LETTERS TO THE EDITOR

Inhibition of T cell proliferation by human alveolar macrophages

The demonstration by Upham *et al*[1] that human alveolar macrophages selectively inhibit proliferation of T cells by secretion of unidentified effector molecules raises the question as to whether pathological processes in the lung characterised by extensive macrophage recruitment or activation can have a systemic effect on T cell development.

It has been shown in several studies that patients with pulmonary tuberculosis who are not infected by HIV often show a lymphopenia principally affecting the CD4+ T cells.[2 3] This appears to be a transient phenomenon as the CD4+ count reverts to normal after successful therapy.[3] A similar transient CD4+ lymphopenia has also been observed after antigenic bronchial provocation in asthmatic subjects.[4]

It would be of great interest to determine whether this systemic phenomenon is due to the same mechanism as the one described by Upham *et al*, whether it accounts (at least in part) for the so-called "idiopathic CD4+ T lymphopenia syndrome",[3] and whether it affects the balance between Th1 and Th2 cells which may be critical to the pathogenesis of both asthma and tuberculosis.

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1 Upham JW, Strickland DH, Robinson BWS, *et al*. Selective inhibition of T cell proliferation but not expression of effector function by human alveolar macrophages. *Thorax* 1997;**52**:786–95.
2 Beck JS, Potts RC, Kardjito T, *et al*. T4 lymphopenia in patients with active pulmonary tuberculosis. *Clin Exp Immunol* 1985;**60**:49–54.
3 Pilheu JA, De Salvo MC, Gonzalez J, *et al*. CD4+ T-lymphocytopenia in severe pulmonary tuberculosis without evidence of human immunodeficiency virus infection. *Int J Tuberc Lung Dis* 1997;**1**:422–6.
4 Gerblich A, Campbell AK, Schugler MR. Changes in T-lymphocyte subpopulations after antigenic bronchial provocation in asthmatics. *N Engl J Med* 1984;**310**:1349–52.

AUTHORS' REPLY Studies in a variety of species[1–3] indicate that a substantial proportion of the recirculating T cell population is sequestered for significant periods during transit through the lung vascular bed, and many of these cells extravasate and move into the lung interstitium. The initial trapping of T cells in transit is due, at least in part, to local endothelial expression of inflammation associated molecules such as ICAM-1. This process is partially selective for recently activated T cells, and T lymphoblasts generated at immunoinflammatory foci distal to the lung readily enter the lung and therefore contribute to the local immunological milieu.[3 4] Moreover, the extremely large size of this peripheral lung T cell population indicates that this is a physiological process which operates continuously in normal individuals,[1–3] and it is conceivable (in our view highly likely) that it is further amplified in immunoinflammatory diseases in which high numbers of activated T cells are present in the circulation.[4]

As inferred by Dr Grange, these T cells are subjected to the powerful downregulatory influence of lung macrophages during their transit through lung tissue, resulting in a variety of functional changes including loss of proliferation capacity.[1 3 5] While the precise mechanisms employed by the macrophages to modulate T cells are incompletely understood, it is clear that their overall efficiency in this regard is a reflection of their maturation/activation status.[6] The suggestion that amplification of this process during inflammatory diseases characterised by enhanced lung macrophage recruitment/activation may result in significant effects on the overall recirculating T cell compartment is thus worthy of more detailed investigation.

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1 Strickland DH, Thepen T, Kees UR, *et al*. Regulation of T-cell function in lung tissue by pulmonary alveolar macrophages. *Immunology* 1993;**80**:266–72.
2 Pabst R, Binns RM, Licence ST, *et al*. Evidence of a selective major vascular marginal pool of lymphocytes in the lung. *Am Rev Respir Dis* 1987;**136**:1213.
3 Holt PG, Kees UR, Schon-Hegrad MA, *et al*. Limiting-dilution analysis of T cells extracted from solid human lung tissue: comparison of precursor frequencies for proliferative responses and lymphokine production between lung and blood T cells from individual donors. *Immunology* 1988;**64**:649.
4 Reynolds HY. Lung inflammation: normal host defense or a complication of some diseases. *Annu Rev Med* 1987;**38**:295.
5 Strickland D, Kees UR, Holt PG. Regulation of T-cell activation in the lung: isolated lung T cells exhibit surface phenotypic characteristics of recent activation including down-modulated T-cell receptors, but are locked into the G_0/G_1 phase of the cell cycle. *Immunology* 1996;**87**: 242–9.
6 Holt PG. Regulation of antigen-presenting cell function(s) in lung and airway tissues. *Eur Respir J* 1993;**6**:120–9.

Adenosine and adenosine antagonism in asthma

I read with interest the excellent update on adenosine by Polosa and Holgate.[1] An important use of this challenge agent is demonstrated and adenosine antagonism as a potential treatment for asthma is revisited. However, the role of adenosine as a mediator of asthma is somewhat inconsistent with several functional observations.

Besides the fact that adenosine has dual effects in many systems, data are available—particularly involving the pharmacology of enprofylline (3-methyl xanthine)—which suggest that the therapeutic efficacy of theophylline (1,3-dimethyl xanthine) in asthma may not reflect adenosine antagonism.[2] This latter aspect is significant because theophylline, at therapeutic concentrations, effectively antagonises adenosine (at receptors and functionally in vivo).

Qualitatively different from theophylline, enprofylline does not antagonise the physiological/pathophysiological actions of adenosine[2] yet enprofylline and theophylline share several pharmacological actions including cardiac stimulation, microvascular antiexudative activity, and a range of smooth muscle relaxant effects although enprofylline is consistently about three times more potent than theophylline.[2] Equally, enprofylline is about three times more potent than theophylline in asthma as a bronchodilator,[2] as an inhibitor of histamine-induced bronchoconstriction,[2 3] as an inhibitor of late phase reactions,[2] and in maintenance therapy.[2] Indeed, it is only under artificial conditions when asthmatic subjects inhale adenosine that theophylline provides greater protection than enprofylline.[3]

In contrast to its efficacy in the treatment of asthma, enprofylline lacks several well known clinical effects of theophylline such as diuretic activity, CNS arousal effects, free fatty acid releasing effects, and gastric secretory effects.[2] This distinct human pharmacology is evidence for the clinically effective adenosine antagonism of theophylline and indicates that enprofylline tonically suppresses volume and acidity of gastric secretion, natriuresis, free fatty acid release, etc.[2] One might therefore conclude that adenosine antagonism should probably be avoided in asthma therapy because it may be associated with less desirable excitatory extrapulmonary effects.

Antagonism of A_{2b} adenosine receptors by enprofylline may explain the "adenosine hypothesis".[1] By inferring this, Polosa and Holgate lend greater weight to in vitro observations that disagree with the anti-asthma potency ratio between enprofylline and theophylline that may require 300 μM drug concentrations for effective function (inhibition of mast cell release) than, for instance, to the work by Clarke *et al*[3] which showed that theophylline, but not enprofylline, protects against adenosine induced obstruction in asthma (see also references 18 and 21 in the review by Polosa and Holgate[1]).

If the clinical efficacy of the xanthines in asthma cannot be explained by adenosine antagonism, phosphodiesterase inhibition may offer an alternative explanation but, unfortunately, there are also doubts about this[4]—hence the widely promoted non-xanthine phosphodiesterase IV inhibitors cannot rely on theophylline for any predictable clinical efficacy. Perhaps both adenosine antagonism and phosphodiesterase inhibition are examples of how theoretically attractive mechanisms may prevent unbiased exploration of truly important in vivo modes of action of anti-asthma drugs.[4]

Incidentally, enprofylline was discovered by unexpected observations in complex biosystems.[4] Such exploratory in vivo work, if allowed, will continue to be a source of novel drugs; when successful, one should not be surprised to learn that the discovered class of drug was not predicted by reductionist research paradigms. The new efficaceous compounds may thus unravel novel mechanisms—for example, omeprazole and the acid pump—or, as with the experimental drug enprofylline, the new properties will seriously question the therapeutic relevance of a widely held mechanism.

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1 Polosa R, Holgate ST. Adenosine bronchoprovocation: a promising marker of allergic inflammation in asthma? *Thorax* 1997;**52**:919–23.
2 Persson CGA, Pauwels R. Pharmacology of antiasthma xanthines. In: Page CP, Barnes PJ, eds. *Handbook of experimental pharmacology: pharmacology of asthma*. Berlin: Springer, 1991: 207–23.

3 Clarke H, Cushley MJ, Persson CGA, *et al*. The protective effects of intravenous theophylline and enprofylline against histamine- and adenosine-5'-monophosphate-provoked bronchoconstriction: implication for the mechanisms of action of xanthine derivatives in asthma. *Pulmonol Pharmacol* 1989;**2**:147–54.
4 Persson CGA. In viva veritas. The continuing importance of discoveries in complex biosystems. *Thorax* 1996;**51**:441–3.

AUTHORS' REPLY We read with interest the letter from Professor Persson but we remain somewhat confused about the point or points he raises. The review we wrote was intended to draw attention to adenosine bronchial provocation as a potential new marker of airway inflammation in asthma, which may be useful both clinically and to assess the action of anti-inflammatory drugs such as topical corticosteroids.[1] Because it was originally thought that enprofylline was free of A_2 receptor antagonist properties it was argued that adverse effects of xanthines operating through this receptor could be avoided.[2] It was also stated that, because enprofylline did have pharmacological and therapeutic actions in asthma, it was unlikely that adenosine antagonism could be involved. As pointed out in our review, it is now known that there exist two types of adenosine A_2 receptor designated A_{2a} and A_{2b}.[3 4] While enprofylline has little or no effect against A_{2a} receptors, it is a selective, albeit weak, antagonist at the A_{2b} receptor—the adenosine receptor subtype found both on canine[5] and human[6 7] mast cells. Thus, if adenosine is released in pharmacologically active concentrations in asthmatic airways, for which there is good evidence, then enhancement of mast cell mediator release via A_{2b} receptors is a probable scenario. As a consequence, enprofylline could have produced at least some of its therapeutic effect in asthma by inhibiting A_{2b} receptor mediated mast cell releasability. This may or may not have had implications for the clinical efficacy of enprofylline, which is only a weak A_{2b} antagonist, but the A_{2b} receptor does present a potential new therapeutic target for asthma against which new drugs might be developed.[8]

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1 Taylor DA, Jansen MW, Harris JG, *et al*. Airway responsiveness to AMP: a sensitive method to evaluate the dose-response relationship of an inhaled steroid in asthma. *Eur Respir J* 1997;**10**(Suppl 25):295s.
2 Persson GG, Andersson K, Kjellin G. Effects of enprofylline and theophylline may show the role of adenosine. *Life Sci* 1986;**38**:1057–72.
3 Feoktistov I, Biaggioni I. Characterisation of adenosine receptor in human erythroleukaemia cells. Further evidence for heterogeneity of adenosine A2 receptors. *Mol Pharmacol* 1993;**43**:909–14.
4 Brackett LE, Daly JW. Functional characterization of the A_{2b} adenosine receptor in NIH 3T3 fibroblasts. *Biochem Pharmacol* 1994;**47**:801–14.
5 Auchampach JA, Jin X, Wan TC, *et al*. Canine mast cell adenosine receptors: cloning and expression of the A3 receptor and evidence that degranulation is mediated by the A_{2b} receptor. *Mol Pharmacol* 1997;**52**:846–60.
6 Feoktistov I, Biaggioni I. Adenosine A_{2b} receptors evoke IL-8 secretion in human mast cells. *J Clin Invest* 1995;**96**:1979–86.
7 Xiaowi Jin. PhD Dissertation, University of Virginia, Charlottesville, 1996.
8 Feoktistov I, Polosa R, Holgate ST, *et al*. Adenosine A_{2b} receptors. A novel therapeutic target in asthma? *Trends Pharm Sci* 1998 (in press).

BOOK REVIEWS

Progress in Respiratory Research Series. Volume 29. Updates in Advances in Lung Cancer. J H Schiller. (Pp 192; $160.00). Switzerland: Karger, 1997. 3 8055 6557 7.

Reasonably digestible reviews of recent clinical trials in the management of lung cancer are rare and, in general terms, this 11 chapter book is welcome. The emphasis here is on the use of chemotherapy and radiotherapy in the management of lung cancer, with eight of the 11 chapters considering these aspects, and the other three are concerned with chemoprevention, palliative medicine, and molecular biology.

Nine of the 11 authors are from the USA. The chapters take the form of a traditional review and are reasonably well set out with an average of about 50 references for each topic. The strengths of the book are the comprehensive assessment of novel drug therapies, with separate chapters for paclitaxel/carboplatin, gemcitabine, and docetaxel in non-small cell lung cancer, and a separate chapter on novel drugs for small cell lung cancer, including the topoisomerase-1 inhibitors, carboplatin, and the taxanes.

Sadly, the volume lacks an adequate introduction by the Editor, which would have been useful if it had been able to point out the "major messages" from each of the chapters—for example, bringing out the importance of the recent meta-analysis of trials of prophylactic cranial irradiation in responding small cell lung cancer, or the superiority of standard intravenous regimens over low dose oral etoposide in this disease. Surgery gets no mention at all, and nor does endobronchial therapy. This is a pity since there have been major advances in our understanding of the role of endobronchial treatments, and the literature, particularly that relating to brachytherapy, is badly in need of review. Likewise, I found the chapter on palliative medicine disappointing with no consideration of psychosocial problems or some important major physical symptoms such as cough and pleural disease, and a misplaced discussion here of the meta-analysis of chemotherapy in non-small cell lung cancer. The best chapter, in my view, was that by Wagner on radiation therapy in small cell lung cancer which was a well set out discussion of the attempts that have been made to optimise local control by altering the timing and fractionation of thoracic radiotherapy, together with an up to date discussion on prophylactic cranial irradiation. The book is just about up to date enough to include the results of the important MRC study on continuous hyperfractionated accelerated radiotherapy for non-small cell disease (CHART), which must now be considered as one of the few studies on radiotherapy recently to have shown an improvement in survival compared with local control.

This book will not appeal to the non-specialist, though it would be a useful starting point for doctors or groups who want an up to date background account as a preliminary to designing their own studies or choosing a pattern of management for their patients. Inevitably, in a fast moving field such as the assessment of novel drug therapies for lung cancer, a book like this will rapidly become out of date and, as with guidelines, I would estimate that "an update of this update" will probably be needed within a couple of years.—MFM

Tuberculosis. W N Rom, S M Garay, eds. (Pp 982). Boston: Little, Brown and Company, 1995.

When asked to review this book last year I devised my own "sightation index" to assess its worth to me as a respiratory physician with the responsibility for a tuberculosis service. First a sit down to get acquainted with each other. It is big, attractive, well laid out and easy to grasp, but somewhat let down by the index. The first sections on history and epidemiology are as interesting as a *British Medical Journal* Christmas issue, but potentially more expensive to read in the bath—I enjoyed them. The 28 colour photos are cheerful and useful, except three brown-on-brown immunoperoxidase stains which make the eyelids droop, presumably the reason why photograph 23 of the eye is presented upside down.

During the year it sat on my shelf four colleagues borrowed the book and said it was very useful. My personal "sightation index" was 10, nearly equalling my most popular text book. I scored the usefulness of each sightation on a scale from O (no value) to 3 (excellent). I searched for *M szulgai* (useful about soft tissue infection and antibiotic sensitivity but little regarding lung infection, score 2/3), how to give BCG in the thigh (nothing, 0/3); management of multi-drug resistant tuberculosis (excellent, 3/3), renal tuberculosis (excellent review and helpful discussion of the role of nephrectomy and oral steroids, 3/3); *M bovis* (good review and references, 3/3); management of BCG complications (subcutaneous abscess not mentioned, vague advice on therapy, 0/3), medical and surgical management of tuberculosis empyema (most useful, 3/3); TB in prisons—sorry, correctional institutions or "tax supported exposure chambers for tuberculosis" (useful but review limited to problem in USA, some unrealistic recommendations, 2/3); advice on standard drug therapy (useful summary of ATS recommendations but not of drug dosages, 2/3); and directly observed therapy (again no summary of intermittent dosages, 2/3).

So the borrow index was 4, my "sightation index" was 10, and usefulness score 66%. That's pretty good (BCG apart), and I am very pleased to have it available. So should you, if you have an interest in or responsibility for a tuberculosis service.—JTM

NOTICE

New Drugs for Asthma

A two-day conference on "New Drugs for Asthma" will be held at the National Heart and Lung Institute, Imperial College School of Medicine, London on 16 and 17 June 1998. For further details please contact Caroline Elliott at IBC UK Conferences Ltd, Biomedical Division, Gilmoora House, 57–61 Mortimer Street, London W1N 8JX, UK. Tel: +44 (0)171 453 2701; Fax: +44 (0)171 631 3214; email caroline.elliott@ibcuk.co.uk