Inflammatory and immune reactions associated with inorganic dust exposure: comparison between patients with and without clinical lung involvement

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Clinically stable silicotics do not show marked bronchoalveolar lavage (BAL) differences compared to normals. In nonsmoking silicotics, we found only a small significant lymphocyte increase, an absolute IgG increase and a marked neutrophilia, probably related to concomitant chronic bronchitis [1]. Some subjects suffered heavy silica dust inhalation at work but without chest X-ray signs of silicosis or blood-alveolar barrier impairment at the time of admission.

In certain conditions of exposure to known hypersensitivity pneumonitis antigens, comparison of exposed subjects with and without overt disease has revealed the presence in a relevant percentage of exposed, apparently healthy individuals of alveolar parameters comparable to those found in conditions of active disease [2, 3].

BAL findings were compared in subjects exposed to silica dust, with or without silicosis, in order to reveal differences of pathogenetic and clinical relevance. The 36 subjects were, or had been, exposed to silica dust at work (40% tunnel diggers, 40% foundry workers, 20% ceramic workers). They were grouped according to smoking habits [4, 5]. Case histories and respiratory function data are shown in table 1. Diagnosis of silicosis was established on the basis of well-documented exposure to silica dust and typical chest X-ray involvement assessed by two independent observers and defined according to the ILO classification.

The patients underwent BAL during fibreoptic bronchoscopy performed for diagnostic reasons (cough or haemoptysis of undefined origin) or as volunteers. Three 50 ml boluses of saline were injected and recovered for separate cytological analysis including total cell count and cell differentials [5]. Biochemical analysis consisted of total protein determination and albumin, IgG and IgA evaluation [4]. Statistical comparison was made using Student's t-test for independent data.

Lung function evaluation demonstrated a prevalent obstructive pattern of respiratory impairment. Restrictive limitation and reduced diffusing capacity, characteristic of advanced silicosis, were seen in only a few patients (10%). Cytological and biochemical reference values were published previously [1]. BAL cytological and biochemical data are reported in tables 2 and 3. Simple exposure in nonsmokers was associated with a cellularity significantly lower than in silicotics ($p<0.01$) but in both cases total cells did not appear significantly increased in comparison to normals. All subjects (smokers and nonsmokers) had significant neutrophilia ($p<0.03$) compared to normals. Nonsmoking silicotics had significantly more total protein than simply exposed subjects ($p<0.01$) and normals ($p<0.01$) (table 2). IgG/albumin was significantly increased ($p<0.05$) in nonsmoking silicotics compared to normals. Smoking silicotics and simply exposed subjects did not appear to have relevantly different levels of total proteins. Protein levels were significantly increased in both groups compared to smoking normals ($p<0.03$).

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Table 1. – Case history, respiratory function and X-ray data of silica exposed subjects

Case series	Nonsmokers	Smokers
No. of patients		
Silicosis	13	11
Simple exposure	7 (1 F)	7
Age yrs		
Silicosis	59.6±9.1	57.9±10.5
Simple exposure	50.3±7.1	58.3±7.3
Years of exposure		
Silicosis	22.2±9.2 (7–40)	24.7±14.4 (5–44)
Simple exposure	19.3±10.2 (2–23)	27.9±12.4 (15–47)
Years passed since latest exposure		
Silicosis	10.6±14.4 (0–46)	8.8±13.9 (0–35)
Simple exposure	10.9±10.6 (0–31)	6.0±9.5 (0–25)
Respiratory function data %pred		
FEV_1		
Silicosis	75.1±18.9	70.7±18.6
Simple exposure	72.0±12.4	74.6±10.1
FVC		
Silicosis	75.0±10.3	76.8±13.7
Simple exposure	85.0±11.3	80.5±11.9
DLCO		
Silicosis	78.3±14.9	79.7±17.8
Simple exposure	>90	>90
Degree of chest X-ray involvement		
Silicosis	p 1/1 (4)	p 1/1 (3)
	p 1/2 (3)	p 1/2 (1)
	p 2/2 (3)	q 2/2 (4)
	q 2/2 (3)	p 2/2 (4)
Simple exposure	p 0/0 (5)	p 0/0 (4)
	p 0/1 (2)	p 0/1 (3)

FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; DLCO: diffusing capacity for carbon monoxide. Brackets indicate range or no. of subjects.

Table 2. – BAL cytological and biochemical data of exposed nonsmoking subjects

	Silicosis	t-test	Simple exposure
Recoveries ml	71.1±27.4	NS	75.1±19.6
Cytological data			
Cells·ml^{-1} × 10^3	216.3±70.0	p<0.01	145.0±46.1
Macrophages %	82.7±13.9	NS	81.1±6.4
Lymphocytes %	9.5±6.9	NS	11.4±3.2
Neutrophils %	5.1±6.4	NS	3.6±3.1
Eosinophils %	0.14±0.14	NS	0.35±0.23
Basophils %	0.03±0.06	NS	0.1±0.14
Si/S	1.45±0.8	NS	1.24±0.66
Biochemical data (proteins, mg % ml)			
Total proteins	15.3±6.7	p<0.01	6.05±2.3
Albumin	4.6±2.5	NS	2.5±1.5
IgG/albumin	0.26±0.22	NS	0.37±0.49
IgA/albumin	0.06±0.06	NS	0.05±0.05

BAL: bronchoalveolar lavage; NS: nonsignificant; Si/S: semiquantitative microanalytical evaluation of the cell silicon content expressed as silicon to sulphur ratio.

Table 3. – BAL cytological and biochemical data of exposed smoking subjects

	Silicosis	t-test	Simple exposure
Recoveries ml	69.7±19.9	NS	64.9±21.5
Cytological data			
Cells·ml^{-1} × 10^3	462.5±176.7	NS	332.1±143.7
Macrophages %	84.5±11.9	NS	85.1±7.5
Lymphocytes %	8.1±3.8	NS	7.4±4.2
Neutrophils %	5.5±7.7	NS	3.7±3.0
Eosinophils %	0.61±0.94	NS	1.15±1.17
Basophils %	0.11±0.20	NS	0.08±0.07
Si/S	1.99±1.2	NS	1.64±1.3
Biochemical data (proteins, mg % ml)			
Total proteins	15.8±4.4	NS	19.7±14.5
Albumin	5.2±4.2	NS	6.7±5.7
IgG/albumin	0.46±0.24	NS	0.39±0.47
IgA/albumin	0.08±0.11	NS	0.05±0.05

For abbreviations see legend to table 2.

The presence of a large amount of silica dust in pulmonary alveoli does not necessarily result in permanent progressive damage or relevant alveolitis.

In smokers there are no differences in cytological or biochemical data between simply exposed and silicotic patients. The slight differences seen between nonsmoking silicotics and exposed subjects are probably overcome as a result of smoking.

We analysed the three recoveries of each BAL separately. The neutrophilia found was usually progressively diluted from the 1st to the 3rd aliquot [6], demonstrating a prevalently bronchial origin of neutrophils. The clinical condition of our silicotic patients often deteriorates because of chronic bronchitis rather than progression of interstitial fibrosis.

CHRISTMAN *et al.* [7] found a significant lymphocytosis in the BAL fluids of nonsmoking workers exposed to silica but not affected by silicosis. Our study did not confirm this finding. Christman's subjects were still exposed to silica at work, whilst in our case only 5/20 nonsmokers and 4/18 smokers were still exposed in the work place. Among those 9 workers only 2 smoking silicotics showed an absolute (but not percentage) lymphocyte level above normal. Freshly ground silica has been shown to have the potential to produce far more damage [8] particularly with regard to generation of free radicals. This may explain why recent exposure can show inflammatory and immunological alterations not seen in subjects with an exposure of older cessation.

Nonsmoking subjects are more suitable for comparing differences between clinical silicosis and simple exposure, since smoking habits tend to homogenize the BAL features of control, silicotic and simply exposed individuals. As, apart from a higher level of cellularity and total proteins, the BAL features of nonsmoking silicotics were superimposable on those of subjects with simple exposure, we conclude that the most common BAL parameters are not useful from a clinical (diagnosis of silicosis) or investigative point of view. Insight into pathogenesis should improve when it is possible to characterize the chemical mediators released by human alveolar macrophages more accurately. It has been demonstrated that the alveolar macrophage is able to stimulate and inhibit fibroblast activity [9], the balance probably varying with subject, conditions and time elapsed since last exposure. With cessation of exposure the clinical situation (fibrosis) may remain steady for many years whilst the chronic bronchitis usually tends to deteriorate progressively, particularly in smokers. We tried to match groups according to age, duration of exposure, smoking habit, time since last exposure and type of exposure. Objectivity of data is often uncontrolled when obtained by patient's self-reported history. We tried to check exposure by objective criteria (polarized microscopy and semiquantitative X-ray microanalysis). The normal criteria for clinical diagnosis of silicosis or asbestosis is of controversial reliability [10, 11]. Histological evaluation would be preferable but before utilizing invasive procedures a clear benefit for the patient must be demonstrated.

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Airway inflammation and late asthmatic reactions

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Sensitized subjects may develop symptoms of asthma after exposure to isocyanates at work [1, 2]. After challenge with isocyanates in the laboratory, they develop immediate, late and dual asthmatic reactions [3]. Dual and late asthmatic reactions are more frequent than early reactions after challenge with isocyanates [4], and like allergen-induced dual and late reactions, have probably more relevance to the history of asthma than immediate reactions. Late asthmatic reactions are usually more severe, last longer, respond to steroids but not to bronchodilators and are more resistant to therapy. Subjects sensitized to toluene diisocyanate (TDI) who develop dual or late reactions continue to have asthma upon cessation of exposure [5]. The mechanism of the late asthmatic reaction is unknown. TDI may cause late asthmatic reactions and increase bronchial responsiveness by causing an acute inflammatory reaction in the airways.

Sensitized subjects were examined during late asthmatic reactions induced by exposure to TDI in the laboratory. The late asthmatic reactions were associated with a transient increase of bronchial responsiveness [6], an increase of neutrophils, eosinophils [7], leukotriene B_4 (LTB_4) and albumin [7] in bronchoalveolar lavage fluid. These reactions were prevented by pretreatment with prednisone [8] but not with the non-steroidal, anti-inflammatory agent indomethacin [9]. Aerosolized steroids alone, *e.g.* beclomethasone [10, 11], completely inhibit late asthmatic reactions induced by TDI. Theophylline [10] has only a partial effect. Verapamil [10], ketotifen [12], salbutamol alone, atropine [13] and cromolyn [10] have no protective effect.

These studies support the hypothesis that bronchoconstriction and airway inflammation are involved in the late asthmatic reaction induced by TDI, and that polymorphonuclear leucocytes are required for hyper-responsiveness to occur. One of the inflammatory mediators (*i.e.* LTB_4) (1a) has been measured during late asthmatic reactions induced by TDI. The structure and source of all chemotactic factors which attract neutrophils and eosinophils into the airspaces and of the mediators released by these cells must be identified.

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