challenge is the universally recognised and accepted method of diagnosis for EIB in elite athletes. What still needs to be more clearly determined is the exact level of fall of FEV₁ in response to challenge in elite athletes which represents an abnormal response.

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Smoking cessation and airway inflammation in COPD

Why does airway inflammation persist after the smoking stops?

J C Hogg

Important new observations on the behaviour of T lymphocytes and plasma cells following prolonged smoking cessation in patients with COPD

The toxic gases and particles generated in tobacco smoke come into contact with lung tissues each time a puff of smoke is inhaled, and this tissue injury recurs in a cyclic fashion as each cigarette is smoked. A 20 pack year smoking history indicates that the subject's lungs have received 20 of these short cyclic exposures per day for a cumulative total of 7300 exposures per year and 146 000 exposures over the lifetime of their smoking habit. This complex pattern of acute upon chronic inhalation injury reduces the innate defences of the lung by interfering with mucociliary clearance,¹ diminishing the inflammatory cytokine response to other stimuli,² and disrupting the epithelial barrier.^{3–4} The tissue damaged by the smoke becomes infiltrated with innate and adaptive inflammatory immune cells and, even though tobacco

smoke exposure may suppress the immune response,⁵ the lymphoid cells collect to form the follicles with germinal centres that document the presence of the adaptive immune response.⁶ The antigens that drive this immune response have not been clearly identified, but both microbial antigens that accumulate as a result of colonisation and infection of the lower respiratory tract, and possibly autoantigens created within injured lung tissue, have been implicated.^{6–8}

The classic longitudinal study of chronic bronchitis and emphysema conducted by Fletcher and associates in the late 1950s and 1960s established that only 20–25% of smokers develop airflow limitation.⁹ These investigators also observed beneficial effects from stopping smoking that have been confirmed in early stage (GOLD 1 and 2) disease by

a randomised controlled trial.¹⁰ The fact that COPD is limited to a susceptible minority of smokers,⁹ and those that successfully stop smoking both slow their rate of decline in forced expiratory volume in 1 second (FEV₁) and delay their death,^{9–10} is not easy to reconcile with cross sectional observations on lung tissue pathology where the chronic inflammatory response that is thought to drive the process is observed in everyone that smokes and seems to persist long after the smoking has stopped.^{6–11–12} Although this discrepancy has been partially reconciled by observations indicating that the response to tobacco smoke is amplified in the minority of smokers that develop COPD,^{13–14} the precise mechanisms for either the amplification step found in association with the group that develop COPD or the persistence of the inflammatory immune response following the removal of the smoking stimulus remain to be clarified.

Lapperre and colleagues¹⁵ address this problem in this issue of *Thorax* in a study of 114 patients in GOLD stages 2 and 3 COPD who were not receiving either inhaled or oral steroids at the time of the study. There were 99 men, and 42 had quit smoking for a median time of 3.5 years. They found that, as a group, the ex-smokers had higher numbers of CD4+ lymphocytes and plasma cells than current smokers while there was no difference in the numbers of neutrophils, macrophages, or CD8+ cells

between the groups. However, when they divided the ex-smokers into short term (stopped <3.5 years) and longer term (stopped >3.5 years) ex-smokers, those who had stopped the longest had lower CD8+ T cell numbers and increased plasma cell counts. Based on these observations, they propose that T lymphocyte and plasma cell numbers respond to current smoking status whereas other inflammatory cells do not, and suggest that the presence of either an ongoing microbial stimulus or the development of autoimmune disease drives this lymphocyte response. These new and important observations on the behaviour of T lymphocytes and plasma cells following prolonged smoking cessation deserve further attention for several reasons.

Although Fletcher *et al* thought that smoking cessation reduced the rate of decline in expiratory airflow with age even in the late stages of the disease,⁹ the only randomised controlled trial showing that the rate of decline in FEV₁ is slowed by stopping smoking was conducted in relatively young patients (mean age 48 years) with mild (GOLD stage 1 and 2) disease.¹⁰ What happens to the rate of decline when smoking cessation is the only intervention in older subjects with more severe disease has not been studied in a randomised controlled fashion and could be quite different because the pathology in the early stages of COPD might be easier to reverse than that found after COPD has progressed. A cross sectional study of small airway pathology across the GOLD categories of COPD has shown that the decline in

FEV₁ is more closely associated with a repair and remodelling process that thickens the airway wall than with the extent and severity of the inflammatory immune response.⁶ It also showed that there is a sharp increase in the adaptive component of the inflammatory immune response in the severe (GOLD stage 3) and very severe (GOLD stage 4) categories of COPD where the airway wall thickening was the greatest.⁶ Laperre and colleagues provide new insight into this problem by providing data indicating that the lymphocytes that control the adaptive response are driven by antigen following prolonged smoking cessation. These observations should stimulate those who are interested in this problem to conduct the experiments required to determine whether microbial or autoantigens drive the adaptive immune response in the late stages of COPD, and to determine what links can be found between this adaptive immune inflammatory response found in the late stages of COPD and the thickening of the airway wall by the repair and remodelling process.

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