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EDITORIAL

The British hypothesis revisited

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Forty years ago, British investigators developed the hypothesis that recurrent bronchial infections were the reason that some smokers developed progressive airways obstruction and other did not [1]. The classical studies of FLETCHER *et al.* [2] were designed to test this proposition. They carried out a prospective study of working males, noting the frequency of respiratory infections, sputum quantity and quality, and rate of loss of lung function in the form of forced expiratory volume in one second (FEV1). They found that chronic cough and sputum production, and recurrent respiratory infections did not relate to lung function decline. They concluded that the chronic bronchitis syndrome (cough, sputum and episodes of acute bronchitis) was an epiphenomenon in so far as the development of chronic obstructive pulmonary disease (COPD) was concerned; both chronic bronchitis and COPD were caused by smoking, but the two were not related. This made sense, since chronic bronchitis symptoms largely reflected pathology in major conducting airways, and airways obstruction was related to lesions in small airways and the lung parenchyma.

This view of the pathogenesis of COPD was essentially unchallenged for many years, in a large part because it was hard to do a better study that that of FLETCHER *et al.* [2]. However, recent data suggest that there may be some truth in the British hypothesis. Smokers with chronic cough and sputum may have more rapid rates of FEV1 loss than those without these symptoms [3]. Two groups have reported that recurrent respiratory infections are associated with accelerated loss of lung function in COPD patients [4, 5] and lung function decline has been related to bacterial counts in sputum [6]. Recently, experiments investigating the hypothesis have involved inflammatory markers and expectorated sputum.

The study of BANERJEE *et al.* [7], in the current issue of the *European Respiratory Journal*, employed such techniques. They looked at induced sputum in stable patients with moderate to severe COPD, who were taking inhaled corticosteroids, using quantitative bacterial cultures and measurements of inflammatory markers. All the patients had positive bacterial cultures and, in 40%, the organisms were pathogens, largely the usual suspects: *Haemophilus influenzae, Moraxella catarrhalis* and *Streptococcus pnuemoniae*. As compared to patients with nonpathogens, patients with pathogens in their sputum had higher levels of inflammatory markers in their sputum, higher sputum neutrophil differential counts, higher plasma fibrinogen levels and worse quality of life as assessed by the St George's Respiratory Questionnaire. The authors conclude that in stable patients, the sputum reflects ongoing inflammation that is more striking when pathogens are present and that this impacts on quality of life. The study seems well done and is clearly presented. There are, in my opinion, several interesting issues raised by the study, including the stability of the patients, the importance of pathogenic as opposed to nonpathogenic bacteria, and the evidence of a systemic response to bronchial inflammation.

Both local and systemic inflammatory responses have been repeatedly demonstrated in COPD patients during exacerbations [8, 9], and this is hardly surprising. The evidence for inflammatory responses in stable patients is less well documented but not unprecedented [9–11]. The obvious question is whether the inflammation underlying these responses is important in terms of ongoing damage to the airways and lungs. Is there such a thing as chronic infection of the airways and is it important in the pathogenesis of COPD? The original British hypothesis suggested that this might be the case and recent evidence, including that of BANERJEE *et al.* [7], is compatible with this idea.

The data of BANERJEE *et al.* [7] indicate that pathogenic bacteria cause more inflammation than nonpathogens. This seems entirely reasonable, although others have found that inflammatory indices and rate of decline of lung function have been related to bacterial load without specification of pathogenicity [6, 10], and there was considerable overlap of inflammatory indicators between patients with and without pathogens in the study by BANNERJEE *et al.* [7]. A number of explanations are possible, but none have been confirmed. Nominal nonpathogens might be capable of causing airway inflammation in damaged airways. There is always the chance of a sampling problem with sputum cultures and bacterial pathogens might have been missed. Finally, nonbacterial organisms might be responsible for chronic airways inflammation.

BANERJEE *et al.* [7] found that plasma fibrinogen levels were higher in patients with sputum pathogens than in those without. Others have shown increased fibrinogen levels in stable COPD patients with detectable respiratory syncytial virus [8]. Fibrinogen and C-reactive protein blood levels were inversely related to FEV1 in the American NHANES study [11]. Thus, there is no shortage of evidence that the inflammation associated with COPD elicits a systemic response. However, the finding of BANERJEE *et al.* [7] that patients with bacterial pathogens and increased indices of airway inflammation had reduced quality of life as compared to COPD patients without bacterial pathogens [7] is unique to my knowledge. This is hard to explain, and the best BANERJEE *et al.* [7] can do is ascribe the difference to a questionable difference in the frequency of previous exacerbations. Obviously, this finding needs to be replicated.

So, where do we now stand in relation to the British hypothesis? It seems clear that exacerbations of chronic obstructive pulmonary disease do accelerate lung function decline and that chronic bronchitis is not entirely irrelevant to the progress of airways obstruction. The contribution of chronic airways infection to the process is not clear. The study of BANERJEE *et al.* [7] suggests that it may be an important influence, but more data are needed, relating evidence of such infection to accepted clinical outcomes. It is still possible that

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data derived from expectorated sputum reflects events occurring in major airways that are not important in the obstructive process. One final note is that most of the data concerning chronic infection-inflammation concerns bacterial infection. This is tantalising in that ameliorating bacterial infection is something that seems within our present powers, although designing a protocol to do this safely represents a serious challenge.

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