# 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 sanitorium 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 Study[11] 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 review[4] 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/$10^6$ 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]