Acute Experimental Silicosis

Lung Morphology, Histology, and Macrophage Chemotaxin Secretion

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The acute inflammatory reaction in the lungs of guinea pigs produced by the intratracheal injection of silica was assessed by histologic studies and whole-lung lavage 1, 2, 4, 7, and 14 days after the intratracheal instillation of quartz particles or saline. In addition, lavaged macrophages were cultured in vitro, and the media were assayed for chemotactic factors. This exposure to silica produced a neutrophilic inflammatory response around terminal bronchioles that was well developed within 1 day after injection. Four days after injection, neutrophils were replaced by mononuclear cells; and by 7 days, loosely organized granulomas and collagen deposition were detected in the interstitium. The number of neutrophils (PMNs) recovered by lavage from experimental animals was greatest 1 day after injection and was significantly greater ($P < 0.01$) than that for controls at all time points. In contrast, the number of macrophages recovered by lavage did not exceed control levels until 7 days after injection and remained elevated thereafter. Thus, the cells recovered by lavage tended to mirror the changes seen in the inflamed lung. In experiments utilizing blind-well chemotactic chambers, both peritoneal exudate neutrophils and macrophages migrated toward supernatants from cultures of alveolar macrophages lavaged from silica-exposed animals in greater numbers ($P < 0.02$) than toward supernatant from control animal macrophage cultures at each time point. Migration of normal alveolar macrophages toward supernatants from all cultures was minimal. Thus, exposure to silica in vivo appears to be a potent stimulus for the release of neutrophil and monocyte chemotactic factors by alveolar macrophages in vitro. The correlation between the types of inflammatory cells identified in the lung both microscopically and by lavage and the chemotactic factors released in vitro by alveolar macrophages from these lungs suggests that alveolar macrophages play a role in mediating pulmonary inflammation in this form of experimental silicosis (Am J Pathol 1982, 109:27-36)

We found that silica particles produced an intense and rapidly evolving pulmonary inflammatory response. One day after injection, neutrophil infiltration of the interstitium and air spaces was prominent, but by Day 7, there was a marked shift to mononuclear cells. In addition, the types of cells recovered in the lavage fluid paralleled the pulmonary histopatho-

IN CHRONIC EXPERIMENTAL SILICOSIS, the inflammatory response that accompanies pulmonary fibrosis has been well characterized.1 We have shown previously that the predominant inflammatory cells in this chronic model of pulmonary fibrosis consist of macrophages and neutrophils. However, knowledge about the acute response to intratracheal injection of silica is much less extensive. Therefore, efforts to improve our understanding of the early inflammatory events in experimental silicosis and to elucidate their mechanisms are warranted. In this study, we examined the lungs histopathologically, quantified the cells obtained by whole-lung lavage, and assayed the secretion of chemotaxins in vitro by lavaged macrophages recovered in the first 2 weeks following the intratracheal injection of quartz.

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logic features during the 14 days after silica injection. Finally, alveolar macrophages from the animals with silicosis released more chemotactic factor for neutrophils and macrophages than lavaged macrophages from control animals. These results demonstrate that the intratracheal injection of silica produces an acute inflammatory response in the lung that progresses rapidly toward the responses seen in chronic experimental silicosis and suggest that alveolar macrophage-derived chemotaxins play a role in mediating this inflammatory response.

Materials and Methods

Animals

Male Hartley outbred guinea pigs (West Jersey Biological, Wenonah, NJ) weighing between 350 and 450 g were used for all studies. They were housed in open quarters in the University of Pennsylvania Department of Laboratory Animal Medicine and observed 4-5 days prior to intratracheal injection for signs of illness.

Animal Protocol

The results presented were derived from three cohorts of animals. Each cohort consisted of an experimental group receiving intratracheal silica and a control group receiving intratracheal saline. The animals in each cohort were given injections on the same day and sacrificed on Days 1, 2, 4, 7, and 14 following injection. Each cohort was given injections at different times during the course of the study. Experimental animals received 50 mg of silica suspended in 1 ml of sterile saline. Control animals received 1 ml of sterile saline. The silica particles were prepared from a sample of Min-U-Sil (Pennsylvania Glass Sand Corp., Pittsburgh, PA) as previously described in detail. Briefly, the silica particles were boiled in 1 N HCl to remove Fe₂O₃ contaminants and rinsed four times in distilled water. The particles were heated, sterilized at 200 °C for 2 hours, and stored under sterile conditions. To rule out the possibility of endotoxin contamination of the particles, a limulus lysate assay (Difco, Detroit, MI), sensitive to 0.05 ng/ml of endotoxin, was performed with appropriate controls. No endotoxin was present in our silica preparation. Cultures of the silica particles were sterile on repeated determinations. Size analysis by scanning electron microscopy revealed that 79% of the particles were between 1 and 5 μ in average diameter and 21% were <1 μ. All injections were made by the transtracheal route, as previously described. The overall mortality was 6.1% in a total of 33 experimental animals and 3.1% in a total of 32 control animals.

Morphologic Studies

Fixation and Gross Examination of the Lungs

The lungs were fixed by intratracheal instillation of 10% Bouin's solution. After the lungs had been fully expanded with fixative, the trachea was tied and the lungs immersed in fixative for 24 hours. Following fixation, the right upper and lower and left upper and lower lobes were removed from their bronchi and cut serially in the sagittal plane and examined for consolidation.

Histologic Examination

The midline sagittal section from each of the four lobes was embedded in paraffin. Sections 6 μ thick were cut and stained with hemotoxylin and eosin, Mallory trichrome, and reticulin (modified Foot's) stain.

Cytologic Studies

Lung cells were obtained by a standard lavage as previously described. In brief, isolated lungs were lavaged with 10-15-ml aliquots of cold calcium and magnesium-free Hanks' balanced salt solution (MHBSS) (Grand Island Biological Company, Grand Island, NY [GIBCO]). The first 15 ml of lavage fluid was discarded. The lavage was continued until 200 ml of fluid was recovered. The fluid was centrifuged at 400 g at 4 °C for 10 minutes, and supernatant was removed. The cell pellet was washed twice with MHBSS and suspended in RPMI 1640 (GIBCO) medium. A total cell count was made on a model Zf Coulter Counter (Coulter Electronics, Hialeah, FL). Recovery of cells was expressed as the number of cells per 100 ml lavage fluid. Smears for differential counts were made with a cytocentrifuge (Shandon, Sewickley, PA) and stained with Diff-Quik (Harleco, Philadelphia, PA). Viability was determined by exclusion of trypan blue dye.

Macrophage Culture

A total of 10.0 × 10⁴ viable alveolar macrophages (AM*) from each experimental and control animal were suspended in 5 ml of RPMI 1640 and 10% heat-inactivated fetal calf serum (GIBCO) and incubated in 100-mm tissue culture grade Petri dishes (Corning Glass Works, Corning, NY) at 37 C in 5% CO₂. After 1 hour, the nonadherent cells were removed by washing of the monolayer three times with warm MHBSS. Following the last wash, 10 ml fresh serum-
free RPMI 1640 was added and the adherent cells incubated for 2 hours at 37°C in 5% CO2. The culture medium was aspirated and centrifuged at 1000g for 20 minutes. The supernatant was removed and stored at −20°C until tested for chemotactic activity.

Adherence of the AMϕ in culture was determined in separate experiments as follows. First, cells that were not adherent after 1 hour of culture were collected and counted. The number of nonadherent cells was subtracted from the number of cells plated, for the number of adherent cells. After the subsequent 2-hour incubation period, during which very few cells detached, medium was gently removed and the monolayer stained with Diff-Quik for determination of the percentage of adherent cells that were macrophages. We multiplied this value by the number of adherent cells to get the number of adherent macrophages per plate and then divided it by the number of macrophages plated (10 × 106) to get the fraction of plated macrophages that adhered. Adherence was quantified in this way for cells taken from experimental and control animals at each time point.

Chemotactic Factor Assay

Macrophage culture supernatants were tested for their ability to attract neutrophils and macrophages in blind-well chemotactic chambers (Neuroprobe, Bethesda, MD) as previously described in detail. In brief, responding alveolar macrophages were obtained by pulmonary lavage of normal guinea pigs. Responding peritoneal neutrophils and macrophages were obtained by peritoneal lavage at 18 hours and four days, respectively, after injection of sterile thioglycollate.

Two hundred μl of fluid containing the chemotaxin was placed in the lower compartment of the chemotactic chamber, and 200 μl of the responding cell suspension was placed in the upper compartment. Responding cells were suspended in Gey’s balanced salt solution (GIBCO) plus 2% bovine serum albumin. For macrophages, the responding cell concentration was 1.5 × 106 cells/ml (pH 7.0), the compartments were separated by 5-μm-pore polycarbonate filters (Nucleopore Corp., Pleasanton, CA), and the chambers were incubated at 37°C in humidified air for 90 minutes. For neutrophils, the responding cell concentration was 2.2 × 106/ml (pH 7.20), a 3-μm filter separated the compartments, and the incubation period was 45 minutes. The filters were removed, dried, stained with Diff-Quik, and mounted in oil on glass slides. The number of responding cells migrating through the filters in 10 oil immersion fields (OIFs) was counted. The chemotactic response was defined as the mean ± SE of the number of migrated cells per OIF for triplicate filters.

All supernatants were tested in 1:2, 1:4, and 1:8 dilutions. In addition, we tested supernatants from Day 2 and 14 animals undiluted and at 1:16 and 1:64 dilutions to develop a dose-response relationship.

Statistics

All results are expressed as the mean ± SEM. Statistical significance was determined by the unpaired Student t test.

Results

Morphologic Findings

Consolidation was seen on the cut surfaces of lungs from animals sacrificed 1 day after injection of silica. It was usually confined to the parenchyma surrounding proximal airways and rarely reached the pleural surfaces. In animals sacrificed 2 days after injection, however, consolidation was more extensive, extending into the parenchyma between proximal airways and beneath the pleura. Pleural inflammation did not become grossly apparent until 4 days after injection. The pleural involvement seemed to be an extension of underlying parenchymal infiltration. On average, consolidation occupied approximately 50% of the cut surface of the lower lobes and 25% of the upper lobes in these animals. The gross findings in lungs from animals sacrificed 7 and 14 days after injection were similar to those in animals sacrificed after 4 days.

Microscopically, focal inflammatory infiltrates were seen around terminal bronchioles in animals sacrificed 1 day after injection of silica. The alveoli in these areas contained a mixed cellular exudate. The neutrophil was the predominant inflammatory cell, but macrophages were also present (Figure 1A). The alveolar architecture was well preserved, and the interstitium was not heavily infiltrated. In 5 of the 6 animals in this group, edema was seen in alveoli surrounding the focal infiltrates. However, only a few inflammatory cells were seen in the edema fluid. The capillaries in these areas were not congested. A large amount of fluid was rarely found in the alveoli that were filled with inflammatory cells.

Over the next 3 days, the inflammatory reaction to the injected silica shifted from neutrophil to mononuclear cell infiltration of the alveolar space (Figure 1B). However, neutrophils were still numerous. The
The inflammatory response 1 day after the intratracheal injection of quartz. Alveoli adjacent to terminal airways contain large numbers of neutrophils and lesser numbers of macrophages. The alveolar septa are minimally infiltrated. (H&E, x 325)

Four days after injection, some alveoli still contain neutrophils, but macrophages are now the predominant inflammatory cells. The alveolar interstitium is densely infiltrated, and in some places macrophages have formed loosely organized granulomas as seen in the center of this photomicro-
C—By 7 days after injection, granulomas are more numerous. Infiltration of the alveolar spaces persists, with mononuclear cells being most numerous. A scattering of neutrophils is also seen. (H&E, x 130)

D—Granulomas are slightly larger by 14 days after injection. This photomicrograph demonstrates their predilection to arise next to terminal airways, which appear to be distorted by this process. (H&E, x 130)
alveolar septa became much thicker due to the infiltration of mononuclear cells. The vast majority of silica particles (detected by polarized light) were localized to the infiltrated areas. Most of the particles were inside macrophages, but a few were in neutrophils. Rarely, particles were seen within macrophages in uninflamed areas of lung. Inflamed alveoli were usually lined by hyperplastic Type II pneumocytes. The alveolar architecture was difficult to discern because many alveoli were packed with silica-laden macrophages. The most intense reaction occurred around terminal bronchioles, the walls of which appeared disrupted. Plugs of inflammatory cells (neutrophils and macrophages) often appeared to obstruct the lumen of these airways. The focal alveolar edema seen in animals sacrificed 1 and 2 days after injection was not found in any of the 6 animals examined 4 days after injection.

By 7 days, mononuclear cell infiltration of the alveolar interstitium was even more marked, and small histiocyte granulomas were seen (Figure 1C). Most of the macrophages within granulomas contained silica particles. Particle-laden cells were also seen in more diffusely infiltrated alveolar septa. The air spaces, which contained particle-laden macrophages and a few neutrophils, were widely spaced due to thickening of the alveolar interstitium. Hyperplasia of lining cells was again prominent. The microscopic appearance of lungs from animals sacrificed 14 days after injection was similar to that of animals after 7 days (Figure 1D). An additional finding of note in the animals sacrificed after 7 and 14 days was the deposition of collagen. Lacy strands of eosinophilic material that stained blue with Mallory trichrome coursed through the inflamed alveolar interstitium and developing granulomas.

The lungs of control animals appeared normal except for a few pinpoint infiltrates on the cut surfaces. These lesions were seen in 2 of 3 control animals sacrificed at each time point. Microscopic examination revealed mononuclear cell infiltration of the alveolar spaces with sparing of the alveolar interstitium. The remainder of the pulmonary parenchyma appeared normal (Figure 2). The appearance of these focal in-

![Figure 2](Image)

**Figure 2** - A representative section from the lungs of control animals to demonstrate the microscopic appearance of the focal consolidations noted grossly. Since the same lesions were seen in 2 of 3 control animals sacrificed at each time point, they probably were not related to the intratracheal injection of silica. (H&E, × 130)
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bers of greater signification recovered from that sacrificial animals. Numbers are expressed per 100 ml of lavage fluid recovered. Values are the means ± SE of 7 experimental and 5 control animals for each time point. The number of days after intratracheal injection is given on the abscissa. The number of neutrophils recovered from experimental animals was significantly greater than that from control animals for all time points (* P < 0.01).

filtrates was similar in all of the control animals irrespective of the time they were sacrificed.

Lavage Results

Neutrophil recovery was greatly increased in experimental animals sacrificed 1 and 2 days after injection, compared with control animals. For animals sacrificed later, recovery was less but still exceeded recovery in the control animals (Figure 3). Thus, the proportion of neutrophils in lavage fluid paralleled the cellular response seen in the lungs of experimental animals. The yield of eosinophils was also increased, compared with that of control animals, but only in experimental animals sacrificed 14 days after injection (6.8 ± 0.5 versus 1.9 ± 0.5 x 10^6; P < 0.01).

In contrast, the recovery of macrophages from animals sacrificed 1, 2, and 4 days after injection of silica was comparable to that of control animals. Not until 7 days after injection was there a significant increase in the recovery of macrophages (78.1 ± 11 versus 45.0 ± 4.9 x 10^6; P < 0.01) (Figure 4). This was so despite the presence of an intense mononuclear cell infiltration in the lungs of experimental animals sacrificed 4 days after injection.

Total cell recovery followed a pattern similar to that of alveolar macrophage recovery (Figure 5). On Days 7 and 14, the number of bronchoalveolar cells recovered from the experimental group was significantly greater than controls (122 ± 7.3 versus 38 ± 8.0 x 10^6 on Day 14; P < 0.001). Because large numbers of neutrophils were recovered from animals sacrificed 1 day after injection of silica, the total cell yield in this group was also greater than in the control group (P < 0.05). On Days 2 and 4, however, total cell yield was comparable in experimental and control animals.

The viability of cells recovered from experimental animals at all time points was significantly lower than controls. The mean value for viability of cells recovered from experimental animals for all time points was 80.6% ± 5%, compared with 93.0% ± 3.1% for cells from control animals (P < 0.02). The variation in viability of cells obtained at different times after injection was less than 5% for experimental and control groups.

Figure 3—Number of neutrophils recovered by whole lung lavage from experimental (silica) and control (saline) animals. Numbers are expressed per 100 ml of lavage fluid recovered. Values are the means ± SE of 7 experimental and 5 control animals for each time point. The number of days after intratracheal injection is given on the abscissa. The number of neutrophils recovered from experimental animals was significantly greater than that from control animals for all time points (* P < 0.01).

Figure 4—Numbers of macrophages recovered by whole lung lavage from experimental and control animals expressed per 100 ml of lavage fluid recovered. Values are the means ± SE of 7 experimental and 5 control animals for each time point. The number of macrophages recovered from experimental animals was not significantly different from that from controls until Day 7 (* P < 0.01).

Generation of Chemotaxins for Neutrophils by Cultured Lung Cells

Greater numbers of neutrophils migrated toward supernatants from experimental AM± cultures than toward supernatants from control AM# cultures (Figure 6). Furthermore, the magnitude of migration toward supernatants from experimental animal cultures was nearly as great as that toward the positive control, F-formyl-methionyl-phenylalanine (FMP), a potent neutrophil and macrophage chemotactic factor for the guinea pig. The concentration of supernatant from experimental and control animal cultures that produced optimum migration was usually a 1:2 dilution, but
sometimes migration was greater toward undiluted supernatant. Migration toward higher dilutions of supernatant from both experimental and control animals was consistently less than that toward undiluted or a 1:2 dilution of supernatant.

The amount of neutrophil chemotactic activity in supernatants as a function of when the alveolar macrophages were collected is shown in Figure 6. Macrophages lavaged 2 days after injection of silica produced the peak response. The activity was 92% of positive control, compared with 78–82% of the positive control for activity in supernatants of cultures of cells collected at the other time points (P < 0.05).

Migration of neutrophils toward supernatants from control animal cultures was consistently greater than random migration in the chemotactic assay (ie, only medium in the lower compartment) at all time points. Thus, AMφ from control animals also elaborated neutrophil chemotaxins in vitro. The magnitude of migration toward control supernatants, however, never exceeded 50% of the response to FMP (positive control).

To determine whether the density of macrophages in culture influenced the release of neutrophil chemotactic factor, we plated AMφ cells from experimental animals sacrificed at Day 2 and Day 14 at 10⁴, 10⁵, 5 × 10⁵ and 10⁶ cells per 100-mm plate. The amount of neutrophil chemotaxon in these supernatants was directly proportional to the number of cells plated (not shown).

Generation of Chemotaxins for Macrophages by Cultured Lung Cells

As was the case for neutrophils, more stimulated peritoneal macrophages migrated toward AMφ culture supernatants from experimental animals than toward AMφ culture supernatants from control animals. The amount of chemotaxon(s) for macrophages in supernatants from cultures of cells collected at different times after injection of silica varied more widely than the amount of chemotactic factor for neutrophils (Figure 7). In cultures of cells collected 1 day after injection of silica, macrophage chemotactic activity was only 50% of positive control (FMP), but in supernatants from animals killed after 2 days it exceeded positive control. Activity in cultures of animals killed at 4, 7, and 14 days, was similar, about 95% of positive control. The relationship between chemotactic activity in the medium of lavaged AMφ and the time after injection was similar for the controls, but the amount of chemotaxon released by cells from controls was significantly less than experimental animals (P < 0.01). As was the case for neutrophils, the amount of chemotaxon for macrophages in supernatants from experimental and control animals also

Figure 5—Numbers of total lung cells recovered by whole lung lavage from experimental and control animals expressed per 100 ml of lavage fluid recovered. Values are the means ± SE of 7 experimental and 5 control animals. The number of total lung cells recovered from experimental animals was not significantly different from that from control animals until Day 7 (* P < 0.01).

Figure 6—Migration of PMNs in blind-well chambers toward alveolar macrophage culture supernatants from experimental (silica) and control (saline) animals expressed as the number of cells migrating through a micropore filter per oil immersion field. Values are the means ± SE of 7 experimental and 5 control animals for each time point. The number of days after intratracheal injection of silica or saline is given on the abscissa. Neg. Contl.: Migration toward negative control, Gey’s balanced salt solution (GBSS) and 2% bovine serum albumin (BSA). Pos. Contl.: Migration toward positive control, FMP × 10⁻⁴ M in GBSS and 2% BSA. Migration was always greater toward experimental culture supernatants, compared with control culture supernatants (P < 0.05).
The most likely source of the chemotaxes found in the culture supernatant is the alveolar macrophage, because this was the predominant cell type in the cultures. In addition, we have previously shown that normal macrophages exposed to silica in vitro release chemotaxes for neutrophils. Thus, the bulk of chemotaxes detected in the medium of cells from experimental animals was probably produced by macrophages exposed to silica in vivo. It is possible, however, that some of the chemotaxes for neutrophils found in supernatants of experimental animal cultures are derived from neutrophils. This possibility can be ruled out only if neutrophils can be completely eliminated from the culture, something we were unable to achieve in this study.

Additional evidence for the participation of macrophage-derived chemotactic factors in the acute response to silica was the time course of the appearance of chemotaxes for neutrophils (Figure 6) and the correspondence between this pattern and the influx of these cells in the lung. That the highest level of chemotaxes for neutrophils was found in cultures of cells collected 2 days after injection of silica instead of after 1 day was somewhat unexpected. But the lower level of chemotaxes for neutrophils in supernatants generated from cells collected on later days corresponded to the decrease in the numbers of neutrophils seen in the lung. Even though production of chemotaxes for neutrophils by cells collected from experimental animals at these later dates appeared to decline, the amount of chemotactic activity in the supernatants always exceeded controls. Similarly, the recovery of neutrophils from these animals was always greater than from controls. Furthermore, since fewer macrophages from silica-exposed animals adhered in culture, compared with macrophages from control animals, the chemotaxes found in the supernatants of experimental animal cell cultures were produced by fewer alveolar macrophages.

Of course, chemotactic factors derived from lung macrophages are only one of several possible mechanisms in producing the acute inflammation seen in experimental silicosis. Other chemotactic factors such as C5a or C5a des Arg may play a role as they do in other systems. The effect of C5a on vascular permeability may also explain some of the alveolar edema seen on Days 1 and 2. Immune complexes have been described in human silicosis and can amplify chemotactic factor production by AM4, but in this model the development of immune complexes is unlikely, since the time course was too short. Also, the modulation of the neutrophil chemotaxes by the AM4 occurs through mechanisms that are unknown. However, the time course and magnitude of

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**Discussion**

This study demonstrates that the intratracheal injection of quartz particles into guinea pigs produces an intense neutrophilic inflammatory response in the lung that evolves over several days into the type of mononuclear cell reaction characteristic of chronic experimental silicosis. The mechanisms producing the rapid influx of neutrophils in this model are largely unknown. A role for macrophage-derived chemotactic factor for neutrophils in this response is suggested by the finding that lung cells from these animals exposed to silica in vivo release potent chemotaxes for neutrophils in vitro. Presumably, these factors are released in vivo and in part lead to the accumulation of neutrophils in the lung.
macrophage-derived chemotaxins for neutrophils seen in this study strongly suggest a role for this mechanism in producing the inflammatory response seen in acute experimental silicosis.

We recognize that the distribution of silica particles might be somewhat different with an inhalational route of challenge. Studies are clearly indicated to clarify the differences in the response in guinea pigs with the use of these two methods.

Also of importance in this study was the correlation between the types of cells in lavage fluid and the inflammatory response seen histologically. For the neutrophilic response, cells recovered by lavage were a good reflection of the histopathologic features of the lungs, although an exact correlation requires knowledge of the efficiency of retrieval of PMNs, something we did not measure in this study. On the other hand, the correlation for macrophages was not as good. As noted, the infiltration of macrophages into the lungs of experimental animals was prominent on Day 4 after the injection and well advanced by Day 7 (Figures 1B and C). Increased numbers of macrophages were seen on Days 1 and 2. Interestingly, however, the number of macrophages recovered by lavage did not correlate well with the histopathologic features of the lungs on Days 1, 2, and 4. The numbers of macrophages recovered from these animals were disproportionately low, compared with the degree of macrophage infiltration in the lung. By 7 days after injection, an increased number of macrophages were recovered in the lavage fluid and reflected the increased number of macrophages observed in histologic sections. The reasons for the discrepancy are not clear. It may have been due to obstruction of inflamed terminal bronchioles with cell debris and neutrophils. Macrophages in the airspaces distal to the obstructed bronchi were probably inaccessible to lavage. Alternatively, newly arrived macrophages in the lung on Days 1–4 may have been more adherent and not removed by lavage. But even a temporary discrepancy is important, because lung lavage has been proposed as a valid means of identifying the inflammatory cells involved in a variety of interstitial lung disorders.⁹

Chemotaxins for macrophages found in supernates of cell cultures from experimental animals killed on Day 1 were modest (50% of positive control). In cultures from animals killed on Day 2, they reached their highest level and were distinctly elevated in cultures of cells from animals sacrificed on later days (Figure 6). Thus, as was the case for neutrophils, there was a rough correlation between chemotaxin production for macrophages in culture and macrophage infiltration in vivo. Furthermore, the continued high level of chemotaxin production for macrophages seen in the animals killed on Day 7 and 14 is also consistent with a current hypothesis on the formation and maintenance of granulomas in the lung.¹⁰

In conclusion, we believe that the early release of potent chemotactic factors from alveolar macrophages in the intact animal is one mechanism initiating the inflammatory response in acute experimental silicosis. Furthermore, the pattern of continued release of chemotactic factors by alveolar macrophages correlates with the course of lung inflammation seen serially in histologic sections and sampled by lung lavage.

References