Asthma nervosum

To the Editors:

The name ''asthma nervosa'' [1] is linguistically incorrect. *Asthma* is a Greek neutral noun in a language that tries hard to keep its genders apart. *Nervosa* is a Latin adjective and this language also does not mix the genders: *nervosa* is feminine (as are *anorexia* and *bulimia*, two conditions for which *nervosa* is appropriate). Therefore, we should refer to *asthma* as *nervosum* (both neutral). This may sound slightly odd in English, and therefore, I would have no objection to ''nervous asthma''. However, if we want to pay tribute to the Classics, we should try to use them as correctly as possible.

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Respiratory *Chlamydophyla pneumoniae* resides primarily in the lower airway

To the Editors:

We read with interest the article by WANG *et al.* [1], which explored inflammatory phenotypes in adults and children with acute asthma. Their findings noted a striking paucity of *Chlamydophyla pneumoniae* organisms, even in patients with acute, neutrophilic asthma, and they concluded that: ''The aetiology of neutrophilic asthma is unknown and is not explained by the presence of current active *C. pneumoniae* infection.'' This is in direct contrast to recently published studies that used a similar cohort of patients [2]. A closer look at the results of the study by WANG *et al.* [1] revealed that while the authors used authentic quantitative PCR techniques to identify *C. pneumoniae* DNA, they utilised sputum samples for detection. It has been well established that *C. pneumoniae* resides primarily in the lower airway and is recovered much more reliably from bronchoalveolar lavage (BAL) fluid, as clearly demonstrated by MARTIN *et al.* [3].

Responding to a question about the future of PCR as a diagnostic tool for respiratory *Chlamydia* and *Mycoplasma* respiratory tract infection, M. Kraft, a co-author of the manuscript by MARTIN *et al.* [3] and an internationally recognised respiratory infectious disease expert, reiterated: ''As demonstrated by the present study, PCR remains the only reliable way of demonstrating chronic infection. But PCR requires collecting relevant samples. The lower airway samples we need for diagnosis require invasive bronchoscopy'' [4]. Indeed, viable *C. pneumoniae* have been successfully cultured from the BAL fluid of paediatric patients with chronic, severe asthma and the culture data correlated with the PCR (all culture-positive samples were also PCR-positive) [2]. Therefore, the absence of *C. pneumoniae* in the sputum samples used by WANG *et al.* [1] is not surprising. There is no question that under certain conditions of severe respiratory disease caused by *C. pneumoniae* the organism will be found in the sputum. However, in milder cases of acute infection, and in presumptive chronic infection, the chlamydial inclusions are most likely to be found in the macrophage or bronchial epithelial cells of the lower respiratory tract, making detection from induced sputum difficult and imprecise [3].

It may be that chronic, rather than acute, *C. pneumoniae* infection of only lung dendritic cells is a causative factor in asthma [5]. SCHRÖDER *et al*. [5] reported that adoptive transfer of dendritic cells from *C. pneumoniae*-infected mice was sufficient to induce an ''asthmatic'' phenotype in recipient animals. If this is found to be a relevant mechanism in human asthma, then direct microbiological diagnosis of *C. pneumoniae* by PCR, or by any method, will be even more difficult than has been anticipated, even by us. This, however, further strengthens the argument that asthma is a heterogeneous disease and this heterogeneity in inflammatory phenotype, as well as response to treatment, might be a direct result of the aetiology. While much work remains to be done in terms of deciphering the mechanisms underlying its involvement in the asthmatic process, the published data and ongoing work leave little doubt that *C. pneumoniae* plays an important role in asthma pathogenesis.

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From the authors:

We thank W.C. Webley and D.L. Hahn for their correspondence regarding our article [1]. In our study, we hypothesised that *Chlamydophyla pneumoniae* infection may be an aetiological agent for noneosinophilic forms of asthma and sought to test this hypothesis using a sensitive and validated PCR for *C. pneumoniae*. We did not detect *C. pneumoniae* and concluded that *C. pneumoniae* infection was unlikely to be the cause of noneosinophilic asthma. We stand by these results because we studied a large number of subjects, who were carefully classified into inflammatory asthma phenotypes and who were assessed using valid methods. Induced sputum samples material from the lower airways, as evidenced by the recovery of pulmonary macrophages in the sample. It is a useful technique for assessing lower respiratory tract infection, and widely used for this purpose [2]. In particular, induced sputum can detect *C. pneumoniae* infection when it is present [3]. A recent multicentre study, which used bronchoscopic biopsy, reported a similar rate of *C. pneumoniae* detection to ours (one out of 92 samples) [4].

W.C. Webley and D.L. Hahn propose that *C. pneumoniae* may preferentially reside in lower airway cells that are out of the sampling range of induced sputum. This hypothesis could be directly tested by a study comparing induced sputum to bronchoalveolar lavage samples for *C. pneumoniae* detection. However, we think this is biologically implausible based on other published data [3, 4]. Furthermore, how does *C. pneumoniae* infection cause inflammation and asthma in airways (*e.g.* large airways, for example) in which it is not present, and yet it does not cause an inflammatory reaction in parts of the lung where it is proposed to be present (*e.g.* alveoli)?

Defining the role of *C. pneumoniae* in airway diseases such as asthma and chronic obstructive pulmonary disease is an important issue. Research in this area has been held back by the inability to reliably and reproducibly detect *C. pneumoniae* in airway samples, and the inconsistent results of treatment studies. PCR has now been able to overcome many of these technical limitations [3, 4]. If *C. pneumoniae* is indeed relevant to chronic inflammatory airway disease, we may need to consider different mechanisms other than the simple chronic infection hypothesis. For example, the timing of *C. pneumoniae* infection and the resulting immune reprogramming may influence the development and phenotypic expression of asthma. Based on our recent modelling work, *C. pneumoniae* infection during active sensitisation may induce a neutrophilic asthma phenotype through immune reprogramming and does not require chronic *C. pneumoniae* infection for the expression of neutrophilic asthma [5]. Our recently published data are consistent with this hypothesis [1], and this may also explain why studies of treatment directed at *C. pneumoniae* are not clearly positive in asthma. In childhood asthma, the timing of *C. pneumoniae* infection in early life may induce immune reprogramming and subsequent asthma [6]. These mechanisms might also explain the associations between *C. pneumoniae* antibody (immune) responses that are linked with asthma, often in the absence of detectable organisms.

We think it is time to accept that the published data do not support chronic infection as the main mechanism in the modulation of asthma through *C. pneumoniae*. There are other possibilities, which focus on the timing of infection and subsequent immune reprogramming; our efforts could be put to use designing studies that test for these effects in human asthma.

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