

those unregistered with GPs and those in anomalous positions—such as asylum seekers—will remain and will require alternative initiatives. Are sticks necessary as well as carrots—as in The Netherlands which links residency permits with TB screening? The autonomy of the individual in decisions about their own healthcare is fundamental in the UK and many other countries. The rights of those who actually have infectious TB which is a risk to others are, though, already constrained in the UK both by Act of Parliament (Public Health Act 1984) and potentially by decisions of the Courts. An extension of these limitations to those who merely might have active TB or who might get it in future would be a very hot political issue. TB, though, is already a hot political issue,⁴ and a rational, informed and wide-ranging debate is overdue. The present system is not adequate, and the 'status quo' is no longer a sensible or scientific position, but merely x-raying all potential immigrants would be worse. Answers as to the utility, yield and cost of various screening strategies should be readily obtainable at little additional cost because of the heterogeneity of what actually is being done across England and Wales, in both primary and secondary care, and sometimes across the interface between the two.

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Live and let die: is neutrophil apoptosis defective in severe asthma?

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Patients with severe asthma make up a relatively small proportion of the total population of patients with asthma yet account for a disproportional amount of asthma-related morbidity and healthcare utilisation.^{1 2} These patients are usually highly symptomatic, difficult to treat and can be extremely refractory to current treatments. As a consequence, understanding the mechanisms underlying this

particular form of asthma is of paramount importance.

Morphological examination of the asthmatic airway reveals epithelial desquamation, thickening of the reticular basement membrane, mucus gland hyperplasia, goblet cell differentiation, angiogenesis and smooth muscle hypertrophy.³ In addition to these structural changes, an inflammatory cell infiltrate is evident within the airways comprising eosinophils, mast cells, lymphocytes and neutrophils. While eosinophils are the most characteristic inflammatory cell type present in mild to moderate asthma, the neutrophil seems to take centre stage more often in patients with severe disease. In fact, the neutrophil is one of the earliest inflammatory cells recruited to the airways following allergen exposure and is particularly evident in bronchoalveolar lavage samples and bronchial and trans-bronchial biopsies from patients with

corticosteroid-resistant asthma, occupational asthma and fatal asthma as well as those with acute exacerbations.^{4–6} Furthermore, measures of asthma severity such as forced expiratory volume in 1 s correlate directly with the number of neutrophils present in the sputum and bronchial wall.^{7,8} There is also evidence of neutrophil activation and impaired function in the asthmatic airway.^{9,10} Moreover, neutrophil elastase is recognised to be highly histotoxic and results in epithelial and eosinophil activation, increased vascular permeability and promotion of transforming growth factor β release which is linked to airways remodelling.

Given the propensity of neutrophils to die quite readily by 'constitutive' (ie, inbuilt time-dependent) apoptosis when studied *in vitro*,¹¹ one major puzzle in airways research has been to determine how and why neutrophils persist in such large numbers in the asthmatic airway. It is also uncertain why some patients with severe asthma have an inflammatory response dominated by neutrophils while others have an eosinophil-dominated pattern of disease. Explanations include genetic and epigenetic diversity, unrecognised environmental effects such as occult occupational exposures or viral infection, and inherited or acquired differences in responses to treatment, in particular sensitivity to glucocorticosteroids. Intriguingly, human biopsy studies support the concept that inhaled corticosteroids, while highly effective in reducing eosinophilic inflammation in the airways, may be associated (perhaps causally) with a rebound increase in the number of airway neutrophils.¹²

For neutrophils to accumulate within the lung, an orderly procession of cell/endothelial interaction, transcellular or pericellular transmigration and some degree of enhanced survival or defective egress is required. Based on sputum analysis, the principal signal coordinating neutrophil influx in severe asthma appears to be the cysteine-X-cysteine (CXC) chemokine interleukin 8 (IL-8; cysteine-X-cysteine chemokine ligand, CXCL),¹³ with additional contributions from IL-17,¹⁴ leukotriene B4 (LTB4), anaphylatoxins, growth-related oncogene a (GRO-a, CXCL1) and epithelial activating peptide 78 (ENA-78, CXCL5).¹⁵

Neutrophils access the lung parenchyma via pulmonary capillaries, a process which is strongly influenced by exposure of these cells to systemic priming agents that influence the size, shape, deformability and hence pulmonary transit time of this cell. In contrast, granulocytes arriving in the airway wall exit via the bronchial circula-

tion at a post-capillary level and migrate via a classic 'rolling-tethering' paradigm involving (1) P-selectin glycoprotein ligand-1, E-selectin ligand-1 and L-selectin mediated rolling; (2) chemokine-mediated cell activation; and (3) β_2 -integrin-dependent adhesion and diapedesis where granulocytes move into tissues.¹⁶ As noted, a significant proportion of neutrophils cross the endothelial barrier by endocytosis, an active RhoG-dependent engulfment process, prior to negotiating the pericyte sheath and passing through 'pre-perforated' regions of the basement membrane.¹⁷ The migration of neutrophils into the airway wall may facilitate the subsequent ingress of eosinophils.¹⁸

Once recruited into the airway, the neutrophil is left with a limited number of options which include transepithelial migration into the airway lumen, a process which some authors have suggested may represent a regulated and active disposal route for airway granulocytes¹⁹; migration back into the circulation (either directly or indirectly via lymphatics); trans-differentiation into macrophage cells²⁰; cell death; or sustained residence. Neutrophil apoptosis (in contrast to necrosis) results in recognition and engulfment by macrophages, which is rapid and in itself promotes the resolution of inflammation and the restoration of normal tissue architecture.²¹ The removal of neutrophils in this way serves to prevent the release of cytotoxic contents and thus protect host tissues. The precise timing and magnitude of neutrophil apoptosis in the asthmatic airway has been difficult to determine *in vivo* but offers a plausible exit strategy for these cells and one that has been observed in a number of other conditions characterised by airway neutrophilia. Consequently, factors that prolong the neutrophil lifespan by blocking apoptosis or impairing the clearance of apoptotic cells may be detrimental to this process and contribute towards the intense neutrophilic inflammation observed. Indeed, in the case of the eosinophil, it has been extremely difficult to identify any evidence of apoptosis within the microenvironment of the airway wall, despite the fact that these cells undergo apoptosis readily once they escape into the airway lumen.²²

Unsurprisingly, neutrophil apoptosis turns out to be a highly regulated process. Recognised 'survival factors' include lipopolysaccharide, granulocyte-macrophage colony-stimulating factor, type I and II interferons, survivin and, rather surprisingly, hypoxia and glucocorticosteroids.^{23–26} With regard to

the signalling pathways implicated in neutrophil survival, the PI3-kinase/AKT, NF- κ B, HIF-1 α and Mcl-1 pathways all seem to play substantial and context-specific roles (see Cowburn *et al*¹⁵). Any or all of these mediators may contribute to an 'apoptosis-resistant' granulocyte phenotype which, if operational in the airway wall of patients with asthma, might severely impede neutrophil clearance.

The presence of eosinophil- or neutrophil-specific survival factors within the airways of such patients has been much debated but little explored. In this issue of *Thorax*, Uddin and colleagues confirm, using induced sputum, that a proportion of patients with severe atopic asthma have predominantly neutrophilic rather than eosinophilic inflammation (*see page 684*).²⁷ Moreover, far fewer apoptotic neutrophils were evident in the former group, inferring a survival advantage for neutrophils in this cohort of patients. They were also able to show that the sputum sol phase recovered from the neutrophil-dominated patient group delayed apoptosis of naïve blood-derived neutrophils. Unfortunately, experiments using a series of blocking antibodies and a panel of 'best guess' pharmacological inhibitors were unable to characterise the survival factor(s) further. Such clinical studies are challenging at the best of times, and the group deserves considerable credit for generating this data set. There are inevitable caveats including the intersubject variability in the number of apoptotic airway neutrophils observed, the use of induced sputum which provides only an indirect readout of the cellular microenvironment within the airway, the lack of biopsy data to examine the tissue rather than luminal compartment, and the very low numbers of apoptotic cells present at any one time (<4% in this study). Critically, this study—in common with other reports—offers no insight into the true kinetics of neutrophil and eosinophil trafficking, nor any quantification of neutrophil clearance. It is possible, for instance, that the elevated level of neutrophil apoptosis seen in the severe 'neutrophilic' group reflects a failure of apoptotic cell recognition and removal (efferocytosis) rather than a true defect in apoptosis onset, as has been reported in the context of cystic fibrosis. The study is important, however, as it lends support to the view that neutrophil apoptosis and/or clearance may be defective in patients with asthma and shows that survival factors exist in the airway lining fluid which are specifically enriched in the

context of severe asthma. Identifying the neutrophil survival factor(s) present in this patient group is clearly an important next step and, if targetable, may form the basis of a new therapeutic approach for this difficult-to-treat patient group.

While this study provides further evidence that neutrophil apoptosis may be deregulated in severe asthma, a number of key questions remain. We need to understand the dynamics of cell migration into and out of the airway wall and determine the true residency times and the relative contribution of apoptosis and, indeed, other non-apoptotic death mechanisms such as autophagy, NETosis²⁸ and cytolysis in granulocyte clearance. We also need to understand the signals that block apoptosis in the airway wall (yet seemingly not in the airway lumen) and to determine what drives the switch from eosinophil- to neutrophil-dominated inflammation. Drugs which target the removal rather than the arrival of granulocytes in tissues are now emerging,²⁹ and such agents may offer an important adjunct to current asthma treatments.

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British Thoracic Society Pleural Disease Guidelines - 2010 update

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INTRODUCTION

Pleural disease remains common, affecting over 3000 people per million population each year. It therefore presents a significant contribution to the workload of respiratory

physicians. These guidelines attempt to summarise the available evidence to aid the healthcare professional in delivering good quality patient care.

AIMS AND OBJECTIVES OF THE GUIDELINE

Since the last BTS pleural disease guidelines were published in 2003¹ a large number of good quality primary research papers have been published and the guidelines need to reflect this new data. In addition, there was a need to develop new sections on local anaesthetic (LA) thoracoscopy and thoracic ultrasound to reflect changes in clinical practice.