with good AQI according to US-EPA (<12.5 $\mu g \cdot m^{-3}$) in the car parking area and inside the Bella Center, with a level of 6.0 ± 1.7 and 3.0 ± 0.9 $\mu g \cdot m^{-3}$, respectively. Peak values were 12.5 $\mu g \cdot m^{-3}$ and 12.0 $\mu g \cdot m^{-3}$, respectively. However, outside in front of the Bella Center with smokers, mean $PM_{2.5}$ was 17.8 ± 7.5 $\mu g \cdot m^{-3}$ with a peak of 98.9 $\mu g \cdot m^{-3}$ ($p<0.03$, as compared with inside the venue), which is a step down in AQI. $PM_{2.5}$ along the motorway was only 4.6 ± 0.7 $\mu g \cdot m^{-3}$ with a peak value of 8.7 $\mu g \cdot m^{-3}$. Inside the restaurant, high concentrations of $PM_{2.5}$ were found (165.1 ± 8.5 $\mu g \cdot m^{-3}$) with a peak value of 372.2 $\mu g \cdot m^{-3}$, with a ''very unhealthy'' AQI. Official outdoor $PM_{2.5}$ mean $\pm$ SEM recorded in the town for the time interval of all the measurements was 5.7 ± 0.4 $\mu g \cdot m^{-3}$. Overall, mean values observed with smokers in front of the Bella Center and inside the restaurant were significantly higher than the outdoor parking place, indoor Bella Center, motorway and Copenhagen outdoor official data ($p<0.05$ and $p<0.001$, respectively).

Indoor and outdoor air quality monitoring through an entire day showed that in a country where outdoor air quality is generally good, as in Denmark, the presence of ETS worsens both indoor and outdoor PM concentrations. In the restaurant with smokers we observed very high $PM_{2.5}$ levels, with an AIQ classified as ''very unhealthy'', as reported by previous studies [7]. PM also reached significant values outdoors where smokers gathered to smoke, confirming previous field surveys at outdoor patios [10]. By appreciating this issue, ERS organisers advised participants not to smoke in front of the Congress venue, a suggestion that also implies coherence with doctor's role model, an issue that still deserves attention.

Understanding the importance of indoor *versus* outdoor pollution and the issue of environmental tobacco smoke as both an indoor and outdoor pollutant can contribute to a better knowledge of environmental tobacco smoke exposure risk.

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COPD: an inhaled corticosteroid-resistant, oral corticosteroid-responsive condition

To the Editors:

Few areas of respiratory medicine have generated as much controversy as the use and purpose of long-term corticosteroid treatment in chronic obstructive pulmonary disease (COPD). However, several recent large, placebo-controlled studies have clarified the role of long-term treatment with inhaled corticosteroids [1–3]. There is now consistent evidence that inhaled corticosteroid treatment, even in high doses, is not associated with a clinically significant reduction in the rate of decline of forced expiratory volume in one second (FEV_1). Treatment is associated with a modest reduction in the

frequency of more severe exacerbations, particularly in patients with more severe disease [1, 4] and in those who have a good bronchodilator response to short-term treatment with oral prednisolone [5, 6].

The limited effects seen with inhaled corticosteroids is surprising, given that induced sputum evidence of corticosteroid-responsive eosinophilic airway inflammation is present in up to 40% of patients with stable moderate and severe COPD disease [7–10], and a higher proportion of patients studied at the time of an exacerbation [7]. Moreover, short-term treatment with oral corticosteroids does seem to be associated with significant benefits in patients with exacerbations of COPD [11]. Early, uncontrolled studies with long-term, low-dose prednisolone have suggested substantial treatment-associated reductions in exacerbation frequency and rate of decline in FEV_1 [12, 13].

These findings raise the possibility that COPD is an inhaled corticosteroid-resistant, oral corticosteroid-responsive condition. Two recent studies provide direct support for this view. Both studies were placebo-controlled crossover trials involving ~60 patients with moderate and severe COPD. The first study investigated 2 weeks of prednisolone 30 $mg \cdot day^{-1}$ [8] and the other inhaled mometasone 400 μg daily for 6 weeks [9]. Both studies showed that the treatment-associated improvement in FEV_1 and quality of life scores increased progressively from the lowest to highest tertile of baseline sputum eosinophil count, consistent with a close, and perhaps causal, association between eosinophilic airway inflammation and the response to corticosteroids. However, the beneficial effects of oral prednisolone were substantially greater than those of inhaled mometasone. This was particularly the case with the sputum eosinophil count, which was reduced six-fold by prednisolone, but was unaffected by mometasone. Another recent study has shown that a management approach with the additional aim of reducing the sputum eosinophil count below 3% is associated with a 62% reduction in severe exacerbations of COPD requiring hospitalisation, when compared to traditional symptom-based management [14]. Anecdotally, we found in this study that it was often necessary to use oral prednisolone to achieve significant reductions in the sputum eosinophil counts in the intervention group.

A potential mechanism for the different effects of inhaled and oral corticosteroid resistance in COPD is that functionally important corticosteroid-responsive eosinophilic airway inflammation is confined to the distal lung, a site that is accessed by oral, but not inhaled, corticosteroids. Interestingly, studies in severe asthma show that oral, but not inhaled, corticosteroids reduce alveolar nitric oxide, strongly suggesting that this marker of distal lung inflammation reflects inflammation in a site that is differentially accessed by systemic and inhaled corticosteroids [15].

Other explanations consider a more absolute corticosteroid resistance in COPD, suggesting smoking and oxidative stress impair the ability of corticosteroids to recruit histone deactylase-2, which leads to transcription of pro-inflammatory genes [16]. This is not consistent with the observed difference in the clinical and anti-inflammatory efficacy of oral and inhaled corticosteroids.

If COPD is associated with an inhaled corticosteroid-resistant but oral corticosteroid-responsive functionally important distal eosinophilic airway inflammatory response, it follows that long-term treatment with oral corticosteroids might be associated with improvements in meaningful longer-term outcomes in patients with COPD, such as exacerbation frequency and decline in lung function, particularly when there is evidence of eosinophilic airway inflammation. Of course, long-term therapy with oral corticosteroids has a high potential for adverse effects in an elderly frail population, although the risk benefit may be acceptable if the maintenance dose is low and if care is taken to monitor and prevent osteoporosis, especially in the context of patients with severe disease suffering an expected 5-yr survival of 24–30% [17]. There is also the potential that effective anti-inflammatory therapy will be associated with a reduction in markers of systemic inflammation and reduced morbidity and mortality from associated conditions, such as coronary heart disease [18].

In a sense, experience with oral corticosteroid treatment in COPD parallels, but lags behind, experience with oral corticosteroid treatment in rheumatoid arthritis where opinion has swung from extreme enthusiasm to therapeutic nihilism and back to a view where they are helpful when used in low doses in selected patients [19].

We believe that the respiratory community will ultimately come to a similar conclusion. The time has come to investigate the effects and cost-effectiveness of long-term low-dose oral corticosteroid therapy in patients with chronic obstructive pulmonary disease who have evidence of eosinophilic airway inflammation.

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The sulphoxidation of *S*-carboxymethyl-L-cysteine in COPD

To the Editors:

Mucolytics, such as *S*-carboxymethyl-L-cysteine, have a role to play as an adjunct in the treatment of chronic obstructive airway disease, but their apparent unreliability has led to divided opinion concerning their usefulness [1–3]. The failure to achieve any measurable benefit with some patients presumably reflects underlying interindividual differences within the patient cohort, and not that the drug itself is without efficacy. In this respect, one major topic affecting clinical efficacy of a drug is its disposition and fate following administration, and, in particular, those factors that influence its subsequent metabolism and deactivation.

The metabolic fate of *S*-carboxymethyl-L-cysteine, an extensively used and widely available mucoactive drug, is now known to be complex. Detailed and rigorous studies in humans have revealed that the biotransformation of the drug varies widely within the same individual, with little sulphoxide (sulphur oxygenated) metabolites being produced following night-time administration [4]. This seemingly trivial observation is crucial, as recent work indicates that this drug functions as a free radical scavenger [5, 6] and that, in this respect, the sulphide (parent compound) is the active species with the sulphoxide metabolites (already oxidised) being inactive. Thus, a night-time intake of the drug should be more beneficial to the patient than daytime administration. However, this diurnal variation in metabolism (deactivation) is overlaid on an underlying genetic polymorphism that gives the patient population a spread of *S*-carboxymethyl-L-cysteine sulphoxidation capacities [7] (fig. 1). Those individuals who are relatively efficient sulphur oxidisers will rapidly produce inactive oxygenated metabolites, whereas those who have a relative deficiency in this process will be exposed to the active sulphide for a longer period of time, effectively mimicking the night-time dosing situation. In efficient sulphoxidisers, the standard dose of the drug may well have little effect. The underlying enzymology of these reactions is not yet clear, but two cytosolic enzymes, cysteine dioxygenase and phenylalanine 4-hydroxylase, have been implicated [8].

It is evident that a ''broad brush stroke'' approach to therapy with this particular mucolytic agent will not work for everyone. The recognition that the same dose of *S*-carboxymethyl-L-cysteine will not be equally effective for all patients should enable this part of the therapeutic regimen to be tailored to each individual patient, or subgroup, of patients. Removing or withholding treatment because it appears ineffective in some subjects is manifestly incorrect for that proportion of the