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 indi-
vidual 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 1994) 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-ray 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
on a case-by-case basis. The present
system is not adequate, and the
‘status quo’ is no longer a sensible or
scientific position, but merely x-ray all
potential immigrants would be worse.

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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, under-
standing the mechanisms underlying this
particular form of asthma is of paramount
importance.

Morphological examination of the asth-
matic airway reveals epithelial desqua-
mation, 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 eosin-
ophils are the most characteristic inflam-
matory 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

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corticosteroid-resistant asthma, occupational asthma and fatal asthma as well as those with acute exacerbations. 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. There is also evidence of neutrophil activation and impaired function in the asthmatic airway. 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, one major puzzle in inbuilt time-dependent apoptosis when to die quite readily by ‘which is linked to airways remodelling. Additional contributions from IL-17, 14 in the number of airway neutrophils. 12 effective in reducing eosinophilic inflammation that inhaled corticosteroids, while highly human biopsy studies support the concept that neutrophils are predominant in 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 factors 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.

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), 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).

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-

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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, NETosis 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, and such agents may offer an important adjunct to current asthma treatments.

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