Stability of eosinophilic inflammation in COPD bronchial biopsies

To the Editor:

In their recent research letter, Higham *et al.* [1], provide valuable data analysing in detail the sources of variability in eosinophil counts in the lamina propria of large airway biopsies from COPD patients, described as "inflammation". The population of COPD they studied seems somewhat atypical from the average COPD patient in having a high median blood eosinophil count of 400 per µL and median bronchodilator reversibility of 15%, potentially consistent with an atopy/asthma-overlap phenotype. Even so, there is arguably no evidence for an inflammatory process being present in the airway sub-epithelial tissue layer. Indeed, interestingly the eosinophil count in the airway tissue was quite closely related to that in the blood, suggesting perhaps that it more reflected movement of cells between these two compartments rather than any local concentration.

Reasons for questioning the lack of evidence for an airway inflammatory process in the letter include the lack of a normal control group, which when reviewed is surprisingly common in the current COPD literature [2]. Further, there was no estimate of total cell count to put the eosinophils into perspective.

Our group published a comprehensive survey of absolute and percentage cell counts in normal and COPD airways [2] and showed that in COPD the total cell count in the lamina propria was approximately 2000 per mm^2 while in normal controls there were about twice as many. Thus, we found that COPD airways are markedly hypocellular and hypovascular, more reflecting an ongoing fibrotic process. This challenges the current paradigm of COPD being an "inflammatory disease" of the airway wall [3].

In terms of airway wall (laminal propria) eosinophil numbers, Higham *et al.* [1] actually found low absolute eosinophil counts, with a median of approximately 30 per mm^2, which would give a percent count of 1% but with confidence limits extending to zero (using our total cell counts from Eapen *et al.* [2]). We have also previously found that eosinophils were very few in number in both typical early COPD and normal control airway walls with no obvious difference between them; they were numerically by quite a way the most minor cell type of those quantified, *e.g.* neutrophils were 5% and CD8+ lymphocytes 9% of total, with the latter the only one significantly different from normal. Overall, therefore, we would suggest, and in agreement with the data of Higham *et al.* [1], that the low and variable eosinophil numbers present the airways in COPD patients, is not consistent with the term "inflammation".

Finally, with regard to the analysis of variability provided by Higham *et al.* [1], the original 1986 paper by Bland and Altman [4] indicated that log transformation, rather than data splitting, was the approach advocated if needed for the common situation where variability increases with the mean of measurements [4, 5]. Can the authors therefore clarify whether their dichotomising, which they transparently described as an arbitrary cut-off, was "*post hoc*" and why this approach advocated by Bland and Altman was not used?

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A claim for cellular inflammation in tissues needs the full picture, with total cell count and full differential counts, and not just data on one specific cell type, in addition to details of what normal looks like https://bit.ly/2G0Tpob

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