

nitrogen dioxide is defined as: "The 98th percentile of hourly means should not exceed 104.6 ppb." The underlying reason for specifying an upper percentile rather than an absolute limit is that extreme values are liable to be erratic, occurring in a highly local or transient manner or even as a result of instrument malfunction. In one year there are 8760 hours; the 98th percentile of hourly means is defined as the 176th highest hourly mean measured. Only if this exceeds 104.6 ppb is the relevant ED directive contravened. The limit value, designed to safeguard health with regard to exposure to nitrogen dioxide, was set with knowledge of the likely log-normal distribution of hourly mean concentrations. Though hourly means could exceed 104.6 ppb on 175 occasions per year, with occasional maxima up to three or four times that value, damage to health would not be expected.

In discussing WHO air quality guidelines for sulphur dioxide and smoke Dr Britton fails to point out that safety factors of 2 for effects on morbidity and mortality and of 1.5 for decrements of lung function were included when the guidelines for combined exposure to sulphur dioxide and particulate matter were defined.²

It should also be noted that the data on which the joint guideline was defined did not permit separation of sulphur dioxide and black smoke in terms of effects; it would thus be more appropriate to quote the number of days when the joint guidelines were exceeded than each one separately. Furthermore, WHO guidelines for black smoke² have not been defined on an hourly basis and the 24 hour guideline is currently quoted² as 125 µg/m³ rather than 100 µg/m³. The figure of 100 µg/m³ occurs in the World Health Organisation report of 1979.³ In that report a range of 100–150 µg/m³ was defined.

R L MAYNARD
R E WALLER
Department of Health,
Hambial House,
London SE1 6TE

The above are the opinions of the authors and should not be taken as representing those of the Department of Health.

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AUTHOR'S REPLY I thank Drs Maynard and Waller for their comments on my article, and their clarification of the various guidelines and limits on atmospheric pollution levels. I suspect that I am not alone in finding them a little confusing. The point I wanted to make in the article is that in the study by Sunyer *et al* (their ref 1) everyday variations in usual levels of atmospheric pollution had small but measurable effects on respiratory morbidity. The vast majority of this variation was well within all of the guidelines and limits. We need guidelines for monitoring and enforcing pollution controls, but if there was any doubt before it is surely now evident that pollution that does not contravene existing guidelines still causes respiratory morbidity. The question is whether this degree of morbidity is an

acceptable or necessary price to pay for economic development and, if it is, how much society should be prepared to accept.

JOHN BRITTON
Respiratory Medicine Unit,
City Hospital, Nottingham NG5 1PB

Pulmonary function in chronic renal failure: effects of dialysis and transplantation

In their article (June 1991;46:424–8) Drs A Bush and R Gabriel referred to decreased carbon monoxide transfer (TLCO) in four groups of patients with chronic renal failure. Apparently, their TLCO values were corrected for haemoglobin, which was low in most of their patients. Thus the decreased TLCO should be attributed to causes other than a low haemoglobin pool. The authors speculated that it was due to interstitial lung fibrosis, caused by chronic subclinical oedema.

These authors' results differ from those of others. TLCO is usually reduced in uraemic patients because of coexisting anaemia; adjusting to a normal haemoglobin concentration therefore produces normal TLCO values.^{1,2} In the population they studied, however, the underlying cause could not be determined from their data. Interstitial fibrosis with resulting deterioration of the membrane TLCO component (Dm) is the only possible factor. The authors did not perform chest radiography, which could have helped to resolve the issue. Moreover, there are even more sensitive tools for such evaluation—specifically high resolution computed tomography and a separate determination of Dm and the vascular component of the TLCO: pulmonary capillary blood volume (Vc) and the reaction rate of carbon monoxide with haemoglobin (theta, θ). According to the theory of Roughton and Forster—expressed as $1/TLCO = 1/Dm + 1/\theta Vc - \theta$ increases with increased haemoglobin. Without measuring the components of TLCO therefore, even after adjustment for haemoglobin, one cannot determine whether Dm or Vc predominantly affects the overall TLCO. There are also reports that haemodialysis (their group 3) per se affects TLCO,¹ which was not considered by the authors. In the sample that we studied¹ the effect of haemodialysis was a reduction in TLCO of about 10%, due entirely to a decrease in Vc of about 20%, which we attributed to a decrease in blood volume with consequent reduction in Vc.

ŽELJKO DUJIĆ
Department of Physiology,
Zagreb University School of Medicine in Split
58000 Split,
Republic of Croatia
DAVOR ETEROVIĆ
Department of Nuclear Medicine,
JADRANKA TOCILJ
Department of Pulmonary Medicine,
Clinical Hospital Split
45800 Split,
Republic of Croatia

- 1 Dujic Ž, Tocilj J, Ljutic D, Eterovic D. Effects of hemodialysis and anemia on pulmonary diffusing capacity, membrane diffusing capacity and capillary blood volume in uremic patients. *Respiration* 1991;58:277–81.
- 2 Petermann W, Entzian P, Barth J. Lung function in uremic patients on chronic hemodialysis [abstract]. *Am Rev Respir Dis* 1988;137(suppl):A480.

AUTHOR'S REPLY We thank Professor Dujic and colleagues for their interest in our paper and for raising some interesting points. Our

findings of a reduced TLCO even after correction for anaemia is in accord with the findings of other workers^{1,2} not cited in their own paper.³ We agree that the pathological cause of the physiological abnormalities could not be determined; we did not think that additional radiography was justified when we designed the study, but agree that in the light of our findings quantitative computed tomography⁴ would be of great interest. The issue of the meaning (if any) of attempting to measure Dm and Vc separately has been debated at length elsewhere.^{5,6} The theoretical problems include non-uniform DL/VA in the real lung, the dangers of extrapolating back to the intercept beyond the data points, and the profound effects that oxygen itself has on the pulmonary circulation, altering the variable one is trying to measure. There is also experimental evidence that Dm is insignificant.⁷ Thus we believe that TLCO does indeed measure the amount of blood (or, strictly, haemoglobin) within the pulmonary capillary bed. We did consider in detail the acute effects of haemodialysis on the lungs^{8,9}; the acute fall in TLCO takes place early in the dialysis, and it has reverted almost completely to predialysis values by the end of a six hour dialysis. We studied our patients within 24 hours of dialysis, to try to minimise the effects of accumulation of lung and body water between dialyses. Our final speculations are confirmed to some extent by pathological studies¹⁰; we agree that a new computed tomography, biopsy, or necropsy study is needed to determine the underlying pathology.

A BUSH

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Haematological effects of inhalation of N-formyl-methionyl-leucyl-phenylalanine in man

We read with interest the description by Dr M J Peters and colleagues (April 1992;47:284–7) of temporary peripheral blood leucopenia, in particular neutropenia, immediately following the inhalation of the tripeptide N-formyl-methionyl-leucyl-phenylalanine (FMLP) in normal subjects, accompanied by activation of peripheral blood neutrophils as measured by chemiluminescence.

We agree that the likely mechanism is

sequestration (not true "margination") in the pulmonary microvasculature. We would, however, suggest that such a rapid retention and subsequent release is much more likely to be due to changes in cell deformability, which is now generally believed to be the initiating factor in leucocyte sequestration before an increase in adherence. The importance of cell deformability as a determinant of neutrophil sequestration within human lungs has been demonstrated.¹ We² and others³ have shown that the effect of this tripeptide *in vitro* is to increase neutrophil rigidity within seconds by assembly of F-actin. Such a change is much more rapid than any up regulation of either leucocyte or endothelial adhesion ligands, which require minutes to hours.

It is attractive to speculate that the inhalation of FMLP, either by a direct effect across the alveolar capillary cellular barrier or by indirect action via mediators released from macrophages or mesenchymal cells, impairs the deformability and hence transit of neutrophils through the pulmonary vascular bed.

COLIN SELBY
ELLEN DROST
BILL MACNEE
Respiratory Medicine Unit,
Department of Medicine (RIE),
University of Edinburgh,
City Hospital,
Edinburgh EH10 5SB

- 1 Selby C, Drost E, Wraith P, MacNee W. In vivo neutrophil sequestration within lungs of humans is determined by *in vitro* "filterability." *J Appl Physiol* 1991;71:1996-2003.
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AUTHOR'S REPLY Consideration of potential mechanisms for the neutropenia induced by *N*-formyl-methionyl-leucyl-phenylalanine inhalation is necessarily complex but reduced neutrophil deformability, for the reasons stated, may be important. The rapid onset of neutropenia suggests that it is a result of slowed passage through the pulmonary or systemic microcirculation or both—effectively margination. Margination could be produced either by reduced deformability or increased neutrophil-endothelial adhesion but more probably both mechanisms operate, whether simultaneously or sequentially. The occurrence of cutaneous flushing, which presumably is a result of the release of vasodilator mediators, in synchrony with neutropenia, indicates that the neutrophil has the capacity to respond in ways other than merely reducing its deformability within the time span of maximal neutropenia. Furthermore, we do not know the true time course of the phase of increased margination. Within 10–15 minutes of FMLP inhalation there is a "rebound" neutrophilia, indicating that there must be release of white cells from a reserve pool or pools, possibly bone marrow. The duration of enhanced margination may be much longer than the observed period of neutropenia, with continuing margination and neutropenia obscured by these newly circulating cells. If that is so, one might argue that enhanced adhesiveness, because it may be longer lasting, is relatively more important.

Because present evidence does not allow a definitive conclusion about the relative importance of the above mechanisms in the produc-

tion of neutropenia, we did not ascribe a particular weight to each possibility. Using radiolabelled cells, we were unable to show leucocyte influx into the lungs during neutropenia. This may well be an imperfect technique. Nevertheless, in the absence of other published evidence, we cannot safely assume that margination, after neutrophil activation by an inhaled rather than an intravenous agent, takes place predominantly in the pulmonary circulation.

MATTHEW J PETERS
Department of Thoracic Medicine,
Royal Brompton National Heart and Lung Institute,
London SW3 6LY

BOOK NOTICES

Mediators of Pulmonary Inflammation.

Edited by M A Bray and W H Anderson. (Pp 688; \$165 USA and Canada, \$189.75 elsewhere.) New York: Dekker, 1991. ISBN 0-8247-8442-1.

Ten years ago workers investigating the science of their own particular respiratory disease rarely found common ground with people in other areas. For example, researchers in emphysema were concerned with matrix turnover whereas researchers on asthma focused on airway smooth muscle. They felt as if they were worlds apart. Now it seems that we can find more in common. This is not because of the altruistic desire of researchers in one area to listen to and help workers in other areas—rather the evolution of knowledge has revealed that a chronic inflammatory process, based on a persistent influx of inflammatory and immune cells, drives these disease processes. Thus, although they have different pathological outcomes, there are at least some common pathways and in some cases it is the different site of inflammation (that is, airways or lung parenchyma) that may be critical. In research terms, this has been a very useful development because information gained by research directed at one respiratory disorder is proving relevant to another. From the title of this book by Bray and Anderson it seemed that we may have had a treatise exploring this area of commonality between respiratory diseases, focusing on the mediators implicated in the different disorders. This is not the case. Instead the authors focused on inflammatory mediators in the airways, particularly in the setting of asthma. This was a shame because the first chapter, by Reid, gives us an excellent perspective on the different lung diseases, whetting our appetite regarding the overlap, which, it seemed, might be further explored. The authors explain in the preface that they are unrepentant about their focus on asthma, choosing to elaborate on new findings in a disease where, as they say, "much of the excitement is concentrated." I feel obliged to tell you that this reader did not get over-excited, though there were some excellent chapters and the book is a useful compendium on mediators being explored in asthma research, at least up to 1990. The book competes strongly with other recent publications giving updates on developments in asthma research. There were the usual problems in a book of this type, covering a rapidly evolving area. There were few references after 1990 and in

some chapters no references past 1988. This problem is highlighted for the interleukins (ILs), a family of mediators released by lymphocytes that often have proinflammatory effects. In one table the properties of IL-1–IL-6, believed to be most important at the time of writing, are listed. We are now up to IL-13 and many of the more recently discovered interleukins have been implicated in respiratory disease and asthma. Finally, one opportunity lost by these and other authors in this area was a lack of attempt to rationalise the terminology, which is so confusing to all but those intimately concerned. Thus the terms lymphokine, cytokine, growth factor, autacoid, paracrine agent, monokine, and mediator were used interchangeably, confusing those unfamiliar with the area, who are already punch drunk coping with the countless number of acronyms used to describe inflammatory mediators. In summary, this is a useful book for those requiring an introduction to inflammatory diseases of the lung and a detailed account of some areas of asthma research. It is not, as the title suggests, for readers trying to get an overview of the role of inflammatory cells and mediators in the wide spectrum of inflammatory lung diseases. To this end the authors may have better located their audience, and disappointed fewer readers, if they had chosen a more appropriate title reflecting the asthma focus of the book.—GEOFFREY J LAURENT

British Medical Bulletin: A Series of Expert Reviews—Asthma. Edited by P J Barnes. (Pp 225; £33.) Edinburgh: Churchill Livingstone, 1992. ISBN 0007-1420, 0 443 047189.

This is one of a series of "expert reviews" of various medical topics, produced quarterly by the British Council. This particular edition reviews recent advances in asthma in 19 chapters. Each is concise, well referenced, and preceded by an abstract summarising the content. The subjects covered are predominantly those of pathophysiology and include the currently popular areas of cell biology and immunology. In addition, topics not included in standard texts are reviewed—for example, the tracheobronchial vasculature, plasma exudation, and oedema in asthma. This book makes no attempt to provide a complete text on asthma but examines specific aspects in which recent advances have been made; it appears to be aimed at the physician with some background understanding of the condition. The first nine pages, however, are devoted to a clinical definition of asthma, which I suspect is unnecessary for most potential readers. The book suffers from a few problems. Cross referencing between the chapters of different authors, although attempted, is poor overall. Very recent developments have not been included in the text, which reflects the major difficulty of producing really up to date reviews in the form of an edited, hardback book with many authors. In particular, the section devoted to the epidemiological studies implicating β_2 agonists in asthma deaths does not mention the Spitzer study, and "New therapeutic approaches" discusses cyclosporin in two short sentences. Overall, I enjoyed reading this book and found some of the chapters very helpful indeed. I suspect its place is in the hospital library rather than on the study bookshelf.—CMR