Lymphocyte-Macrophage Alveolitis in Nonsmoking Individuals Occupationally Exposed to Asbestos

William N. Rom, M.D., M.P.H., F.C.C.P.; and William D. Travis, M.D.

A disordered immunologic activity has been observed in humans and animal models of asbestosis and silicosis. To characterize the lung immunologic response following long-term occupational exposure to asbestos, bronchoalveolar lavage (BAL) was performed on 28 nonsmoking individuals. Increased BAL lymphocytes were observed in one third. Lung lymphocytes were predominantly of the CD4+ helper-inducer subtype with increased CD4+/CD8+ ratio and increased surface expression of DR antigen consistent with the activation phenotype. Histologic evaluation of lung tissue from two individuals with lymphocytic-macrophage alveolitis and asbestos exposure revealed an infiltration of alveolar walls with chronic inflammatory mononuclear cells (lymphocytes). Interferon gamma was spontaneously released by BAL cells from 19 (76 percent) of 25 of the individuals with asbestos exposure and only one of ten normal controls. The release of interferon gamma by BAL cells could be further stimulated with concanavalin A and suppressed by cyclosporine. Although asbestosis is characterized by a predominant alveolar macrophage alveolitis, there is a subgroup with lymphocytic alveolitis and activated lymphocytes participating in the inflammatory response, especially in those without respiratory impairment early in the course of the disease process. (Chest 1992; 101:779-86)

Asbestosis is characterized by an alveolar macrophage alveolitis in the lower respiratory tract associated with thickened alveolar walls due to increased numbers of mesenchymal cells and their products, namely collagen. In nonsmoking individuals, bronchoalveolar lavage (BAL) has also demonstrated a small, but significant increase in neutrophils with a neutrophil chemotactic factor, leukotriene B4, spontaneously released by activated alveolar macrophages. In addition to increases in alveolar macrophages and neutrophils, BAL in asbestosis and silicosis has identified increases in lymphocytes. Asbestosis and silicosis are associated with alterations in systemic immune regulation, including hypergammaglobulinemia, circulating immune complexes, altered CD4+/CD8+ ratios in blood and lung, and reduced responsiveness to recall antigens. Animal models of asbestosis and silicosis have demonstrated increased lymphocytes in BAL fluid, altered responsiveness of lung lymphocytes to lectins, and increases in CD4+ lymphocytes in silicosis with increased CD8+ lymphocytes in asbestosis. To characterize the pathophysiologic role of the lymphocyte in asbestosis, BAL was performed in a nonsmoking group of individuals with >20 years' occupational exposure to asbestos and lymphocyte function evaluated. Our objectives were to clarify the lymphocyte subtype in the alveolitis, to assess activation status by surface markers and spontaneous release of lymphokines, to correlate these with lung function, and to attempt to block lymphokine release in vitro with cyclosporine. Lastly, we had the opportunity to evaluate the histologic features of open lung biopsy specimens from two individuals with lymphocytic-macrophage alveolitis and asbestosis.

METHODS

Study Population

There were 28 male study subjects with occupational exposure to asbestos for >20 years. Asbestos exposure occurred in the construction trades as insulators, boilermakers, plumbers, or sheet metal workers. All study subjects were lifelong nonsmokers or exsmokers for more than five years. All had chest roentgenograms read according to the 1980 ILO International Classification of the Radiographs of the Pneumoconioses as ≥1/0 (Table 1). All asbestos-exposed individuals had bilateral pleural plaques and/or thickening. Pulmonary function tests were performed as described. Normal values were obtained from Morris et al. for forced vital capacity (FVC), forced expired volume in 1 s (FEV1), and FEV1/FVC ratio; normal values for functional residual capacity used to calculate total lung capacity (TLC) were from Bates et al. and normal values for single breath diffusing capacity were from Gaensler and Wright. Respiratory impairment was defined as one of three <80 percent predicted: vital capacity (VC), TLC, or diffusing capacity. Gallium 67 lung scans were performed according to Line et al. Control individuals (n = 16) had normal chest roentgenograms and normal results of pulmonary function tests and no occupational inorganic dust exposure. No study individuals were taking medications.

Bronchoalveolar Lavage

Bronchoalveolar lavage was performed with a flexible fiberoptic

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IFN = interferon; IL = interleukin; mRNA = messenger RNA; PDGF = platelet-derived growth factor; TNF = tumor necrosis factor
bronchoscope using a total of 300 ml in five, 20-ml aliquots in three sites (right middle lobe, lingula, and left lower lobe) as described.\textsuperscript{11} If there was any evidence of airway inflammation during the bronchoscopy procedures, the analysis was discarded. The recovered fluid was pooled and aliquots were taken for determination of cell number and cell differential determined according to Saltini et al.\textsuperscript{2} Cell viability was determined using trypan blue dye exclusion. A differential cell count was performed on 500 cells. Bronchoalveolar lavage lymphocytosis was defined as $>$30 percent, which was the highest value for normal subjects.

**Lymphocyte Function Evaluation**

The lymphokine interferon gamma (IFN-$\gamma$) was quantified from BAL cells after culture for 24 h, at 37°C, at a concentration of 5 $\times$ 10$^6$ cells per milliliter in RPMI-1640 medium in 24-well plates. As a control, parallel wells were incubated in the presence of concanavalin A at 50 mg/mL (Sigma). To inhibit lymphokine release, supernatants were also collected in the presence of cyclosporine (Sandoz Pharmaceuticals, East Hanover, NJ) at 1 $\mu$g/mL, dissolved in alcohol and RPMI-1640 to a final concentration of alcohol of 1 percent.\textsuperscript{11} Interferon was quantified as described.\textsuperscript{11} To determine that the interferon activity was gamma in type, supernatants were incubated with polyclonal antibodies to IFN-$\alpha$ (Interferon Sciences, New Brunswick, NJ) and INF-$\beta$ (National Institute of Allergy and Infectious Diseases, Bethesda, Md), and a monoclonal antibody against IFN-$\gamma$ (Rorer, Springfield, Va).\textsuperscript{11} Serum interferon levels were measured identically.

Bronchoalveolar lavage cells were evaluated by immunofluorescent microscopy to determine the proportions of T cells and to evaluate the ratio of helper/inducer (CD4$^+$, Leu-3-positive) to suppressor/cytotoxic (CD8$^+$, Leu-2-positive) cells. Fluorescein, biotin, or phycerythrin-conjugated mouse monoclonal antibodies Leu-4, Leu-3, Leu-2, and the anti-HLA-DR mouse monoclonal antibody L243 were used (Becton, Dickinson & Co, Sunnyvale, Calif). The BAL cells (5 $\times$ 10$^6$) were aliquoted into 5-vial 96-well plates (Flow Laboratories, McLean, Va) and incubated 30 min with two monoclonal antibodies in 50-ml phosphate-buffered saline solution (PBS) containing 1 percent bovine serum albumin (Sigma) and 0.2 percent sodium azide (Sigma).\textsuperscript{11} Cells were washed three times, fixed for 15 min in 10 percent formalin, and mounted on a microscope slide. The proportion of lymphocytes reacting with each monoclonal antibody was determined by counting 100 cells using immunofluorescence microscopy at $\times$600 magnification with an epifluorescence condenser and fluorescein and rhodamine filter sets.

Interleukin-2 release by lung T cells was assessed as described by Pinkston et al.\textsuperscript{11}

**Statistics**

All values are the mean $\pm$ standard error of the mean. Comparisons of IFN-$\gamma$ release by exposed vs controls used the one-tailed Mann-Whitney U test for nonparametric data. After in vitro stimulation of IFN-$\gamma$ release by concanavalin A, paired samples that approximated a normal distribution were analyzed using the two-tailed Student's t test. Comparing lymphocyte surface markers between asbestos-exposed and controls used the Student's t test. To test the hypothesis that there was an association between the proportion of lymphocytes and exposure to asbestos, we used the Fisher's exact test. The level of significance accepted was p<0.05.

**RESULTS**

Individuals with occupational asbestos exposure had irregular roentgenographic opacities with all of the asbestos-exposed persons having pleural changes as well (Table 1). None had hilar or paratracheal adenopathy. Reduced lung function (VC, TLC, and/or Dco <80 percent predicted and FEV/FVC >100 percent predicted) consistent with restrictive impairment was found in half of the individuals with asbestos exposure: (13/28, 46 percent). Mean values for gallium 67 lung scan indices were six times greater for asbestos-exposed individuals compared with controls (Table 1).

There were more total cells per milliliter recovered in BAL from asbestos-exposed patients than from controls (p<0.001) (Table 1). Although the cell differentials were similar there was a significant increase in percent lymphocytes using the Fisher's exact test (p<0.01). The association was most pronounced at lymphocytes proportions >20 percent. There were 36 percent (10/25) of the asbestos-exposed individuals with percent lymphocytes greater than the highest value for the normal controls (Fig 1) with half (14/28) above 20 percent lymphocytes.

Bronchoalveolar lavage cells were spontaneously releasing IFN-$\gamma$ into the supernatant from 19/25 (76 percent) of the individuals with asbestos exposure and 1/10 (10 percent) of the normal controls (asbestos-exposed 70 $\pm$ 27 units, controls 1.0 $\pm$ 1.0 units, p<0.01, Table 2). Evaluation of supernatants incubated with polyclonal antibodies to IFN-$\alpha$ or IFN-$\beta$ or monoclonal antibody to IFN-$\gamma$ revealed that the activity was blocked only by the monoclonal antibody to IFN-$\gamma$. Almost half (47 percent) of the individuals with asbestos exposure who had BAL cell supernatants positive for IFN-$\gamma$ had percent lymphocytes greater than the

### Table 1—Clinical, Radiologic, Physiologic, and Bronchoalveolar Lavage (BAL) Characteristics of the Study Population*

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Exposure, yr</th>
<th>Roentgenogram</th>
<th>Pulmonary Function Tests†</th>
<th>Total Cells $\times 10^5$</th>
<th>Cell Differential</th>
<th>Lung Scan, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>VC</td>
<td>FEV$_1$</td>
<td>TLC</td>
<td>Dco</td>
</tr>
<tr>
<td>Asbestos</td>
<td>25</td>
<td>0.0</td>
<td>1/0-1/2</td>
<td>87 $\pm$ 3</td>
<td>92 $\pm$ 1</td>
<td>88 $\pm$ 2</td>
</tr>
<tr>
<td>Normals</td>
<td>16</td>
<td>0.0</td>
<td>0/0</td>
<td>99 $\pm$ 2</td>
<td>102 $\pm$ 3</td>
<td>98 $\pm$ 2</td>
</tr>
</tbody>
</table>

*All values presented as the mean $\pm$ SEM.
†Proportion of irregular opacities according to the 1985 ILO International Classification of the Radiographs of the Pneumoconioses.
‡All values are expressed as percentage of predicted. VC = vital capacity; TLC = total lung capacity; Dco = diffusing capacity corrected for volume and hemoglobin; FEV$_1$ = forced expired volume in 1 s.
§AM = alveolar macrophages; L = lymphocytes; N = neutrophils; E = eosinophils.
highest normal control compared with only 17 percent of those with asbestos exposure and BAL supernatants negative for IFN-γ. Conversely, eight of nine asbestos-exposed workers with BAL lymphocytosis were positive for IFN-γ. Asbestos-exposed individuals with normal lung function had almost twice the level of IFN-γ in BAL supernatants and half as many negative samples compared with those with restrictive impairment as defined in the "Methods" section. In contrast, there were no differences among those with BAL lymphocytosis >30 percent vs <30 percent in regard to age, years exposed, pulmonary function, or percentage releasing lymphokines into supernatants.

The BAL cells were incubated with a lectin known to stimulate lymphocytes and 11 of 12 individuals with asbestos exposure had a significant (p<0.05) increase in IFN-γ release (Fig 2, left). To determine if the release of IFN-γ could be inhibited, the same 12 individuals exposed to asbestos whose BAL cells spontaneously released IFN-γ were incubated with cyclosporine in vitro. There was a significant (p<0.05) reduction in IFN-γ release (Fig 2, right). Incubation of BAL cells recovered from normal individuals with chrysoile asbestos in vitro at concentrations from 1 to 100 μg/L failed to stimulate the release of IFN-γ. No IFN-γ was released spontaneously from blood mononuclear cells cultured similarly to BAL cells.

Most of the lymphocytes present in the lungs of the asbestos-exposed individuals were T cells as defined by staining with the Leu-4 monoclonal antibody (90 ± 2 percent). The asbestos-exposed individuals had a significant increase in Leu-3+ helper/inducer CD4+ cells (asbestos-exposed 20 ± 4 percent cells recovered vs normals 9 ± 1 percent cells recovered, p<0.05, Table 2) and an increase in the CD4+/CD8+ ratio (asbestos-exposed 2.9 ± 0.6 vs normals 1.3, p<0.05, Table 2). In addition, the asbestos-exposed individuals had a significant increase in Leu-3+ helper/inducer CD4+ cells expressing DR surface antigen associated with activation (Table 2). All of the asbestos-exposed individuals except one with an elevated CD4+/CD8+ ratio >3 were spontaneously releasing IFN-γ and four individuals with a ratio lower than the controls were not releasing IFN-γ. There were four of 13 asbestos-exposed individuals whose BAL cells spontaneously released interleukin 2 and three of these individuals were also positive for IFN-γ release.

Two individuals had a lymphocytic-macrophage alveolitis confirmed by open lung biopsy. Their case histories are described below.

**CASE REPORTS**

**Case 1**

A 44-year-old male plumber was exposed to asbestos over a 21-year period in building renovation where he removed insulation from pipes. He was a never smoker, was asymptomatic, and had a chest roentgenogram read as a 1/0 profusion of small irregular opacities with bilateral pleural thickening. Results of pulmonary function tests were as follows: VC, 3.85 (77 percent predicted); TLC, 5.39 (74 percent predicted); FEV1, 3.41 (90 percent predicted); FEV1/FVC ratio, 0.92 (124 percent predicted); and diffusing capacity, 27.7 (93 percent predicted). A gallium lung scan was mildly diffusely positive. Bronchoalveolar lavage revealed 72 percent macrophages, 27 percent lymphocytes, 1 percent neutrophils, and several asbestos bodies. An open lung biopsy specimen revealed chronic inflammatory cell infiltrates in the pulmonary interstitium (Fig 3, left). The cellular response was predominantly lymphocytic and no well-formed granulomas were identified (Fig 3, right). The cellular lesions frequently contained dust particles and rare asbestos

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**Table 2—Characteristics of Lymphocytes Recovered from the Lower Respiratory Tract of Individuals with Asbestos Exposure Compared with Normals**

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Asbestos Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals evaluated (n)</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td>Subtypes of lymphocytes (% cells recovered)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leu-3+ (CD4+)</td>
<td>9±1</td>
<td>20±4*</td>
</tr>
<tr>
<td>Leu-2+ (CD8+)</td>
<td>7±1</td>
<td>7±1</td>
</tr>
<tr>
<td>Leu-3+/Leu-2+ ratio</td>
<td>1.3</td>
<td>2.9±0.6*</td>
</tr>
<tr>
<td>Expression of surface antigens associated with activation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DR+ (% Leu-3+ cells)</td>
<td>6±1</td>
<td>21±5*</td>
</tr>
<tr>
<td>DR+ (% Leu-2+ cells)</td>
<td>6±1</td>
<td>12±4</td>
</tr>
<tr>
<td>Spontaneous release of IL-2† (U/10⁶ cells/24 h)</td>
<td>0 (6/10)</td>
<td>7±4 (4/13)</td>
</tr>
<tr>
<td>Spontaneous release of interferon gamma† (U/10⁶ cells/24 h)</td>
<td>1±1 (1/10)</td>
<td>70±27</td>
</tr>
</tbody>
</table>

* p<0.05.
† Numbers in parentheses list number positive over the number tested.
‡ p<0.01.
bodies were observed in the interstitium with an iron stain. His PPD status was negative with a positive mumps skin test.

CASE 2

A 44-year-old male plumber was exposed to asbestos for 17 years renovating boilers and for eight years as a plumbing supervisor. He was an exsmoker beginning at age 16 years and stopped at age 39 years; he smoked an average of one pack per day. He was asymptomatic with a chest roentgenogram read as a 1/1 profusion of small irregular opacities with minimal pleural thickening. Results of pulmonary function tests were as follows: VC, 4.10 (81 percent predicted); TLC, 4.87 (67 percent predicted); FEV₁, 3.48 (97 percent predicted); FEV₁/FVC ratio, 0.88 (119 percent predicted); and diffusing capacity, 25.3 (85 percent predicted). A gallium lung scan was mildly positive. Bronchoalveolar lavage revealed 46 percent macrophages and 54 percent lymphocytes. No asbestos bodies were observed on the cytocentrifuge slide. Open lung biopsy specimen revealed prominent chronic interstitial and peribronchiolar inflammation that was predominantly lymphocytes, multinucleated giant cells especially near small and terminal respiratory bronchioles, dust particles in fibrotic lesions, and intra-alveolar inflammation (Fig 4). Rare asbestos bodies were observed. Several

Figure 2. Modulation of interferon gamma (IFN-γ) release by bronchoalveolar lavage (BAL) cells from asbestos-exposed individuals. Left, Addition of concanavalin A to BAL cells significantly increased IFN-γ release (p<0.02). Right, Addition of cyclosporine to BAL cells significantly reduced IFN-γ release (p<0.05).

Figure 3. Open lung biopsy specimen from case 1, a nonsmoking individual with asbestos exposure and lymphocytic-macrophage alveolitis. Left, Histologic section reveals a patchy chronic interstitial infiltrate consisting primarily of lymphocytes with a few plasma cells (×125). Right, Higher power demonstrates lymphocytes with a few plasma cells infiltrating the interstitium (×500).
released IFN-γ and found that the IFN-γ was predominantly from individuals with increased CD4+ /CD8+ ratios in the recovered lavage fluid. These results are consistent with previous evidence that the IFN-γ may be released by CD4+, CD8+, or natural killer lymphocytes, but the CD4+ subclass releases the largest quantity in disease states.41

Interferon gamma plays a key role in monocyte and alveolar macrophage activation.41,42 When added to alveolar macrophages cultured in vitro, IFN-γ promotes cell fusion and multinucleated giant cell formation in a time- and dose-dependent manner.43 Interferon gamma promotes the synthesis and secretion of interleukin 1 (IL-1) by monocytes in cell culture and IL-1 expands the immune response by increasing the number and activation of local T lymphocytes.41,44,45

Other activation functions of IFN-γ include upregulation of DR1 surface antigens,40,41,47 stimulation of the release of oxidants, superoxide anion, and hydrogen peroxide in vitro, and enhancement of intracellular killing of organisms, including Toxoplasma gondii and Leishmania donovani.42,48,49 Interferon gamma and tumor necrosis factor (TNF-α) act synergistically to induce human myeloid leukemia cell lines HL-60 and U937 to upregulate cytochrome b559, messenger RNA (mRNA), and increase NADPH oxidase activity and H2O2 release after stimulation with phorbol esters.50

In addition, transcription and release of TNF-α and TNF-α receptors are stimulated by IFN-γ.51,52 Interferon gamma enhances mononuclear phagocyte-induced killing of tumor cells.53 Interestingly, fibronectin is released in increased quantities by IFN-γ stimulation, and this matrix protein may be responsible for some of the fibroblast growth-stimulatory activity found in supernatants from patients with sarcoidosis and asbestosis.13,44,56 In contrast, IFN-γ has been shown to suppress c-sis (platelet-derived growth factor [PDGF-B] chain) mRNA and PDGF-A chain mRNA with concomitant less release of PDGF-like proteins into conditioned medium in endothelial cells after IFN-γ exposure.57 Lastly, IFN-γ inhibits c-myc and c-fos gene mRNA induction by PDGF and blocks the G0/G1 to S transition in quiescent BALB/c 3T3 fibroblasts.58

Interestingly, IFN-γ has an inhibitory role on human diploid fibroblast collagen synthesis consistent with a potentially protective role against pulmonary fibrosis.59 Using confluent dermal fibroblasts, IFN-γ caused a concentration-dependent inhibition of collagen synthesis as measured by a decrease in media [14C] hydroxyproline accumulation, a decrease in the procollagen peak on column chromatography, and decreased levels of collagen mRNA on dot blot hybridization with a type I procollagen cDNA probe.60,61 However, IFN-γ upregulates fibroblast collagen receptors, and a larger proportion of newly synthesized

**FIGURE 4.** Open lung biopsy specimen from case 2. A prominent lymphocytic infiltrate is present in the wall of this bronchial. In addition, there is focal, mild infiltration of the adjacent alveolar septae by lymphocytes (× 200).

inconspicuous and rare noncaseating granulomas were seen. His PPD status was negative with a positive mumps skin test. There were no exposures to organic antigens or beryllium.

**DISCUSSION**

Nonsmoking individuals with occupational inorganic dust exposure have an alveolitis in the lower respiratory tract that is dominated by alveolar macrophages, but a subgroup of individuals (one third in the present study) have an increase in the proportion of lung lymphocytes. In asbestos-exposed individuals, these lymphocytes express surface markers consistent with an expansion of the CD4+ helper/inducer subclass, and an activation phenotype with an increased proportion expressing DR1 surface antigen. Morphologic studies of BAL cells from individuals with inorganic dust exposure reveal close interactions between alveolar macrophages and lymphocytes consistent with antigen presentation by alveolar macrophages.39,40 This study provides evidence that lymphocytes in addition to alveolar macrophages are activated and may accumulate in significant numbers following occupational exposure to inorganic dusts. Importantly, any confounding effect of cigarette smoke on the cellular response of the lower respiratory tract was controlled by evaluating lifelong nonsmokers and exsmokers ≥5 years.

We also demonstrated that BAL cells from individuals occupationally exposed to asbestos spontaneously

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Lymphocyte-Macrophage interactions are significantly enhanced in asbestos-exposed individuals. This paper focuses on the role of IFN-γ in these interactions, particularly how it affects the development of interstitial lung disease.

Collagen is deposited in extracellular matrix, possibly related to the effect of IFN-γ in stimulating transcription, translation, and release of fibronectin. Another salutary effect of IFN-γ is its stimulation of natural killer cell activity which may be important in tumor surveillance in asbestos-exposed workers. Importantly, we found that IFN-γ was actually lower in BAL supernatants from dust-exposed individuals with respiratory impairment suggesting a role for IFN-γ release early in the course of asbestosis (eg, at a stage of lymphocytic-macrophage alveolitis) where there may be predominant suppressive effects on fibroblast production of collagen. An exaggerated release of IFN-γ that we found early in the course of asbestosis may have several salutary effects: first, reduction in collagen gene transcription by fibroblasts; second, enhanced macrophage phagocytosis of particles; and third, inhibition of competence genes in the growth cycle. However, IFN-γ also has activities that could be less than auspicious to the asbestos-exposed lung, including stimulation of oxidant release by mononuclear phagocytes and stimulation of fibronectin. In this regard, we have shown that cyclosporine effectively inhibits IFN-γ release by BAL cells in vitro.

Interleukin 2 was released by several individuals with asbestos exposure and lymphocytic-macrophage alveolitis; IL-2 can stimulate IFN-γ production by activated lymphocytes. In addition, IFN-γ can increase IL-2 effectiveness by increasing the expression of IL-2 receptors. Interleukin 2 has also been shown to be chemotactic for CD4+ cells expressing the IL-2 receptor, but not CD8+ suppressor/cytotoxic cells. A significant increase in CD4+ cells expressing DR+ surface molecules has also been observed in BAL cells in sarcoidosis and following in vitro activation of T cells with tetanus toxoid.

Increased BAL lymphocytes have been observed in asbestos-exposed Quebec chrysotile miners without interstitial lung disease, English asbestos workers, asbestosis-exposed factory workers, and asbestos-exposed construction workers. Sprince et al studied 27 nonsmoking asbestos trades workers with less roentgenographic change than the current study (11 with pleural changes and only one with parenchymal changes) and found an immune imbalance favoring helper/inducer T-cell subsets in blood and BAL.

Bronchoalveolar lavage cells from approximately one third of individuals exposed to asbestos contain increased percentage and number of lymphocytes, and these lymphocytes are predominantly CD4+ in asbestosis expressing the DR+ activation phenotype. This lymphocytic-macrophage alveolitis is a diffuse infiltrative process as demonstrated by open lung biopsy specimens. These lymphocytes are activated and release IFN-γ (two thirds) and some also are spontaneously releasing IL-2. The consequences of IFN-γ release may be salutary (enhance phagocytosis, inhibit the fibrotic process) or harmful (stimulate oxidant and fibronectin release) reflecting a careful balance in vivo. Since IFN-γ was reduced in those with respiratory impairment, a longitudinal study of asbestos-exposed workers may help clarify the functional role of these immune modulatory cytokines in the development of interstitial lung disease.

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Lymphocyte-Macrophage Alveolitis in Nonsmoking Individuals (Rom, Travis)
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