It is not these stereological debates that are the source of the controversies about whether or not retinoic acid (RA) induces alveolar regeneration, since the initial positive report by MASSARO and MASSARO [1]. We should instead be concerning ourselves with other biological reasons, such as the extent of initial damage, methods of delivery of RA, the pharmacokinetics of RA, times after dosing, age of the animals etc., as potential causes for these glaringly opposite reports of "RA induces alveolar regeneration" versus "RA does not induce alveolar regeneration".

Nevertheless, it must be acknowledged, as we do in our paper and as the editorial does, that the most important feature of these regenerated lungs is to determine whether they can or cannot take up oxygen efficiently, that is, whether they are fully functional. This is the missing piece of evidence in these and other experiments determining the forced expiratory volume in one second of the mouse or devising a mini-mouse exercise test. However, it would be very surprising if animals had evolved developmental and regenerative mechanisms that resulted in structurally sound but nonfunctional organs. In the words of the playwright "A" stands for absolutely (perhaps).

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References

Pre- and post-bronchodilator spirometric values and the degree of reversibility in patients with COPD

To the Editor:

I thank P. Sterk for an interesting and informative Editorial on the definition and classification of patients with chronic obstructive pulmonary disease (COPD) [1]. However, I cannot help but get the feeling from reading the article that perhaps most, if not all, of the emphasis is placed on the number of alveoli in the human lung. Am J Respir Crit Care Med 2004; 169: 120–124.

From the authors:

H. Fehrenbach is perfectly correct to point out that the assessment of our data is based only on the measurement of mean chord length (Lm) and lung volume estimations, whereas "a whole range of stereological tools is available for more detailed analysis". However, the results were so dramatic that we felt that there was no need for these further, rather esoteric analyses, which would not necessarily have provided any further useful information for understanding the biology of the system. The results were also so clear-cut that errors due to tissue shrinkage (all samples were processed at the same time so this error should be equal anyway) or including the occasional alveolar duct in our computer-based measurements of alveolar Lm (800 measurements per field of view, 30 fields of view per Lm score) were also likely to be insignificant.
criteria for the definition and classification of patients with chronic obstructive pulmonary disease (COPD) [1]. Will it be meaningful to add prebronchodilator values and reversibility to those criteria? It sounds plausible, but I believe it is not justified. The reason for this is that we should distinguish the criteria for the disease from potentially relevant information on the disease.

We all seem to agree that COPD is a disease in which airflow limitation is not fully reversible. The latter points to residual airflow limitation after giving an adequate dose of a bronchodilator; in other words, a lowered ceiling (postbronchodilator value) of spirometry. Would it be helpful to include the reversibility as such? Apart from the different ways of expressing reversibility [2], it appears that the response to a bronchodilator has hardly any diagnostic value for COPD [3], whilst being very poorly reproducible [4]. As indicated in my editorial, this is not unexpected since the prebronchodilator value of forced expiratory volume in one second and, thereby, its reversibility towards the postbronchodilator ceiling value is modulated by variable degrees of smooth muscle contraction. Therefore, the prebronchodilator value, as well as the reversibility, does not seem to be an adequate criterion as to whether airflow limitation is "not fully reversible".

Does this mean that reversibility is a useless index? No, certainly not. The degree of reversibility may point towards clinically and pathophysiologically relevant phenotypes of COPD. What are the determinants of smooth muscle contraction in this disease? We don’t know, but there is recent evidence that patients with a substantial degree of reversibility of their airflow limitation (notwithstanding their abnormal postbronchodilator value) do have certain specific characteristics, such as elevated levels of exhaled nitric oxide and sputum eosinophilia [5], together with blood eosinophilia and reduced levels of neutrophil activation [6]. Hence, indeed, there is a message that needs to be taken seriously in measuring reversibility, despite its poor reproducibility [4]. Taken together, when distinguishing the strict criteria for the definition and classification of chronic obstructive pulmonary disease from other potentially useful information on the clinical phenotype of the disease, D. Lee and myself do seem to agree. I thank him for his comments.

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Additive blockade of β2-integrin adhesion of eosinophils by salmeterol and fluticasone propionate

To the Editor:

In their report of the effects of fluticasone propionate and salmeterol on eosinophil adhesion, Myo et al. [1] correctly considered that fluticasone propionate may have reduced eosinophil adhesion by inducing apoptosis [2–5], but they did not perform the appropriate experiments to test this. Assessment of "cell viability" by exclusion of membrane-impermeant dyes such as trypan blue or propidium iodide will not identify apoptotic eosinophils, which generally have intact plasma membranes [6]. Appropriate methods to quantify eosinophil apoptosis include examination of nuclear morphology and annexin V staining, which if performed would probably have resulted in a different interpretation of the data. Apoptotic cells are clearly not "viable" because cellular functions (including cell adhesion) are significantly impaired. Unfortunately, the term "cell viability" is widely used in scientific literature, but it is imprecise and should be abandoned.

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References