9 **Department of Health**. *Unfinished business: proposal for the reform of the SHO grade—a paper for consultation*. London: Department of Health, 2002; http://www.doh.gov.ukshoconsult/shoreport.pdf..
10 **National Patients Access Team Critical Care Programme**. *Weaning and long term ventilation*. London: Department of Health, 2002; http://www.modern.nhs.uk/criticalcare/5032/5195/weaning_and_ventilation_report.pdf.
11 **Plant PK**, Owen JL, Elliott MW. Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicentre randomised controlled trial. *Lancet* 2000;**355**:1931–5.
12 **Evans T**, Elliott MW, Ranieri M, *et al*. Pulmonary medicine and (adult) critical care medicine in Europe. *Eur Respir J* 2002;**19**:1202–6.

Does COPD have an autoimmune component?

Hypothesis: Does COPD have an autoimmune component?

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A new hypothesis that considers the role of the immune system in the pathogenesis of COPD is explored which, if true, will generate new therapeutic opportunities in this condition.

Chronic obstructive pulmonary disease (COPD) is a major public health problem because: (1) it causes significant morbidity and mortality which is expected to increase worldwide in the near future;[1] (2) it jeopardises the quality of life of the patients suffering from this devastating disease (particularly during exacerbations);[2 3] and (3) it imposes an enormous global healthcare cost.[1] However, because the pathogenesis of COPD is poorly understood, treatment is mostly symptomatic and new therapeutic strategies are limited.[4] In this paper we propose a new hypothesis that considers the largely unexplored role of the immune system in the pathogenesis of COPD. If true, this hypothesis will generate new therapeutic opportunities in COPD.

THE CURRENT VIEW

The Global initiative for the diagnosis, management, and prevention of Obstructive Lung Disease (GOLD) defines COPD as a ''disease state which is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases''.[5] Many studies have attempted to characterise this abnormal inflammatory response. However, this issue is far from resolved because the results of these studies vary according to the severity of the disease (mild, moderate, or severe), the type of controls studied (never smokers, smokers with normal lung function, patients with stable COPD compared with those studied during exacerbations of the disease), the compartment of the lung sampled (central airways, peripheral airways, alveolar space), and/or the bias of the study towards the role of a given cell type.[6] A critical review of this literature[7] indicates the following salient features: (1) all smokers develop airway inflammation; (2) this is amplified in patients with COPD, particularly during exacerbations of the disease; (3) there is a direct relationship between the severity of the disease and the intensity of the inflammatory response; (4) airspace inflammation persists after smoking cessation; (5) all inflammatory cell types (macrophages, neutrophils, lymphocytes, eosinophils, natural killer cells) are implicated in the inflammatory process of COPD; (6) many different mediators released by activated inflammatory cells can damage lung structures; and (7) oxidative stress due to cigarette smoking is important in the pathogenesis of COPD. How all these cells and inflammatory mediators interact and contribute to the disease is presently unclear. Yet, a better understanding of these interactions is mandatory if new therapeutic options are to be developed.[8]

THE QUESTIONS

In this context, we believe that there are three specific questions of particular relevance.

Why do only some smokers develop COPD?

Tobacco smoking is the main risk factor for COPD, but not all smokers develop the disease.[9] Although it is possible that more patients would develop COPD if they did not succumb from other smoking related conditions such as ischaemic heart disease and lung cancer, the fact remains that most smokers do not present with clinically significant airflow obstruction.[8] If we accept that COPD is associated with an abnormal inflammatory response in the lungs,[5] we should concede that excessive inflammation is the key to susceptibility. However, the mechanisms underlying this enhanced inflammatory response in susceptible smokers are completely unknown.

Why does inflammation persist after quitting smoking?

Although relatively small numbers of patients have been studied, several papers have shown that inflammation persists long after the patient has stopped smoking.[10–12] The mechanism(s) underlying this observation are also unknown, but it clearly indicates the existence of some self-perpetuating pathogenic process, initiated but not necessarily perpetuated by smoking, that prevents the normal resolution of the inflammatory response.[13] This type of mechanism seems to operate in many autoimmune diseases.[14]

What are the mechanisms of exacerbations of COPD?

Patients with COPD often present with exacerbations during the course of their disease. These episodes significantly diminish their quality of life,[3] may require admission to hospital,[15] and cause significant mortality.[16] They are characterised by increased airway inflammation.[17–19] However, the mechanisms causing them are unclear. Normally they are explained on the basis of airway infection (viral or bacterial) and/or the effects of air pollution,[20] but evidence supporting the former can be found in only 50–60% of cases[21] and the latter do not seem to be powerful enough to explain the majority of exacerbations.[22] Thus, many of these episodes remain unexplained.

LESSONS FROM AUTOIMMUNE DISEASES

Autoimmune diseases are chronic inflammatory conditions characterised by the loss of tolerance to self-antigens[23] or development of immunity to foreign epitopes that cross react with self-antigens.[24] It is

interesting to consider here that COPD shares many clinical and pathophysiological characteristics of several autoimmune diseases such as rheumatoid arthritis (RA).[23] Firstly, smoking is a risk factor for both COPD[9] and RA.[25] Secondly, once initiated, the inflammatory response of RA is self-perpetuating.[26] To some extent, this may be analogous to the continued airway inflammation seen after cessation of smoking.[10–12] Thirdly, exacerbations occur both in RA and COPD. Yet, while in COPD they are ''explained'' by external factors such as airway infection and air pollution,[20] in RA they are considered an integral part of the disease process, characterised by T cells sensitised to either cartilage epitopes[27] and/or degradation products of intestinal bacteria that mimic them,[26] homing to the synovium and contributing to the maintenance—or amplification of the inflammatory process. Finally, similarities between the inflammatory cells (neutrophils, macrophages, T lymphocytes) and cytokines (tumour necrosis factor (TNF)-α, interleukin (IL)-6, IL-8) involved in the pathogenesis of RA[28–30] and COPD[6 7] are remarkable.

THE HYPOTHESIS

We propose that an acquired immune response to newly created or altered epitopes is an essential component in the pathogenesis of COPD. This hypothesis implies the loss of tolerance to self-epitopes and would qualify COPD as an ''autoimmune'' disease induced by cigarette smoking. If true, this hypothesis may help to answer the questions posed above—namely, why only some smokers develop the disease, why lung inflammation persists after smoking cessation and, perhaps, the underlying pathobiology of some exacerbations of COPD. To support this hypothesis we will review the evidence for alterations of the ''normal'' components of the immune response in COPD and propose several (testable) mechanisms by which autoimmunity may arise in a disease caused by a clearly identified external agent (tobacco smoking).

IMMUNE RESPONSES IN COPD

The normal immune response comprises the innate (natural) and acquired (adaptive) responses.[31] The innate response involves phagocytic cells (neutrophils, macrophages), cells that release inflammatory mediators (mast cells, eosinophils), and natural killer cells.[31] The acquired response requires the proliferation of B and T cells after antigen presentation by specialised cells (macrophages and dendritic cells).[31] Many elements of both types of response are abnormal in COPD.[6 7] Implicitly, although not explicitly, the innate immune response has long been considered as dominating the pathogenesis of COPD, since the traditional proteinase-antiproteinase theory of the pathogenisis of COPD[32] requires the participation of neutrophils and macrophages, which are both prominent elements of such a response.[31] However, the role of the acquired response has largely been ignored. Yet, there is some evidence to support the contention that there is increased acquired immunity in COPD: (1) both helper (CD4+) and cytotoxic T lymphocytes (CD8+) accumulate in the lung parenchyma of patients with COPD[6 7]; (2) B lymphocytes form the core of the so-called bronchus-associated lymphoid tissue (BALT) which has been shown to be significantly increased in smokers[33] and in patients with COPD[34]; (3) smoking is associated with an expansion of the population of antigen presenting cells on the epithelial surface of the lower respiratory tract[35]; and (4) preliminary data from our laboratory suggest an increased prevalence of antinuclear antibody titres in patients with COPD compared with smokers with normal lung function (unpublished data). Whether these abnormalities represent a response to smoking or play a pathogenic role in the development of COPD will have to be explored in future studies.

POTENTIAL MECHANISMS

An aberrant acquired immune response can result from either a defect in the selection, regulation or death of immune cells (T or B lymphocytes) or from the generation of new (self or foreign) antigens.[23] Both possibilities could operate in COPD through several different mechanisms. Tobacco smoking (the main risk factor for COPD) modulates the proliferation[36 37] and death pathways of lymphocytes,[38] can generate new epitopes by either directly oxidising existing proteins[39 40] or indirectly by interfering with the clearance of apoptotic cells,[41] thus exposing anatomically sequestered intracellular antigens to the immune system,[23 42] and upregulates the population of antigen presenting cells in the lungs[35] thus amplifying the capacity to process new antigens. In addition, several factors frequently associated with COPD may also contribute to an acquired immune response. For instance, chronic airway bacterial colonisation is common in COPD.[43 44] In RA intestinal bacteria have been shown to be a source of new antigens contributing to the maintenance of the inflammatory process.[26 45] It is therefore possible that chronic airway colonisation by bacteria may exert a similar effect in COPD. Viral infections[46 47] and oxidative stress created by environmental particles[48] could also contribute to the development of new/altered epitopes. In summary, there are many different potential mechanisms that can theoretically boost an acquired immune response in COPD. The challenge is now to design the appropriate studies (human and experimental) to prove (or disprove) this hypothesis.

IMPLICATIONS

The current view is that chronic inflammation is a key pathogenic element in COPD because it contributes to the decline in lung function that characterises the disease.[5] Available anti-inflammatory treatment (that is, inhaled steroids) does not have a consistent effect on the inflammation in COPD.[49] New therapeutic measures are therefore urgently needed.[4 8] This is particularly important if the airspace inflammation in COPD continues despite quitting smoking.[10–12] If true, the hypothesis proposed here should lead to the development of new therapeutic strategies aimed at immunomodulation. These may both halt the progression of the disease and prevent the episodes of exacerbation. If so, this would contribute enormously to improving the well being of patients with COPD and to decreasing the enormous healthcare burden associated with this disease.[20]

CONCLUSIONS

We have developed a hypothesis that, by reconciling separate observations, may point towards a new and potentially relevant mechanism in the pathogenesis of COPD. However, we recognise that there is, as yet, insufficient evidence to support it. For instance, some of the inflammatory abnormalities described in COPD—such as the expansion of the bronchial associated lympoid tissue and the antigen presenting cell population—may in fact be a physiological adaptation rather than a pathological one. However, we think that there is enough indirect circumstantial evidence to explore this hypothesis further. Indeed, if there was firm evidence to support (or disprove) it, it would not longer be a hypothesis! We hope that researchers in this field agree with us in that it may be worth exploring. If so, we would suggest that studies aimed at detecting the presence of autoantigens, identifying potential epitopes and/or determining any potential relationship between COPD and HLA typing, among others, may eventually provide useful information for the benefit of patients with COPD.

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REFERENCES

1 **Murray CCJL**, Lopez AD. Mortality by cause for eight regions of the world: global burden of disease study. *Lancet* 1997:1269–76.
2 **Okubadejo AA**, Jones PW, Wedzicha JA. Quality of life in patients with chronic obstructive pulmonary disease and severe hypoxaemia. *Thorax* 1996;**51**:44–7.
3 **Seemungal TA**, Donaldson GC, Paul EA, *et al*. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;**157**(5 Pt 1):1418–22.
4 **Barnes PJ**. Chronic obstructive pulmonary disease. *N Engl J Med* 2000;**343**:269–80.
5 **Pauwels RA**, Buist AS, Calverley PM, *et al*. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. *Am J Respir Crit Care Med* 2001;**163**:1256–76.
6 **Cosio MG**, Guerassimov A. Chronic obstructive pulmonary disease. Inflammation of small airways and lung parenchyma. *Am J Respir Crit Care Med* 1999;**160**(5 Pt 2):S21–5.
7 **Saetta M**, Turato G, Maestrelli P, *et al*. Cellular and structural bases of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;**163**:1304–9.
8 **Shapiro SD**. End-stage chronic obstructive pulmonary disease. The cigarette is burned out but inflammation rages on. *Am J Respir Crit Care Med* 2001;**164**:339–40.
9 **Fletcher C**, Peto R. The natural history of chronic airflow obstruction. *BMJ* 1977;**1**:1645–8.
10 **Turato G**, Di Stefano A, Maestrelli P, *et al*. Effect of smoking cessation on airway inflammation in chronic bronchitis. *Am J Respir Crit Care Med* 1995;**152**(4 Pt 1):1262–7.
11 **Rutgers SR**, Postma DS, ten Hacken NH, *et al*. Ongoing airway inflammation in patients with COPD who do not currently smoke. *Thorax* 2000;**55**:12–8.
12 **Retamales I**, Elliot MW, Meshi B, *et al*. Amplification of inflammation in emphysema and its association with latent adenoviral infection. *Am J Respir Crit Care Med* 2001;**164**:469–73.
13 **Van Parijs L**, Abbas AK. Homeostasis and self-tolerance in the immune system: turning lymphocytes off. *Science* 1998;**280**:243–8.
14 **Kamradt T**, Mitchison NA. Tolerance and autoimmunity. *N Engl J Med* 2001;**344**:655–64.
15 **Seemungal TA**, Donaldson GC, Bhowmik A, *et al*. Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000;**161**:1608–13.
16 **Connors AF Jr**, Dawson NV, Thomas C, *et al*. Outcomes following acute exacerbation of severe chronic obstructive lung disease. *Am J Respir Crit Care Med* 1996;**154**:959–67.
17 **Bhowmik A**, Seemungal TA, Sapsford RJ, *et al*. Relation of sputum inflammatory markers to symptoms and lung function changes in COPD exacerbations. *Thorax* 2000;**55**:114–20.
18 **Roland M**, Bhowmik A, Sapsford RJ, *et al*. Sputum and plasma endothelin-1 levels in exacerbations of chronic obstructive pulmonary disease. *Thorax* 2001;**56**:30–5.
19 **Aaron SD**, Angel JB, Lunau M, *et al*. Granulocyte inflammatory markers and airway infection during acute exacerbation of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;**163**:349–55.
20 **Ekberg-Jansson A**, Larsson S, Lofdahl CG. Preventing exacerbations of chronic bronchitis and COPD. *BMJ* 2001;**322**:1259–61.
21 **Gompertz S**, O'Brien C, Bayley DL, *et al*. Changes in bronchial inflammation during acute exacerbations of chronic bronchitis. *Eur Respir J* 2001;**17**:1112–9.
22 **Sunyer J**. Urban air pollution and chronic obstructive pulmonary disease: a review. *Eur Respir J* 2001;**17**:1024–33.
23 **Davidson A**, Diamond B. Autoinmmune diseases. *N Engl J Med* 2001;**345**:340–50.
24 **Albert LJ**, Inman RD. Molecular mimicry and autoimmunity. *N Engl J Med* 1999;**341**:2068–74.
25 **Hutchinson D**, Shepstone L, Moots R, *et al*. Heavy cigarette smoking is strongly associated with rheumatoid arthritis (RA), particularly in patients without a family history of RA. *Ann Rheum Dis* 2001;**60**:223–7.
26 **Toivanen P**. From reactive arthritis to rheumatoid arthritis. *J Autoimmun* 2001;**16**:369–71.
27 **Guerassimov A**, Zhang Y, Banerjee S, *et al*. Autoimmunity to cartilage link protein in patients with rheumatoid arthritis and ankylosing spondylitis. *J Rheumatol* 1998;**25**:1480–4.
28 **Arend WP**. Physiology of cytokine pathways in rheumatoid arthritis. *Arthritis Rheum* 2001;**45**:101–6.
29 **Koetz K**, Bryl E, Spickschen K, *et al*. T cell homeostasis in patients with rheumatoid arthritis. *Proc Natl Acad Sci USA* 2000;**97**:9203–8.
30 **Pitzalis C**, Kingsley G, Murphy J, *et al*. Abnormal distribution of the helper-inducer and suppressor-inducer T lymphocyte subsets in the rheumatoid joint. *Clin Immunol Immunopathol* 1987;**45**:252–8.
31 **Delves PJ**, Roitt IM. The immune system. First of two parts. *N Engl J Med* 2000;**343**:37–49.
32 **Shapiro SD**. Evolving concepts in the pathogenesis of chronic obstructive pulmonary disease. *Clin Chest Med* 2000;**21**:621–32.
33 **Richmond I**, Pritchard GE, Ashcroft T, *et al*. Bronchus associated lymphoid tissue (BALT) in human lung: its distribution in smokers and non-smokers. *Thorax* 1993;**48**:1130–4.
34 **Bosken CH**, Hards J, Gatter K, *et al*. Characterization of the inflammatory reaction in the peripheral airways of cigarette smokers using immunocytochemistry. *Am Rev Respir Dis* 1992;**145**(4 Pt 1):911–7.
35 **Casolaro MA**, Bernaudin JF, Saltini C, *et al*. Accumulation of Langerhans' cells on the epithelial surface of the lower respiratory tract in normal subjects in association with cigarette smoking. *Am Rev Respir Dis* 1988;**137**:406–11.
36 **Vignes S**, Oksenhendler E, Quint L, *et al*. Polyclonal B lymphocytosis and hyper-IgM: immunodeficiency and/or benign lymphoid proliferation associated with tobacco? *Rev Med Interne* 2000;**21**:236–41.
37 **Chan MA**, Benedict SH, Carstairs KC, *et al*. Expansion of B lymphocytes with an unusual immunoglobulin rearrangement associated with atypical lymphocytosis and cigarette smoking. *Am J Respir Cell Mol Biol* 1990;**2**:549–52.
38 **Suzuki N**, Wakisaka S, Takeba Y, *et al*. Effects of cigarette smoking on Fas/Fas ligand expression of human lymphocytes. *Cell Immunol* 1999;**192**:48–53.
39 **Rahman I**, MacNee W. Oxidative stress and regulation of glutathione in lung inflammation. *Eur Respir J* 2000;**16**:534–54.
40 **Cerami C**, Founds H, Nicholl I, *et al*. Tobacco smoke is a source of toxic reactive glycation products. *Proc Natl Acad Sci USA* 1997;**94**:13915–20.
41 **Finkelstein EI**, Nardini M, van der Vliet A. Inhibition of neutrophil apoptosis by acrolein: a mechanism of tobacco- related lung disease? *Am J Physiol Lung Cell Mol Physiol* 2001;**281**:L732–9.
42 **Majo J**, Ghezzo H, Cosio MG. Lymphocyte population and apoptosis in the lungs of smokers and their relation to emphysema. *Eur Respir J* 2001;**17**:946–53.
43 **Monsó E**, Ruiz J, Rosell A, *et al*. Bacterial infection in chronic obstructive pulmonary disease – a study of stable and exacerbated outpatients using the protected specimen brush. *Am J Respir Crit Care Med* 1995;**152**:1316–20.
44 **Zalacaín R**, Sobradillo V, Amilibia J, *et al*. Predisposing factors to bacterial coloniozation in chronic obstructive pulmonary disease. *Eur Respir J* 1999;**13**:343–8.
45 **Toivanen A**. Bacteria-triggered reactive arthritis: implications for antibacterial treatment. *Drugs* 2001;**61**:343–51.
46 **Diaz PT**, King MA, Pacht ER, *et al*. Increased susceptibility to pulmonary emphysema among HIV-seropositive smokers. *Ann Intern Med* 2000;**132**:369–72.
47 **Hogg JC**. Latent adenoviral infection in the pathogenesis of emphysema. *Chest* 2000;**117**(5 Suppl 1):282S–5S.
48 **Li XY**, Gilmour PS, Donaldson K, *et al*. Free radical activity and pro-inflammatory effects of particulate air pollution (PM10) in vivo and in vitro. *Thorax* 1996;**51**:1216–22.
49 **Barnes NC**. Inhaled steroids in COPD. *Lancet* 1998;**351**:766–7.