# COBALT SENSITIVITY IN HARD METAL ASTHMA —HARMFUL EFFECTS OF COBALT ON HUMAN LUNGS

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## ABSTRACT

Twelve workers diagnosed as suffering from hard metal asthma on the basis of peak flow diaries and positive bronchoprovocation with cobalt chloride ($CoCl_2$) were studied for sensitization to cobalt using specific RAST (radioallergosorbent test with Co-HSA (cobalt conjugated human serum albumin) and Co-resin (cobalt conjugated exchange resin), saturated ammonium sulfate precipitation test with radioactive cobalt (Co-SASPT), skin test with $CoCl_2$ by intradermal Co-IDST) and patch (Co-PT) techniques, and lymphocyte stimulation test with $CoCl_2$ (Co-LST).

Eleven of 12 subjects sera which selectively bound $^{57}Co$ were divided into two groups. Seven sera showed evidence of specific IgE antibodies to Co-HSA and/or Co-resin on the basis of comparison with 60 control sera from asthmatic patients without a history of hard metal exposure, while four sera had no reactivity to these solid matrices. Further support for Co reactivity comes from blocking experiments where non-labelled $Co^{2+}$ (1mM) inhibited specific antigen-antibody association. There was a strong relationship between RAST values and wheal diameters with 1% $CoCl_2$ ($r = 0.82$) in the subjects. The results in Co-PT does not agree with those in Co-LST, while correlation was seen in the patients with contact dermatitis. These findings suggest the development of hard metal asthma from cobalt sensitivity, although the involvement of type IV allergic reaction remains unknown.

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# EVALUATION OF PULMONARY REACTIONS IN HARD METAL WORKERS

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## INTRODUCTION

The production of hard metal components of equipments for different technological uses is presently actively expanding in several countries.[9,10] Consequently, the number of workers exposed to risk of inhaling hard metal particles is increasing.

Lung disorders from exposure to hard metals have been known since almost 50 years, and recently cobalt has been recognized as the major responsible agent.[3,8,9] Both asthma and more severe deep lung involvement can occur, with possible evolution in fibrosis.[2,8,9]

In the last two years we had the opportunity to thoroughly investigate two groups of workers exposed to inhalation of hard metals in completely different occupational settings and to evaluate their pulmonary reactions by bronchoalveolar lavage (BAL). The main findings are reported in this paper.

## MATERIALS AND METHODS

### Subjects

Group A consisted of 26 workers, 25 males and one female, 18 smokers and 8 non-smokers, aged from 21 to 64 years (mean 32.9 years), engaged in the production of hard metal tools for 2 to 49 years (mean 10.4 years), and therefore exposed to tungsten carbide, titanium, tantalum and cobalt.

Group B consisted of 5 male workers, aged from 21 to 26 years, all but one non-smokers, engaged only in grinding hard metal tool edges by means of high-speed diamond-cobalt wheels with oily coolants for 1 to 9 years (mean 5 years) in a small workshop, with no proper protective equipments.

Two workers of group A, one non-smoker and one smoker, both 30 years of age, exposed for 7 and 13 years respectively, complained of work-related asthma, but were in remission at the time of study. Two workers of group B, non-smokers, aged 21 and 26, suffered from severe exertional dyspnea and complained of weight loss; they had been exposed for 6 and 5 years respectively, and were no longer exposed since 6 months when first studied.

### Methods

The 31 workers were hospitalized and were investigated by the following protocol: personal and occupational history; routine clinical and laboratory checkup; chest X-rays; lung function tests; patch tests for cobalt and tungsten, and skin tests for common inhalant allergens; bronchoalveolar lavage (BAL); elemental determination by neutron activation analysis in BAL, blood, urine, toenails and pubic hair.

BAL was performed according to the method currently used in our institute, and cytologically examined as described elsewhere.[4] Lymphocyte typing in BAL was performed on cytocentrifuge preparations by monoclonal antibodies in an immunoperoxidase assay, as described in detail elsewhere.[5]

Elemental determination in biological specimens was carried out by neutron activation analysis, as described elsewhere.[7]

## RESULTS AND DISCUSSIONS

In group A, no significant alterations were observed at chest X-rays. Lung function tests showed no significant impairment of the ventilatory function, whereas one subject with asthma and 4 additional workers presented a slight impairment of the pulmonary diffusion of gas.

On the contrary, BAL cytology showed a marked increase of total cells with a high percentage of lymphocytes in the non-smoker asthmatic subject (Table I). Increased percentage of lymphocytes (17%) with total cells somewhat above the highest normal value for smokers was detected also in one of the asymptomatic workers.

A moderate relative or absolute increase of lymphocytes was present in 8 additional workers, one with asthma (Table II). The increase of BAL lymphocytes was mainly due to an increase of suppressor (OKT8+) cells, with consequent inversion or marked reduction of the OKT4/OKT8 ratio, independent from the smoking habits.

Among the 5 young workers of group B, exposed to the fine aerosol spray originating from high-speed wet-grinding of hard metal edges, the two with severe dyspnea showed quite similar clinical features, consisting in diffuse irregular opacities at chest X-rays, associated with a significant restrictive impairment of the ventilatory function.

The cytology of BAL (Table III) showed in both cases an alveolitis of high intensity, characterized by an enormous increase of total cells, with numerous bizarre giant cells, marked eosinophilia, increased absolute number of lym-

Table I

Bronchoalveolar Lavage Cytology in the 26 Hard Metal Workers of Group A (mean values and ranges)

| Cases | No. | Total cells /ml x $10^{-3}$ | % Macrophages | % Lymphocytes | % Neutrophils | % Eosinophils |
|---|---|---|---|---|---|---|
| Asthma | 1 NS | 1800 | 61 | 36 | 0 | 3 |
| | 1 S | 640 | 91 | 7 | 2 | 0 |
| No symptoms | 7 NS | 173 (95-235) | 76 (51-91) | 15 (7-27) | 3 (<1-6) | <1 (0-2) |
| | 17 S | 700 (235-1530) | 91 (80-99) | 6 (<1-17) | 3 (<1-5) | <1 (0-1) |

NS, non-smoker S, smoker

Table II

Bronchoalveolar Lavage Lymphocyte Behavior in Hard Metal Workers of Group A

| No. of cases | | BAL lymphocyte number | Ratio OKT4/OKT8 |
|---|---|---|---|
| 2 | 1 asthma | markedly increased | 0.15 |
| | 1 no symptoms | increased | 0.2 |
| 8 | 1 asthma | slightly increased | 0.35 |
| | 7 no symptoms | | 0.2-0.8 |
| 16 | no symptoms | normal | 0.9 (1 case) |

Table III

Bronchoalveolar Lavage Cytology in the 5 Hard Metal Workers of Group B (individual values)

| Cases | No. | | Total cells /ml x $10^{-3}$ | Macrophages % | Lymphocytes % | Neutrophils % | Eosinophils % |
|---|---|---|---|---|---|---|---|
| Interstitial lung disease | 2 | NS | 3000 | 78 | 3 | 1 | 18 |
| | | NS* | 2475 | 62 | 32** | 3 | 3** |
| No symptoms | 2 | NS | 120-210 | 68-72 | 23-27 | 4-5 | 0-<1 |
| | 1 | S | 375 | 87 | 10 | 2 | <1 |

NS, non smoker S, smoker

* under steroid treatment since two months

** BAL pre-treatment at another institution: Lymphocytes 5%, Eosinophils 60%

phocytes with inverted OKT4/OKT8 ratio (0.52 and 0.58 respectively). The lymphocyte subpopulations in blood were normal.

The BAL findings correlated strictly with the histological features observed at open lung biopsy, performed in one case. In fact, histology showed alveolar filling by large mononuclear cells with occasional giant cells, involvement of the alveolar wall (edema, infiltration by lymphocytes and eosinophils) and hyperplastic alveolar lining, and was therefore typical for a desquamative interstitial pneumonitis.

Patch tests for cobalt were positive only in one case.

The 3 asymptomatic workers of group B showed only a slight increase of lymphocytes at BAL, with decreased OKT4/OKT8 ratios (Table III).

As far as concerns the concentrations of cobalt, tungsten and tantalum in biological specimens, evaluated by neutron activation analysis and presently available only for 11 subjects (including the two with asthma of group A and one of group B with the severe subacute lung disorder), no relation was observed between the presence of disease and the amount of any of the metals. The concentrations of cobalt and tungsten were in most instances one to three orders of magnitude compared to normal mean values (data not shown).

The highest values of all three means were observed, independently from signs and symptoms, in the workers with exposure of longer duration, and this was particularly true for concentrations at sites of deposit such as hair and nails. The behavior of the metals in the various specimens was constantly different and indicative of a relatively high mobility of inhaled cobalt. In fact, cobalt concentrations were the lowest in BAL and the highest in nails, hair and blood, whereas tungsten levels were the highest in BAL and the lowest in blood (median values for cobalt in BAL 4.6 ng/ml, in nails 8000 ng/g, in hair 5550 ng/g and in blood 6.2 ng/ml; median values for tungsten in BAL 348 ng/ml, in nails 5540 ng/g, in hair 875 ng/g and in blood 0.3 ng/ml).

Our findings support the hypothesis that immunological mechanisms play a fundamental role in the pathogenesis of respiratory disorders from exposure to hard metals. The occurrence of asthmatic or interstitial alterations, in fact, seems based on individual hypersusceptibility and not on the degree of occupational exposure.

The relatively low prevalance of respiratory symptoms in group A (2 among 26 workers with severe and often prolonged exposure) also points to individual factors in the pathogenesis of overt disease, and is in agreement with data from the literature.[8]

A lymphocytic alveolitis at BAL with reduced OKT4/OKT8 ratio has been occasionally reported in subjects with hard metal disease or cobalt lung.[1,3,6] However, our finding of a tendency to an increase of lymphocytes of deep lung, with an imbalance of T-lymphocyte subpopulations, in several asymptomatic workers does not seem to have been reported so far, and suggests a more frequent effect of the exposure on the local immune system, whose pathogenetic significance cannot at present be stated.

In group B, the lung pathological changes were more severe and more frequent (2 out of 5 workers). These observations are in agreement with data of the literature, which indicate a higher risk in operations on hard metals involving the use of coolant fluids and producing fine aerosol sprays.[9] In this

group too, however, individual hypersusceptibility seems important, but the type of lung changes suggests different pathogenetic mechanisms. In fact, in agreement with the observations of Davison et al.,[2] the histological and cytological features are not those typical for hypersensitivity pneumonitis.

Even though immunological hypersusceptibility seems to be the most probable pathogenetic factor, the specific immune reactions directly involved in the induction of the different disorders are still poorly understood. Therefore, it is impossible at present to propose sensitive and specific tests for the early identification of hypersusceptible individuals.

In the medical surveillance of exposed workers, the aim should be to detect early respiratory alterations. Lung function tests and BAL in selected cases should be considered at the present time the methods of choice.

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# PULMONARY AND CARDIAC FINDINGS AMONG HARD METAL WORKERS

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## ABSTRACT

Excessive exposure to dust in the cemented tungsten carbide industry has been associated with the development of hard metal disease primarily manifested by asthma, pneumonitis or interstitial pulmonary fibrosis.

We have examined a group of 41 former hard metal workers with a history of mean duration of employment of 10.5 years (SD±5.3). In addition to a high prevalence of respiratory symptoms, abnormal chest radiographs were found in 13 workers, 8 of whom were classified as 1/1 according to the ILO International Classification of Radiographs of Pneumoconioses, 1980. There was an association between roentgenologic findings and right ventricular function as evaluated by radionuclide ventriculography.

These findings suggest that effects of excessive exposure in hard metal processing occur with appreciable prevalence and that it may be feasible to correlate roentgenologic findings according to the ILO Classification with cardiac function in this occupational lung disease.

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# THE PROTEAN MANIFESTATION OF HARD METAL DISEASE

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## ABSTRACT

Seven subjects with hard metal disease have recently been investigated. The subjects included both those involved in the production of hard metal and also users of the finished product. Several underwent bronchoalveolar lavage and the lavage fluid showed the presence of characteristic giant cells that have previously been described in histological sections. Four subjects presented with interstitial fibrosis of uncertain etiology and only subsequently did the diagnosis of hard metal disease become evident. In the other three subjects the condition presented as a hypersensitivity pneumonitis with the chest radiograph showing rounded opacities of varying size. These subjects all had bouts of low grade fever, shortness of breath and fleeting radiographic abnormalities. All of these had restrictive pulmonary impairment and abnormal gas transfer, but following cessation of exposure, there was radiographic clearing and improvement in lung function. In two subjects, however, substantial restrictive impairment and a reduced diffusing capacity persisted, in conjunction with a clear chest radiograph. In both instances, the chest film showed persistent small lung volumes. Although hard metal disease is an uncommon condition, early recognition is important if permanent irreversible damage is to be avoided.

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# INTERACTION OF PARTICULATES WITH OXIDATION PRODUCTS IN WELDING FUMES

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## ABSTRACT

The sudden onset of a generalized pattern of pulmonary fibrosis in a welder using methylene chloride aerosol (antispatter compound) while using an electric arc apparatus, has suggested a mechanism of injury involving highly reactive chlorine species adsorbed on metal particulates.

The simulation of arc welding under laboratory conditions in the presence of methylene chloride aerosol has verified the presence of phosgene ($COCl_2$) in concentration proportional to the quantitative presence of the aerosol. Heated metal surfaces of different ferrous alloys indeed produce phosgene gas in proportion to the amount of methylene chloride. Concentrations of phosgene range from 0.3 to 8.0 ppm., depending on the duration (2–12 min.) of the actual welding procedure and the amount of methylene chloride used (10, 50, 100 ppm).

The histological characteristics of the pulmonary fibrosis studied in biopsy samples obtained from the affected worker are quite consistent with a mechanism involving the reactive chlorine species absorbed on the surface of respirable particulates.

The implication of these observations for the health of welders appears obvious, demanding renewed attention for the safety of this trade.

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