# IMAGING THE PNEUMOCONIOSES IN 1988: A MULTIDISCIPLINARY APPROACH

R. BÉGIN, M.D. • S. Massé, M.D. • A. Cantin, M.D. • G. Bisson, M.D. • D. Bergeron, M.D.

Centre Hospitalier Universitaire, Sherbrooke, Québec, Canada J1H 5N4

## INTRODUCTION

In recent years, it has become increasingly clear, on the basis of human and experimental data, that lung fibrosis associated with mineral dust inhalation was the end-stage phenomenon of a long chronic inflammatory process initiated by the retention of biologically active mineral particles in the lung tissue.

The early stages of lung tissue reaction to mineral dust deposition is characterized by an excessive accumulation and activation of macrophages in the peripheral bronchoalveolar tissue. This is well documented both in animal studies[9] and in humans.[4,5,16] Asbestos dust inhalation produces the fundamental early lesion of asbestosis the peribronchiolar fibrosing alveolitis; quartz dust inhalation produces the more nodular, often perivascular accumulation of macrophages and lymphocytes in the alveolar spaces of lung tissue.

As these mineral dust diseases progress, they are associated with extension of the process to the adjacent alveolar and interstitial lung tissues which leads to diffuse interstitial lung fibrosis. However, we know now that this process can be limited to its early peribronchiolar reaction and leave the lung tissue nearly intact. This is particularly the case for asbestos-induced lung disease. In silica-induced lung disease,[11] after the initial nodular lesion, the process becomes less inflammatory, fibroblasts accumulate in the nodules with excessive deposition of reticulin and collagen in and between the cells in the nodule, and eventually the fibrotic collagenous process aggregates the individual nodules to form masses of fibrotic tissue.

Knowing these fundamental pathological processes, strategies to detect these diseases at an early inflammatory stage have been developed.

## MODES OF DETECTION

### Rales

The observation of bilateral basilar end-inspiratory in asbestos workers with or without asbestosis suggest that auscultatory rales are found in most workers with asbestosis; their profusion correlates fairly radiographic and functional parameters of severity of asbestosis.[3] However, rales are the initial finding of disease in asbestos workers in less than 5% of cases and when present, they likely reflect a fibrotic process already in place. In quartz exposed workers, rales are usually absent and of limited interest in detection of silicosis.

### Chest Radiograph

The standard PA high kilovoltage chest radiograph is the definite indicator of the mineral dust pneumoconiosis and its value has been well established for the detection of both asbestosis and silicosis. However, it has been documented that the chest radiograph can be normal in up to 10% of symptomatic patients with proven interstitial lung disease. In asbestosis, we have documented similar findings,[3-5] and in silicosis substantial pathological changes in the lung tissues have been observed in stone cutters with normal chest radiograph.[11] Thus, whereas chest radiograph is a useful mode of detection of disease, cannot be considered as a sensitive indicator of early disease.

### Computed Tomograph of the Thorax

In asbestos related pleuropulmonary diseases, earlier clinical studies[13,14] on relatively small populations of patients have found that the CT scan was significantly more sensitive than conventional chest X-rays in the detection of disease. We obtained a CT scan of the thorax in 127 long term asbestos workers who were also evaluated by conventional posteroanterior (PA), lateral and obliques (4-view) X-rays, and clinical and functional evaluations.[2] Our analysis of the total scores of the pleuropulmonary changes and profusion of parenchymal opacities shows that the three methods can detect about the same total amount of abnormalities in each subset of workers, which is at variance with previous clinical reports.[13,14] Pleural plaques were scored slightly higher on the four-view films than on the PA film, in agreement with a previous report comparing these methods,[13,14] but pleural plaques were scored significantly lower on the CT scan, mostly because of the lower yields at the costophrenic angles and diaphragms. The largest discrepancies between the three methods were observed in the evaluation of pleural calcifications. On PA films, calcified pleural plaques were often suspected, but could be confirmed by one of the other methods in only two of nine cases. Of the 27 definite pleural calcifications detected in our 127 asbestos workers, however, 14 were detected only by CT scan and all those detected by the PA and four-view films were also observed on the CT scan. Our data on asbestos workers without sufficient criteria for asbestosis but with rigid P-V curve and increased Ga-67 lung uptake show that the CT scan does not detect significantly more pleuropulmonary abnormalities than PA films. With both methods, workers with early asbestos alveolitis could not be separated from those without asbestos alveolitis or asbestosis.

In 58 silica-exposed workers, we have also used computed tomography of the thorax.[7] On the basis of chest radiograph, 6 were without silicosis, 30 had simple silicosis without coalescence or large opacity, 13 had silicosis with coalescence and 9 had silicosis with large opacity. In the presence of simple silicosis without coalescence or large opacity on plain chest film, CT scanning of the thorax revealed conglomerations in 10/30 cases, 70% of which could not be seen with the addition of lateral and oblique chest films. This additional information on the presence of conglomeration is particularly important as it identifies the presence of a complicated disease which could be either early coalescence of silicotic nodules, tuberculosis or other lung processes such as lung tumor. Further investigations documented that of the 10 conglomerations detected by CT scan only, 2 were tuberculous lesions, 1 was a carcinoma and 7 were of silicotic origin. It has been reported in the last year that the use of ultra-thin CT scan cuts (1-2 mm) may improve the imaging of interstitial reticular or nodular lung lesions. However, these clinical observations by others and ourself have not been scientifically validated.

## Gallium-67 Scan

Ga-67 scanning has been used in clinical medicine for over 15 years in the detection of tumors and sites of occult infection, two disease processes associated with chronic inflammation. The mechanisms of localization of the radionuclide in the inflammatory site, however, has been only partially clarified recently. After intravenous injection of the radionuclide, Ga-67 is rapidly bound to serum proteins, transferrin, haptoglobin and albumin, and less than 1% is transferred to the leucocytes. Gallium-67 lung uptake is primarily associated with activated macrophages producing excessive amount of fibronectin[4] and to correlate with histopathological scores of inflammation in lung tissue and with BAL levels of Ga-67 radioactivity retrieval.[4]

In asbestos workers of the mines and mills of Quebec, we have obtained routinely Ga-67 scans in over 300 workers who can be divided into 4 categories:

A = workers without asbestosis and normal scan,
B = workers without asbestosis and abnormal scan,
C = workers with asbestosis and abnormal scan,
D = workers with asbestosis and normal scan.

The workers in groups A and B have chest radiograph in the ILO categories 0/1 or 0/0 and they do not have bilateral rales on auscultation. Their lung volumes are within normal prediction but some 66% of the workers in group B have increased rigidity of the lung pressure-volume curve and exercise induced hypoxemia.[3,11] On lung biopsy, they have a peribronchiolar macrophagic alveolitis. The workers in groups C and D have radiographic changes of category $\geq$ 1/0, the majority of them have bilateral rales and a restrictive pattern of lung function. What differentiates groups C and D is that workers with asbestosis in group C have increased Ga-67 lung uptake whereas those in group D have a normal scan. These differences between groups A and B or C and D are not related to pleural disease,[15] but relate best to the rate of fall of vital capacity; the workers with enhanced Ga-67 lung uptake have increased rates of decline of vital capacity per year.

We have obtained computer-based quantitative analysis of Ga-67 uptake in a group of 46 long term workers exposed to silica dust at work in the granite industry or in foundry and in a group of 13, age, sex and smoking habit matched controls. In the controls, Ga-67 scan index averaged 1.77 $\pm$ 0.46; in the 11 workers exposed to silica dust without silicosis, the index was 3.05 $\pm$ 0.69. In 12 workers with simple silicosis 3.75 $\pm$ 0.70; in 8 workers with silicosis and coalescence it was 7.25 $\pm$ 2.23 and in 15 workers with large opacities it was 7.97 $\pm$ 1.03. These data therefore confirm the work of Siemsen in documenting that Ga-67 lung uptake is enhanced in silicosis and document that in long term silica-exposed workers with or without simple silicosis, Ga-67 lung uptake is increased at 200% control value and when the disease becomes complicated by coalescence and/or large opacity, the Ga-67 uptake is further enhanced to 400% control value.

## Bronchoalveolar Lavage

In the interstitial lung disease which could be related to asbestos exposure, BAL analyses are of interest: 1) to eliminate other etiologies of lung injury, 2) to document asbestos exposure, 3) to support other clinical information, 4) to study the biological mechanisms. Following our initial report of a substantial number of long term workers with abnormal Ga-67 scan in the absence of other criteria for asbestosis,[1] we have investigated several asbestos workers and similar studies were conducted by Dr. Rom at NIH. In these studies, it was documented that macrophages of the bronchoalveolar space of asbestos exposed workers demonstrated marked structural changes, were producing excessive amount of fibronectin, fibroblast growth factor and increase $\gamma$-interferon which could participate in the pathogenesis of asbestosis. In our experimental studies in the sheep model, we have fully reported similar evidences of activated macrophages producing excessive amount of fibronectin, fibroblast growth factor and neutrophil chemotactic factors. Thus, these data document that in support of a diagnosis of early asbestosis (asbestos alveolitis), BAL analyses can provide additional information whicb pertains to several mechanistic features of disease activity.

Among our silica workers presented in the Ga-67 scan section of this paper, we obtained BAL in 17. In the workers without silicosis (group 2), our results demonstrated increases in total cellularity (× 2), macrophage (× 2), lymphocyte (× 1.5), neutrophil (× 4), eosinophil (× 2), albumin (× 2.5) and immunoglobulin IgM (× 5), without increases in fibronectin or procollagen. These data in silica exposed long term workers without overt silicosis are essentially in agreement with the data of Christman et al[10] in documenting the presence of a sub-clinical quartz alveolitis in these workers. In the workers with simple silicosis, cellularity of BAL is further increased, particularly for lymphocytes (× 4 control), neutrophils (× 8 control) but with BAL biochemical results comparable to those of group 2. In the workers with complicated silicosis (coalescence and/or large opacity), cellularity is also increased but, whereas albumin in BAL is now comparable to control, immunoglobulins IgG, IgA, IgM are the

highest, fibronectin and procollagen are highly increased ( $P < 0.05$), which would agree with the current concepts of an activated fibrotic process. Of interest, we have also documented that when the disease was radiographically detectable, there was a significant increase in fibroblast growth factor which was observed even in the absence of coalescence and/or conglomeration.[8]

### Pulmonary Function Tests

In the evaluation of early disease in asbestos workers, several investigators have suggested that spirometry, diffusion and gas exchange studies could identify workers with asbestosis as well as chest radiograph. Futhermore, it has been documented by Jodoin et al,[12] and confirmed in our own investigations that rigidity of the lung pressure-volume curve could be seen in several workers without radiograph changes.[3,4] We have further documented that this finding was usually associated with enhanced gallium-67 lung uptake and when a lung biopsy was obtained, it showed the fundamental early macrophagic peribronchiolar alveolitis associated with early asbestosis. Also we found that early peribronchiolar disease did not significantly reduce the spirometric flow rates but caused a slight increase in upstream resistance only at low lung volumes.[6]

In silica-exposed workers, we have also obtained the usual lung function tests as well as pulmonary mechanics. This is the subject of distinct report.

## DISCUSSION

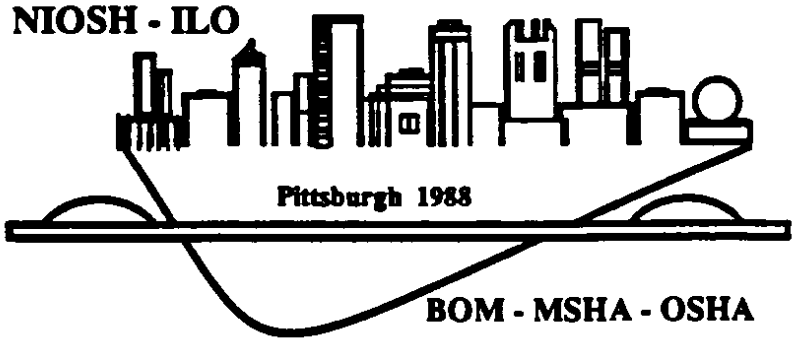
Recent researches in the biology of the mineral dust pneumoconioses have substantially increased our understanding of the sequence of events leading to fibrosis of the lung. Fibrosis in the mineral dust pneumoconioses is an end-stage result of a chronic inflammatory process which is continuously activated by the chronic retention of the mineral particles in the lung tissue. In parallel, in-depth clinical investigations of mineral dust exposed workers with or without pneumoconiosis have identified workers without the classical findings of the pneumoconiosis but with significant abnormalities of CT-scan, lung lavage, Ga-67 lung scan and lung pressure-volume curves similar to those of early disease in the animal studies. These abnormalities can detect the early inflammatory lesion of mineral dust pneumoconioses before its fibrotic stage. Newer approaches to prevent fibrosis of the lung tissue are currently under animal investigation in several laboratories.

## REFERENCES


1. Bégin, R., Cantin, A., Drapeau, G., Lamoureux, G., Boctor, M., Massé, S., Rola-Pleszczynski, M.: Pulmonary Uptake of Gallium-67 in Asbestos Exposed Human and Sheep. *Am. Rev. Respir. Dis.* 127:623-630 (1983).
2. Bégin, R., Boctor, M., Bergeron, D., Cantin, A., Berthiaume, Y., Péloquin, S., Bisson, G., Lamoureux, G.: Radiographic Assessment of Pleuro-pulmonary Disease in Asbestos Workers: Postero-anterior, Four View Films and Computed Tomograms of the Thorax. *Brit. J. Indust. Med.* 41:373-383 (1984).
3. Bégin, R., Cantin, A., Berthiaume, Y., Boileau, R., Bisson, G., Lamoureux, G., Rola-Pleszczynski, M., Drapeau, G., Massé, S., Boctor, M., Breault, J., Péloquin, S., Dalle, D.: Clinical Features to Stage the Alveolitis in Asbestos Workers. *Am. J. Indust. Med.* 8:521-536 (1985).
4. Bégin, R., Bisson, G., Lambert, R., Côté, Y., Fabi, D., Martel, M., Lamoureux, G., Rola-Pleszczynski, M., Boctor, M., Dalle, D., Massé, S.: Gallium-67 Uptake in the Lung of Asbestos Exposed Sheep: Early Association with Enhanced Macrophage-derived Fibronectin Accumulation. *J. Nucl. Med.* 27:538-544 (1986).
5. Bégin, R., Martel, M., Desmarais, Y., Drapeau, G., Boileau, R., Rola-Pleszczynski, M., Massé, S.: Fibronectin and Procollagen III Levels in Lung Lavage of Asbestos Exposed Humans and Sheep. *Chest* 89:237-243 (1986).
6. Bégin, R., Massé, S., Sébastien, P., Bossé, J., Rola-Pleszczynski, M., Boctor, M., Coté, Y., Fabi, D., Dalle, D.: Asbestos Exposure and Retention as Determinants of Airway Disease and the Asbestos Alveolitis. *Am. Rev. Respir. Dis.* 134:1176-1181 (1986).
7. Bégin, R., Bergeron, D., Samson, L., Boctor, M., Cantin, A.: CT Assessment of Silicosis in Exposed Workers. *Am. J. Roent.* 148:509-14 (1987).
8. Bégin, R., Cantin, A., Boileau, R., Bisson, G.: Spectrum of the Alveolitis in Quartz-exposed Humans. *Chest* 92:1061-1067 (1987).
9. Brody, A.R., Hill, L.H., Adkins, B., O'Connor, R.W.: Chrysotile Asbestos Inhalation in Rats: Deposition Pattern and Reaction of Alveolar Epithelium and Pulmonary Macrophages. *Am. Rev. Respir. Dis.* 123:670-679 (1981).
10. Christman, J.W., Emerson, R.J., Graham, W.G.B., Davis, G.S.: Mineral Dust and Cell Recovery from the Bronchoalveolar Lavage of Healthy Vermont Granite Workers. *Am. Rev. Respir. Dis.* 132:393-399 (1985).
11. Craighead, J.E., Vallyathan, N.V.: Cryptic Pulmonary Lesions in Workers Occupationally Exposed to Dust Containing Silica. *JAMA* 244:1939-1941 (1980).
12. Jodoin, G., Gibbs, G.W., Macklem, P.T., McDonald, J.C., Becklake, M.R.: Early Effects of Asbestos Exposure on Lung Function. *Am. Rev. Respir. Dis.* 104:525-535 (1971).
13. Jost, R.G., Sagel, S.S., Stanley, R.J., Levitt, R.G.: Computed Tomography of the Thorax. *Radiology* 126:125-136 (1978).
14. Kreel, L.: Computed Tomography of the Lung and Pleura. *Semin. Roentgenol.* 13:213-225 (1978).
15. Lambert, R., Bisson, G., Lamoureux, G., Bégin, R.: Gallium-67 Thoracic Scan and Pleural Disease in Asbestos Workers. *J. Nucl. Med.* 26:600-603 (1985).
16. Rom, W.N., Bitterman, P.B., Rennard, S.I., Cantin, A., Crystal, R.G.: Characterization of the Lower Respiratory Tract Inflammation of Nonsmoking Individuals with Interstitial Lung Disease Associated with Chronic Inhalation of Inorganic Dusts. *Am. Rev. Respir. Dis.* 136:1429-1434 (1987).

*Proceedings of the VIIth International Pneumoconioses Conference* *Part*
*Transactions de la VIIe Conférence Internationale sur les Pneumoconioses* *Tome*
*Transaciones de la VIIa Conferencia Internacional sobre las Neumoconiosis* *Parte*

# II




Pittsburgh, Pennsylvania, USA—August 23–26, 1988
Pittsburgh, Pennsylvanie, Etats-Unis—23–26 aout 1988
Pittsburgh, Pennsylvania EE. UU—23–26 de agosto de 1988

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Centers for Disease Control
National Institute for Occupational Safety and Health

CDC
CENTERS FOR DISEASE CONTROL

## Sponsors

International Labour Office (ILO)
National Institute for Occupational Safety and Health (NIOSH)
Mine Safety and Health Administration (MSHA)
Occupational Safety and Health Administration (OSHA)
Bureau of Mines (BOM)

November 1990

## DISCLAIMER

Sponsorship of this conference and these proceedings by the sponsoring organizations does not constitute endorsement of the views expressed or recommendation for the use of any commercial product, commodity, or service mentioned.

The opinions and conclusions expressed herein are those of the authors and not the sponsoring organizations.

**DHHS (NIOSH) Publication No. 90-108 Part II**