

LETTERS TO THE EDITOR

Role of viral infections in the inception of childhood asthma and allergies

In his fascinating and challenging article Dr Martinez (December 1994;49: 1189-91) suggests that viral infections occurring early in life may protect against atopy and asthma by driving T helper cells towards a predominantly Th1 phenotype. We wonder whether viral infections of the mother during pregnancy may not also have a part to play in providing some temporary immunity to the infant with related consequences, and suggest that the hypothesis has parallels in mycobacterial disease which suggest a common therapeutic approach.

The relationship shown in many studies between maternal influenza and the subsequent development of schizophrenia in the offspring has never been easy to explain.¹ By extending Dr Martinez's hypothesis, maternal antibodies and cytokines such as interferons might modify the infant's response, even to the establishment of a normal flora, in a way that could predetermine the pattern of T cell responses for life. The recent demonstration of autoantibodies to the 60 kDa heat-shock protein in patients with schizophrenia,² and the alleviation of their symptoms by repeated injections of influenza vaccine,³ may lend support to the concept.

There is evidence that priming or "imprinting" of the immune system by contact with environmental mycobacteria early in life determines whether subsequent BCG vaccination or challenge by a mycobacterial pathogen will induce protective immunity or tissue destroying hypersensitivity.^{4,5} In turn, this has been related to the T helper cell phenotype as Th1 cells elicit protective immunity to mycobacterial pathogens while a mixed Th1/Th2 cell population induces extensive tissue necrosis (the Koch phenomenon) by rendering tissues exquisitely sensitive to killing by tumour necrosis factor.⁶

The T cells in the peripheral blood and lesions of patients with progressive tuberculosis express the IL-4 gene,⁷ and some patients have mycobacteria-specific IgE antibody,⁸ both phenomena being indicative of a Th2 response. There is also evidence of an association between asthma and tuberculosis. Asthma and atopy were found to be considerably more common in a sanatorium population than in non-tuberculous controls, and they had an unfavourable effect on the course of tuberculosis.⁹ In the Ukraine allergic diseases are reported to occur 4-5 times more frequently in patients with tuberculosis than in the general population.¹⁰ It is interesting to note that in the Oxford Record Linkage Study¹¹ there was a highly significant excess of pulmonary tuberculosis prior to admission with schizophrenia.

It has been shown in a number of studies that heat-killed *Mycobacterium vaccae*, a known Th1 adjuvant,⁶ given by intradermal

injection suppresses tissue necrotising hypersensitivity in tuberculosis and induces protective immunity with observable clinical benefit.¹² There is also limited evidence that this immunotherapy is useful in patients with AIDS,¹³ another disease in which it has been postulated that a therapeutic induction of a Th2 to Th1 shift would be protective.¹⁴ It is not known whether immunotherapy with *M vaccae*, possibly in a recombinant form expressing allergen epitopes, would induce a clinically beneficial Th2 to Th1 shift in atopic subjects, although this could easily and safely be investigated. Nevertheless, the experience with tuberculosis indicates that a therapeutic measure to shift the phenotype of the T helper cell population is a practical reality which, in view of the hypothesis of Martinez, could find application to the therapy of asthma and other atopic disorders.

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BAL fluid analysis and HIV-1 infection

The recent review by Drs Agostini and Semenzato (September 1994;49:848-51) contains a number of omissions and inaccuracies that require correction. They hypothesise that HIV-1 reaches the lung either through latently infected blood monocytes that differentiate into resident alveolar macrophages or via infected CD4+ T lymphocytes that migrate to pulmonary lymphoid tissues. A third mechanism is overlooked - namely, that early infection in many HIV-1 positive individuals is accompanied by viraemia where significant levels of "cell-free" virus may be detected in serum or plasma.¹ This cell-free virus may be carried to the lung by the microcirculation system and infect cells other than inflammatory cells (that is, endothelial cells) of the lung. It is now well documented that HIV-1 both infects and replicates in lung fibroblasts^{2,3} and, indeed, these cells may yet prove to be an important reservoir of HIV-1 in the lung.

Drs Agostini and Semenzato preface their discussion by stating that "despite pulmonary complications which are characteristic of advanced phases of HIV-1 infection, the lungs can be infected even in the asymptomatic phase." The authors refer to their previous review⁴ to substantiate this statement but, in a discussion of asymptomatic infection during which four papers are quoted, three refer to studies in patients with AIDS and the fourth is a case report on two AIDS-related complex patients with lymphocytic interstitial pneumonitis. However, they have inexplicably ignored an important study regarding HIV-1 load and cytokine activity in the lung of asymptomatic HIV seropositive patients published by Rich and colleagues in January 1994.⁵ In relation to our own work they go on to suggest that our results are inconsistent - even incompatible - with findings that might be predicted in asymptomatic individuals. The reason for this is that all our published work to date comes from patients with established AIDS. Indeed, all individuals in our studies underwent bronchoscopy for diagnostic reasons. The authors incorrectly state that "HIV-1 can be more readily detected in the BAL fluid of individuals with *Pneumocystis carinii* pneumonia (PCP) than in patients with non-PCP lung infections..." What we have shown is that HIV-1 can be isolated by culture more readily from the cells in BAL fluid of individuals with PCP,⁶ a finding that has been subsequently substantiated by others.⁷ Next the authors state that "retroviral sequences are found more frequently in the lungs of individuals receiving no antiviral chemotherapy than in those receiving treatment with zidovudine (AZT)..." In fact we have shown by polymerase chain reaction (PCR) that HIV-1 DNA could be detected in the BAL cells of 65% of individuals on AZT compared with 64% of patients taking no antiviral chemotherapy.⁸ We also showed that we could isolate HIV-1 in culture from the BAL cells of 52% of AIDS patients on AZT compared with 64% of individuals on no antiviral therapy, but the difference between the two groups was not statistically significant.^{6,8} Subsequent work by us using quantitative PCR methods has shown that there is a reduction in the quantity of HIV proviral DNA/10⁶ BAL cells in AIDS patients on AZT compared with those not on antiviral therapy,⁹ and similar reductions have been observed by others for peripheral blood cells.¹⁰

The authors then state that "it has also been observed that HIV-1 detection in BAL fluid samples is significantly associated with progression to death but not to reduction of pulmonary function tests." Again our results were from patients with AIDS and the reason for the lack of correlation between these two parameters could be due to a masking by the concomitant opportunistic respiratory infection. It is well established that PCP has a profound effect on the carbon monoxide transfer factor (TLCO) in HIV-1 seropositive individuals.¹¹ We reiterate that all our patients underwent bronchoscopy because they had a respiratory episode. It should be pointed out that in our study the mean TLCO value in patients was 46.3 regardless of whether HIV could or could not be cultured from the BAL cells of these individuals.¹² Conversely, direct damage to lung physiology by HIV-1 may occur during the asymptomatic phase, in which case any viral-associated reductions would have occurred in these patients prior to our investigations. Perhaps patients with AIDS should have undergone bronchoscopic examination before and in between respiratory episodes to determine what direct effect HIV-1 may be having on pulmonary function, but this was ethically unacceptable at the time of our studies.

Drs Agostini and Semenzato continue by stating that "detailed analyses are needed to characterise HIV-1 strains completing reverse transcription in the lung in vivo. These data are central to verifying whether the emergence of retroviral variants represents an important factor affecting the pulmonary manifestations of HIV-1 infection." We have already shown that the biological phenotypes isolated from BAL cells of patients with AIDS can be distinguished in all instances so far tested from the corresponding phenotype isolated from a matched peripheral blood sample.¹³ Furthermore, the emergence of more virulent syncytium-inducing HIV-1 variants does occur in BAL cells of some individuals in the terminal stages of AIDS.¹⁴ Genotypic characterisation of these strains is already underway.

They conclude their editorial by stating that "longitudinal studies of BAL fluid findings in a large number of HIV-1 infected patients followed from an asymptomatic stage until the diagnosis of AIDS are necessary to define clearly the natural course of the respiratory illness in HIV-1 infection." As we have recently shown, dramatic longitudinal changes do occur,¹⁴ and now that ethical approval has been obtained, studies with HIV infected, asymptomatic individuals are already underway at St Mary's Hospital in London. Finally, Drs Agostini and Semenzato point out the necessity to establish a cooperative study to investigate the prognostic impact of BAL analysis in a large cohort of patients being drawn from centres in nine European countries. We agree such studies are vital to the understanding of the role of HIV in lung infection.

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AUTHORS' REPLY We are perplexed by the comments of Dr Clarke and associates regarding our recently published editorial. They state that our review contains "a number of omissions and inaccuracies", complaining that we ignored important studies on the pathogenetic mechanisms of HIV disease in the lung. First of all, Dr Clarke and co-authors may not have realised that our paper was not a review but an editorial and, as such, was not intended to include a detailed analysis and quotation of the complete literature published in the field. In this regard, the ultimate goal of our editorial was to encourage cooperative studies to investigate the prognostic impact of BAL analysis in a large cohort of patients.

Apart from this, most of the concepts raised by Dr Clarke and colleagues had already been taken into account in our recent state of the art review published in the *American Review of Respiratory Diseases*.¹ As an example, they state that we omitted an important pathway through which HIV-1 may enter the lung -

namely, cell-free virus that is carried to the lung by the microcirculation - not to mention the possibility that other pulmonary cells, including lung fibroblasts, may be an important reservoir of HIV-1. Both of these concepts and other hypothetical mechanisms of HIV infection of the lung can be found in that review or in another recently published paper.²

Dr Clarke and associates continue by stating that we suggest that "their results are inconsistent, even incompatible". This is not so, and these concerns are not easily comprehensible. We obviously respect their work and the proof is that we quoted (appropriately!) four papers from their group (in a total of 29 references) in our editorial. As the reader can readily check, most of the phrases that we report in our editorial were taken from Dr Clarke's manuscripts.³⁻⁸ Naturally, we did not cite his abstract or the letter which appeared in the *Lancet* on 3 September 1994 which was published after our editorial went to press. For the same reason, we did not quote interesting data recently produced by our group on the HIV-1 infection of lung CD8+ cells recovered from the BAL fluid of patients with AIDS.⁹

To conclude, we have taken the letter by Dr Clarke and coworkers to be a provocative challenge to face new issues in the field. In the past we have read with great pleasure and interest their data in several international referenced journals. In the future we look forward to reading other results from their team with undiminished enthusiasm.

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