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CORRESPONDENCE

The European Network For Understanding Mechanisms Of Severe Asthma study

To the Editor:

We found the results of the European Network For Understanding Mechanisms Of Severe Asthma (ENFUMOSA) study [1] and its accompanying Editorial [2] very interesting and would like to raise two issues, one regarding classification of subjects, and the other concerning pathogenesis. The ENFUMOSA study defined a group with severe asthma, requiring high-dose inhaled corticosteroids who continued to experience severe exacerbations of asthma. These subjects differed from the comparison group by having less atopy and increased sputum neutrophils. It was hypothesised that other environmental factors, such as infections, may be important.

We recently reviewed the inflammatory phenotype and mechanisms of asthma and drew attention to a phenotype of noneosinophilic asthma [3]. These subjects had symptomatic asthma and airway hyperresponsiveness but normal levels of sputum eosinophils. Noneosinophilic asthma was observed to occur in all grades of asthma severity, including steroid-naïve mild asthma [3]. In persistent asthma, the noneosinophilic asthma phenotype was characterised by increased levels of sputum neutrophils and increased interleukin (IL)-8 [4]. Thus, there is a strong alignment between the results of the ENFUMOSA study and our work describing noneosinophilic asthma. Rather than being restricted to severe asthma, as the ENFUMOSA study suggests, this inflammatory phenotype occurs across the severity spectrum of persistent asthma. This suggests that neutrophilic inflammation causing noneosinophilic asthma may by a specific class of asthma, rather than a stage in the progression of asthma. Clarification of this important point will require longitudinal studies.

It would be useful to re-examine the data from the ENFUMOSA study, classified by inflammatory phenotype. There are now reliable data on the normal levels of inflammatory cells in induced sputum [4] and given the reported increased neutrophils in the subjects with severe asthma, this classification may provide important additional information about noneosinophilic asthma. As suggested in the Editorial [2], previous work provided important evidence that severe asthma can be classified based upon inflammatory phenotype into eosinophilic and noneosinophilic severe asthma. This classification provided the first suggestion that severe asthma may involve different inflammatory phenotypes and processes with similar resultant clinical presentation.

The potential mechanisms of noneosinophilic asthma are interesting. We hypothesised that noneosinophilic asthma may represent persistent activation of the innate immune response [3]. Innate immune activation leads to activation of a common transcriptional programme involving nuclear factor κB, IL-8, and consequent neutrophilic inflammation. Infectious agents are key players in the activation of this arm of the immune system. Based on these observations, we would interpret the findings of the ENFUMOSA study as being consistent with infectious agents triggering innate immune activation to explain the clinical observations and inflammatory changes observed in severe asthma. This would also explain why exacerbations continued to occur despite the effects of steroids and their potent antieosinophilic action.

If these hypotheses that noneosinophilic asthma represents a different class of asthma triggered by innate immune activation are correct, then this has important implications for the choice of therapy in asthma.

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From the authors:

We thank P.G. Gibson and J.L. Simpson for their interest and kind comments on the report of the cross-sectional European Network For Understanding Mechanisms Of Severe Asthma (ENFUMOSA) study. We also believe that asthma is a syndrome where different pathogenetic mechanisms are involved in different groups of patients. With regard to airway neutrophilia and asthma subtypes, elite skiers in the Nordic countries often acquire airway hyperresponsiveness and a variable airflow obstruction that may meet clinical criteria for the diagnosis of asthma [1]. The numbers of neutrophils in the bronchial biopsies were twice as high among elite skiers as in a group of subjects with mild asthma, and there was also evidence of airway remodelling as in asthma [2]. However, the histopathology in the elite athletes also displayed dissimilarities, such as bronchus-associated lymphoid tissue aggregates [3]. As also discussed by P.G. Gibson and J.L. Simpson, inappropriate activation of the innate immune response could be one potential mechanism involved in the development of airway hyperresponsiveness and obstruction associated with neutrophilia.

P.G. Gibson and J.L. Simpson raise the possibility that the neutrophilic phenotype we observed among subjects with severe asthma in the ENFUMOSA study was a reflection of one asthma phenotype that is expressed across the spectrum of disease severities, rather than being specifically associated