma with chronic airway obstruction [AS-CAO]) whose prognoses were par-

ticularly grim. I have presented three particular case reports of these syndromes (AAB, CA, and AS-CAO) to medical groups and have asked listeners the following question: are these cases really separate entities or are they different stages in the natural history of the same disease? Regarding the three particular case reports, I know the answer, since I chose to describe the same individual encountered in my practice over a 17-year time span.

Because it has a cross-sectional design, the study by Falck et al cannot directly address the Dutch hypothesis, but does it favor one paradigm over another? My view is that the study of Falck et al supports the Dutch hypothesis because it suggests a common underlying etiopathology (*ie*, chronic infection) in a spectrum of chronic lower respiratory tract illnesses. Furthermore, the study of Falck et al suggests that chronic infection also may be involved in persistent upper airway illnesses. The possibility that *C pneumoniae* provides the link to support the Dutch hypothesis has been mentioned before,[11] and data for serologic evidence for *C pneumoniae* infection in patients with AAB, CA, and AS-CAO[3] are available, but Falck et al provide supporting evidence from the largest series published so far.

Prospective studies of the microbiology of obstructive airways disease will be required to clarify the debate. Such studies are clearly warranted and, in my opinion, will be more valuable if the inclusion criteria are broad, rather than limited to arbitrarily defined subgroups of obstructive airways syndromes. Certainly, one approach is to divide patients into clinical syndromes based on history data alone, but this "splitting" approach does not account for the following: (1) the natural history of obstructive airways conditions that may evolve over a lifetime, (2) the fact that airway disease-related variables (*ie*, age, sex, smoking history, pulmonary function, and markers for atopy) have unimodal and continuous distributions across clinical diagnoses, and (3) the observation that a significant minority of patients with persistent symptomatic reversible airway obstruction cannot be categorized.[9] Because the diagnosis of reversible airway diseases is subject to various interpretations, the results of different studies may be hard to compare. The use of functional inclusion criteria, as advocated also by others,[9] guarantees an unbiased description of the study population.

The final message contained in the study by Falck et al is the importance of practice-based research and laboratory collaboration. Community-based practices are where patients are encountered in a longitudinal fashion over a lifetime. Clinical research in general, as well as asthma research in particular, can benefit from widespread and systematic support for clinicians in practice who also choose to perform collaborative research. In the meantime, we must depend for information on the efforts of the few existing primary care-based clinician-researchers such as Dr. Falck, who is to be commended for his dedication and persistence.

David L. Hahn, MD, MS
Madison, WI

Dr. Hahn is a member of the Department of Family Practice, Dean Medical Center, and Clinical Professor, Department of Family Medicine, University of Wisconsin Medical School.
Correspondence to: David L. Hahn, MD, Arcand Park Clinic, 3434 E Washington Ave, Madison, WI 53704-4155; e-mail: dlhahn@facstaff.wisc.edu

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