INHALED CORTICOSTEROIDS IN THE TREATMENT OF OCCUPATIONAL RESPIRATORY DISEASES (O.R.D.)

J. ROSAL GONCALVES • Isabel Correia • Elena Raymundo • A. Teles de Araújo • M. Freitas e Costa

Clínica de Doencas Pulmonares (FML) and CnL3-INIC-Lisboa-Portugal

INTRODUCTION

The Occupational Respiratory Diseases (O.R.D.) are nosological entities for which it is possible to find a relationship between the dust, gas and aerosols inhalation in the work environment and the disease emergence.

The O.R.D. can display as an interstitial lung disease or a chronic air-flow obstruction. Frequently, the two syndromes overlap[1,2,3,8] and the basic pathogenic mechanisms are similar in both cases depending upon the clinical differences in the characteristics of the inhaled noxious substance and the individual behaviour.

In the pathogenic pathways of O.R.D. the alveolar macrophage fulfils an important role. Its stimulation releases Il_1, activating the T-lymphocyte with release of Il_2, peripheral monocyte recruitment, local T cell proliferation and a B cell stimulation leading to the granuloma formation.[5]

The perturbation of the macrophage cell membrane by stimulus, antigenic or others, causes the activation of the Phospholipase A2, interfering with the membrane phospholipids and leading to the release of arachidonic acid molecules and its metabolites.[11,14] The release of Paf-acether by the alveolar macrophages of these patients,[10,14] and of toxic 02 species has also been demonstrated.

The activated alveolar macrophage also releases fibronectin and Macrophage Derivated Growth Factor, important mediators in the fibrotic process.[1,3,8]

From the destruction of the alveolar macrophage by the cytotoxity of the noxious substance and from incomplete lysosomes results the release of enzymes—elastase and collagenase—contributors to the interstitial lung damage.[8,11]

Also the neutrophils are increased in the alveolar spaces and when stimulated by immune complexes liberate noxious enzymes.[8,11]

Finally in O.R.D. patients, as it happens in other fibrotic diseases, there is an increased number of mastocytes in the interstitial spaces and the released histamine would perhaps have a proinflammatory effect besides its bronchoconstrictive action.[13,15]

From the above mentioned emerges the justification to the use of corticosteroids in the treatment of some O.R.D. patients through its capacity to blockade the interleukins and other mediators release, to inhibit the Phospholipase A2, to diminish the neutrophils adhesivity and chemotaxie and to inhibit the production of histamine.

In clinical trials we had already confirmed that the improvement of the O.R.D. patients under corticotherapy is accompanied by a significant diminishing of the number of T-lymphocytes and rates of Lyso-Paf-acether (the percursor of Paf-acether) and histamine.[13,14]

As the local of the pathogenic process is the epithelial alveolar surface, it seems reasonable to think that the inhaled corticosteroids could perhaps stop them and be useful in the treatment of these O.R.D. patients requiring the use of drugs for their management.

The aim of this study is to evaluate the effectiveness of the inhaled corticosteroids in the treatment of the occupational respiratory diseases.

PATIENTS AND METHODS

We have studied 15 patients with ages ranging between 28 and 66 years, mean age 49 years. Ten of the patients were males and 5 females and two of the men were smokers (Table I).

Nine of the patients had a consistent occupational history of exposition to mineral dusts (5 to silica, 3 to iron and 1 to asbestos) and 6 to organic dust (3 to corck dust and 3 to pigeon dregs)—Table II.

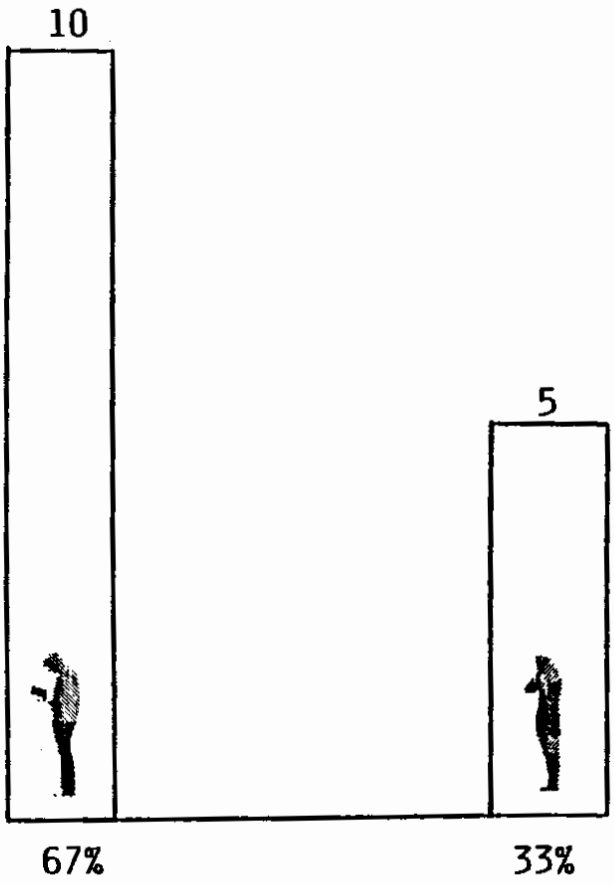
All of them had the disease confirmed through the usual clinical, functional, immunological and histological criteria.

All the patients had been submitted to a clinical inquiry, a standard chest X-ray and a complete functional respiratory study (global body plethysmography) previously to the treatment. The same study has been repeated every three months during one year.

The patients without evidence of ventilatory obstruction were submitted to bronchoalveolar lavage in a subsegment of the middle lobe with 4 syringes of 50 ml of saline serum warmed up to 37°C by a usual technique.[1] In 3 of the patients the bronchoalveolar lavage has been repeated 6 months after the beginning of the treatment.

The patients were submitted to a therapeutic with Budesonide 4 × 200 μg twice a day, via a 750 ml spacer.

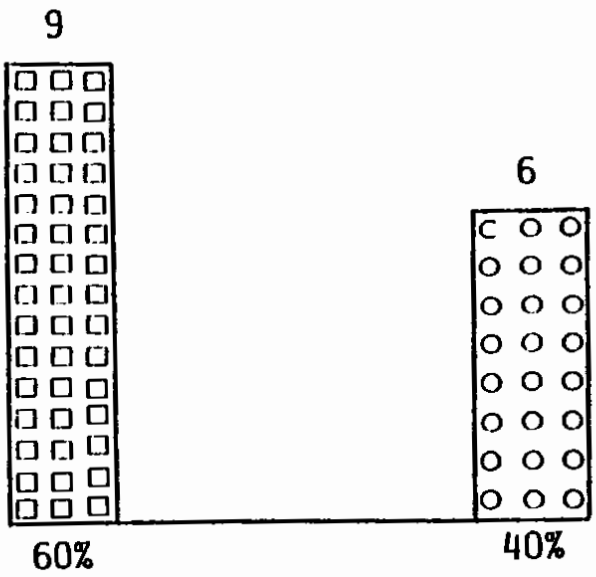
Table I
Patients



TOTAL - 15

MEAN AGE - 49
MAX. " - 66
MIN. " - 28

Table II
Exposition



MINERAL DUST

ORGANIC DUST

As concomitant medication we used in 7 patients inhaled bronchodilators. None of the patients had concomitant or previously oral corticosteroids. All were kept away from their workplace.

As comparison terms we considered a control group of 5 other O.R.D. patients with similar clinical, radiological and functional patterns, also kept away from the workplace in which only oral bronchodilators had been prescribed.

For statistic analysis we used the T test for paired data, differences method.

RESULTS

Before treatment all patients had complaints of exertion dyspnoea, 14 (93%) had cough, 8 (53%) expectoration and 7 (46%) wheezing (Table III).

After the first 3 months of treatment the clinical evaluation stated an improvement of the complaints in 12 (80%) of the patients, increasing progressively throughout the complete period of study.

The only side effects reported were two cases of mild sore throats and one of hoarseness, not being necessary to stop treatment.

In the control group only 3 out of the 5 patients (60%) improved.

All patients of both groups had chest X-ray before treatment evocating interstitial lung involvement expressed by linear and round shadows classifiable as, at least, of the type p 1/1 (UICC/Cincinnati classification). These aspects did not modify throughout the period of the study. However, in three patients with confluent shadows this aspect disappeared during the treatment.

At the beginning of the treatment 4 of the patients had functional obstructive defects, six restrictive defects and 5 had a normal pattern.

From the observation of Table IV it is clear that the Vital Capacity improved during the treatment in 12 of the patients (80%) and from the 3 that did not improve 2 had previously normal values. This improvement is significant ($p < 0.001$).

In what concerns the Total Lung Capacity only 9 of the patients improved (60%) and the difference is not significant (Table IV).

In Table IV the FEV_1 values are analyzed and it is verifiable that there is a significant improvement during the treatment ($p < 0.05$).

On the contrary the Tiffeneau index did not modify significantly with the treatment (Table IV).

In the control group there is no significant modification in any of the studied parameter (Table V).

The eight patients without evidence of bronchial obstruction were submitted to bronchoalveolar lavage. In 4 of them we verified the existence of an alveolitis ($74.5 \pm 71.3 \times 10^4$ cells/ml) and in both groups a significant increase of the lymphocytes percentages—three folds the normal values—(Table VI).

All patients of this group referred improvement in complaints during the treatment and ventilatorily and a significant increase in the values of Total Lung Capacity and Vital Capacity has been found (Table VII).

The three patients in which a second lavage had been performed showed 6 months after the beginning of the treatment, a decrease in the total cell count and in the number of lymphocytes as it is demonstrated in Table VIII.

DISCUSSION

First we must emphasize the difficulty to take conclusions from such a heterogeneous population in what concerns the type of inhaled agressor and the clinical manifestations.

By obvious reasons in a preliminary study we had chosen patients with a relatively mild disease, in which a sufficient

Table III

Complaints

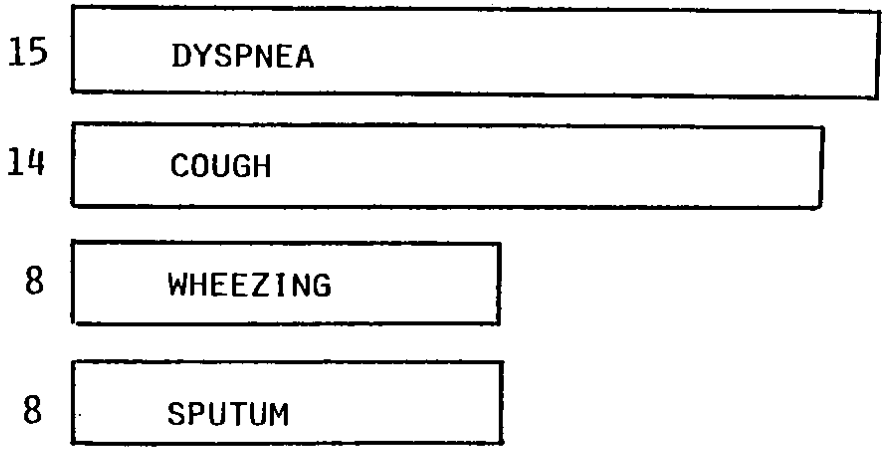
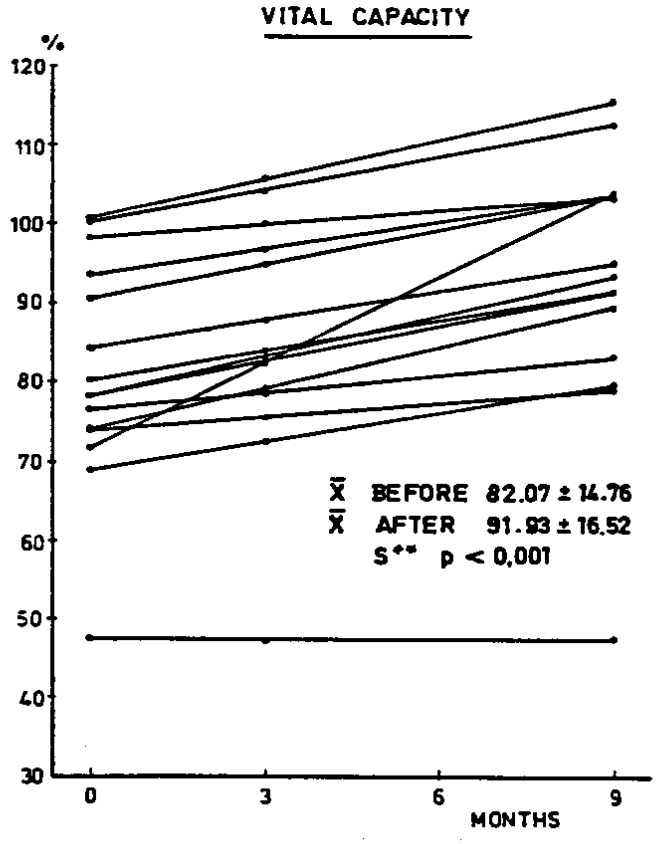
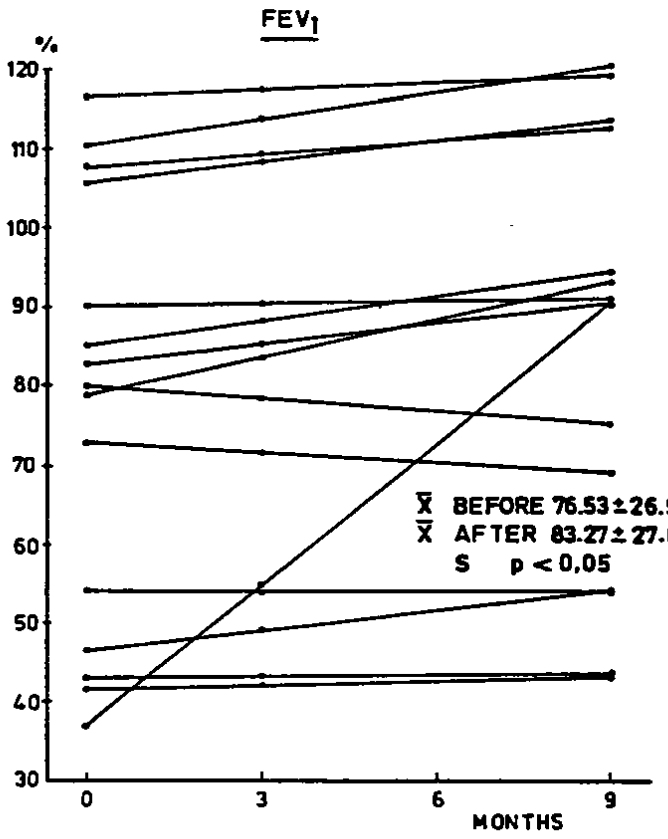
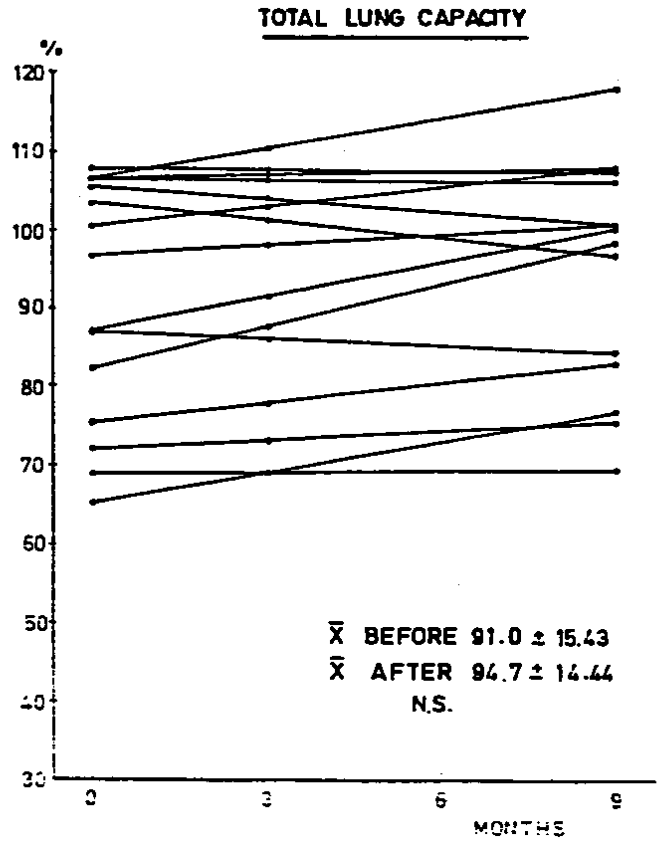


Table IV


VITAL CAPACITY
%
120
110
100
90
80
70
60
50
40
30
0
3
6
9
MONTHS
$\bar{X}$ BEFORE 82.07 ± 14.76
$\bar{X}$ AFTER 91.93 ± 16.52
S** p < 0,001


FEV1
%
120
110
100
90
80
70
60
50
40
30
0
3
6
9
MONTHS
$\bar{X}$ BEFORE 76.53 ± 26.97
$\bar{X}$ AFTER 83.27 ± 27.05
S p < 0,05


TOTAL LUNG CAPACITY
%
120
110
100
90
80
70
60
50
40
30
0
3
6
9
MONTHS
$\bar{X}$ BEFORE 91.0 ± 15.43
$\bar{X}$ AFTER 94.7 ± 14.44
N.S.

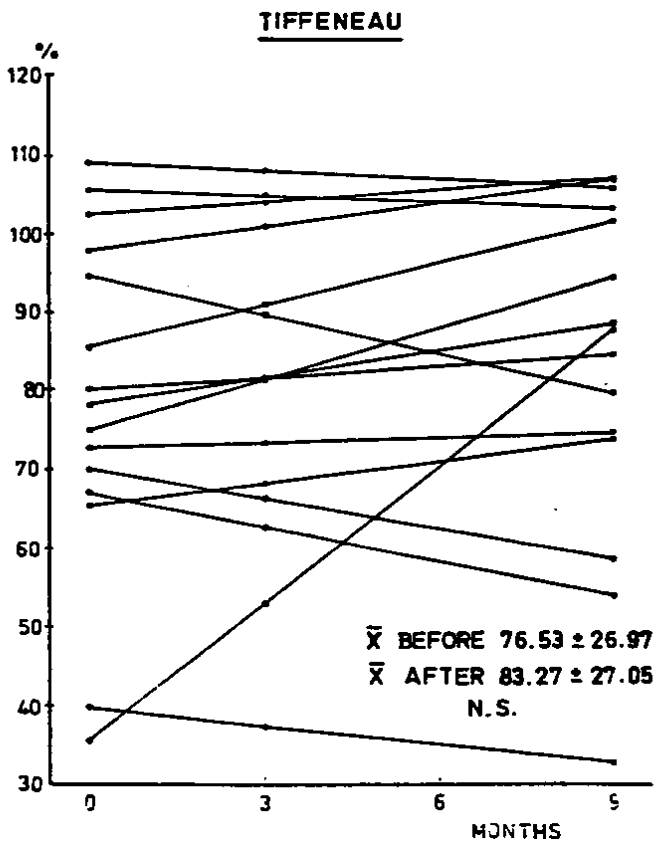
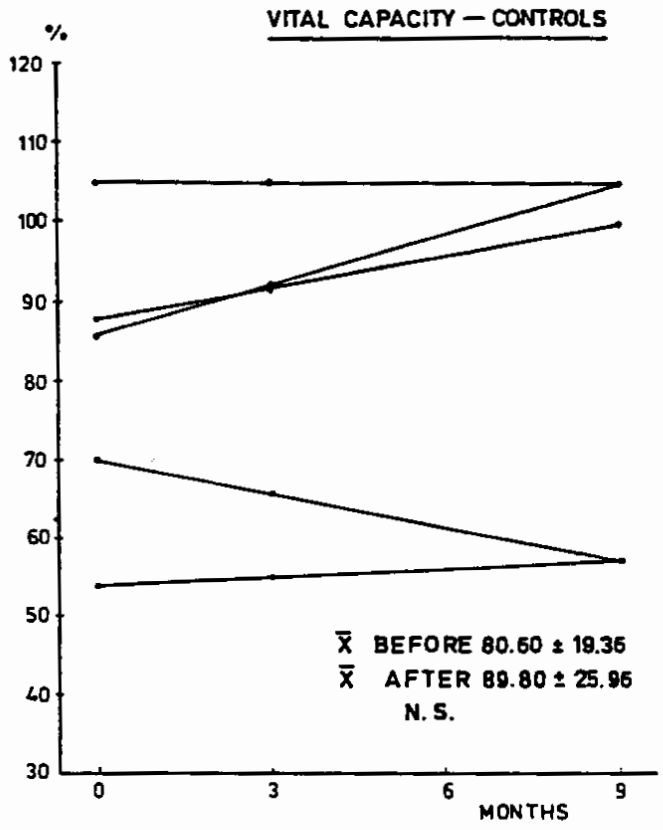
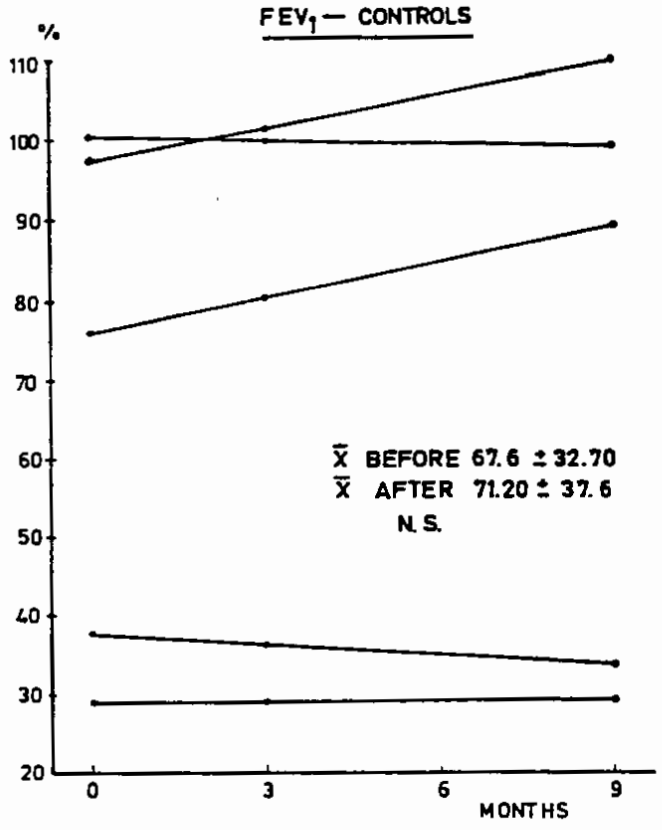
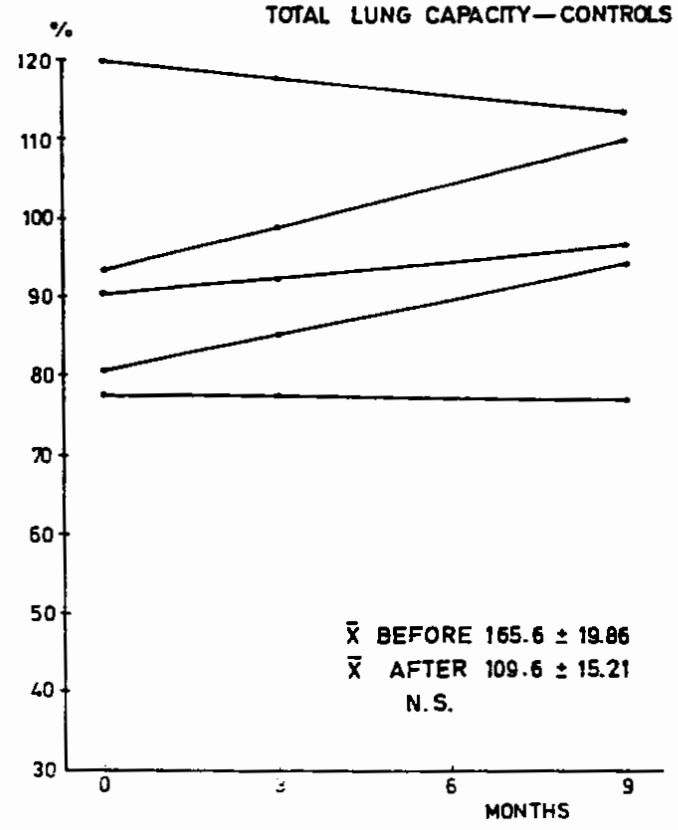
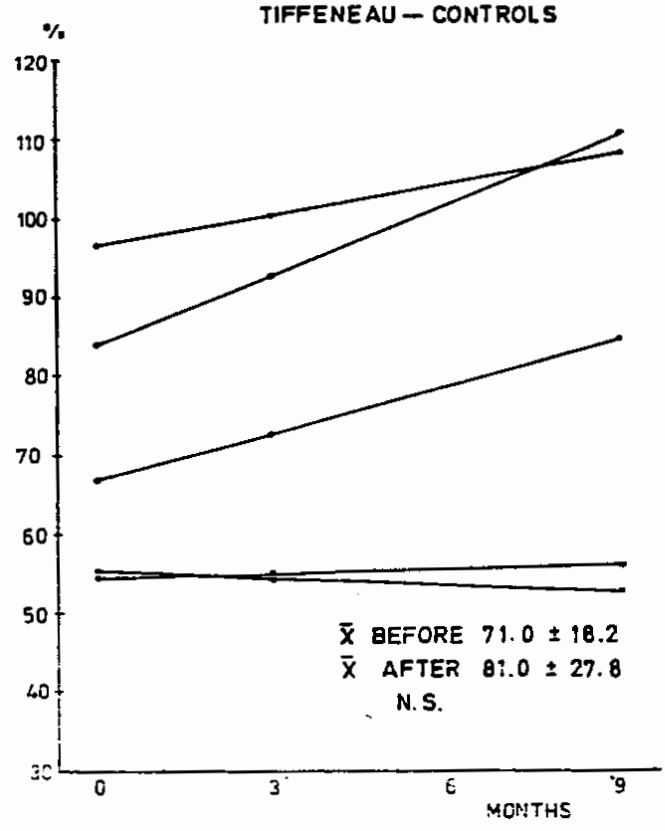

TIFFENEAU
%
120
110
100
90
80
70
60
50
40
30
0
3
6
9
MONTHS
$\bar{X}$ BEFORE 76.53 ± 26.97
$\bar{X}$ AFTER 83.27 ± 27.05
N.S.

Table V


VITAL CAPACITY — CONTROLS
%
120
110
100
90
80
70
60
50
40
30
0
3
6
9
MONTHS
X̄ BEFORE 80.60 ± 19.36
X̄ AFTER 89.80 ± 25.96
N. S.


FEV1 — CONTROLS
%
110
100
90
80
70
60
50
40
30
20
0
3
6
9
MONTHS
X̄ BEFORE 67.6 ± 32.70
X̄ AFTER 71.20 ± 37.6
N. S.


TOTAL LUNG CAPACITY—CONTROLS
%
120
110
100
90
80
70
60
50
40
30
0
6
9
MONTHS
X̄ BEFORE 165.6 ± 19.86
X̄ AFTER 109.6 ± 15.21
N. S.


TIFFENEAU — CONTROLS
%
120
110
100
90
80
70
60
50
40
0
3
6
9
MONTHS
X̄ BEFORE 71.0 ± 18.2
X̄ AFTER 81.0 ± 27.8
N. S.

clinical, radiological or functional support of an interstitial involvement had been found; however, this group included an important number of patients with simultaneous chronic airflow obstruction, sometimes even prevalent.

Supporting the favourable clinical evolution of the patients under inhaled corticotherapy the functional ventilatory parameters that more consistently improved were those related with the interstitial involvement rather than those related with airflow obstruction.

The suggestion of the interest of these drugs in O.R.D. patients is reinforced by the favourable clinical evaluation of the patients with alveolitis, confirmed by bronchoalveolar lavage (BAL) and by the improvement of the cellular parameters of their BAL fluid during the treatment.

The anarchical response of obstructive parameters to the therapeutic measures suggests the interference of other factors in bronchoconstriction independently of corticosteroids action: tobacco, infection, etc.

Besides the interest of inhaled corticosteroids in diseases with airflow obstruction[7,9] it has already been demonstrated in Sarcoidosis that the inhalatory therapy with Budesonide is able to transform the initial cellular, biochemical and immunological abnormalities in the direction of normalization and that the clinically useful doses result in tissue concentrations high enough to be efficacious.[9]

These two perspectives are very important in O.R.D. patients.

In fact a drug sufficiently efficient to reach the alveoli and stop the release of mediators by the immunological and inflammatory effector cells, and simultaneously to persist in the interstitium braking the pathogenic mechanisms due to the persistence of the aggressive particle, would surely have a place in the management of these diseases.

The obtained results seem to provide some evidence of the effectiveness of the purposed treatment, mainly in the interstitial occupational respiratory diseases which is not surprising once admitted the pathogenic mechanisms described above.

Table VI
Bronchoalveolar Lavage

	CELLS	MA	LYMPH.	P.M.N.
WITH ALVEOLITIS n = 4	74,5±71,3	53,8±32,5	39,5±23,2	1,75±1,5
WITHOUT ALVEOLITIS n = 4	18,3± 6,9	63,3±28,6	36,3±28,6	1,0 ±1,4

Table VII
Patients with B.A.L.

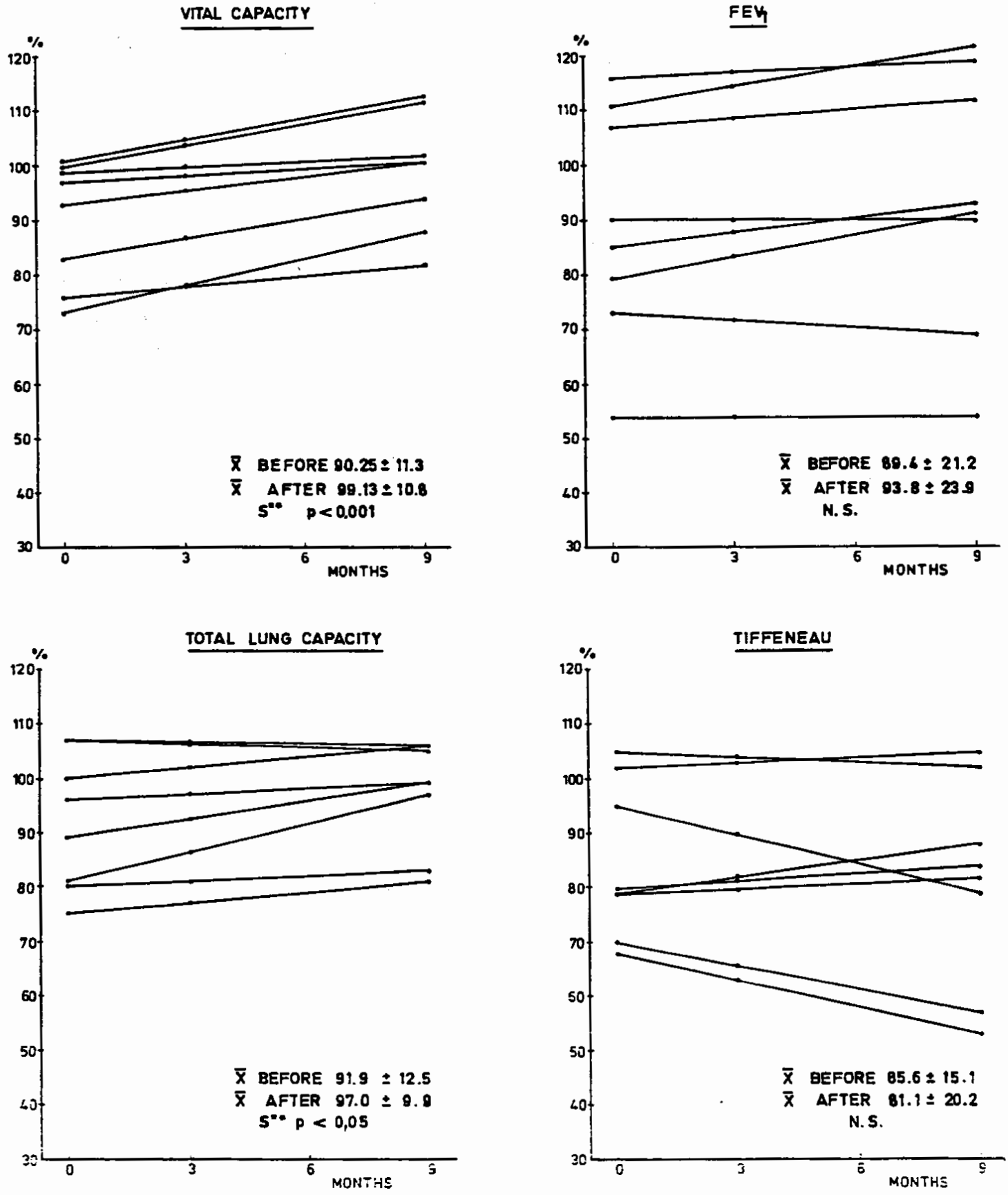
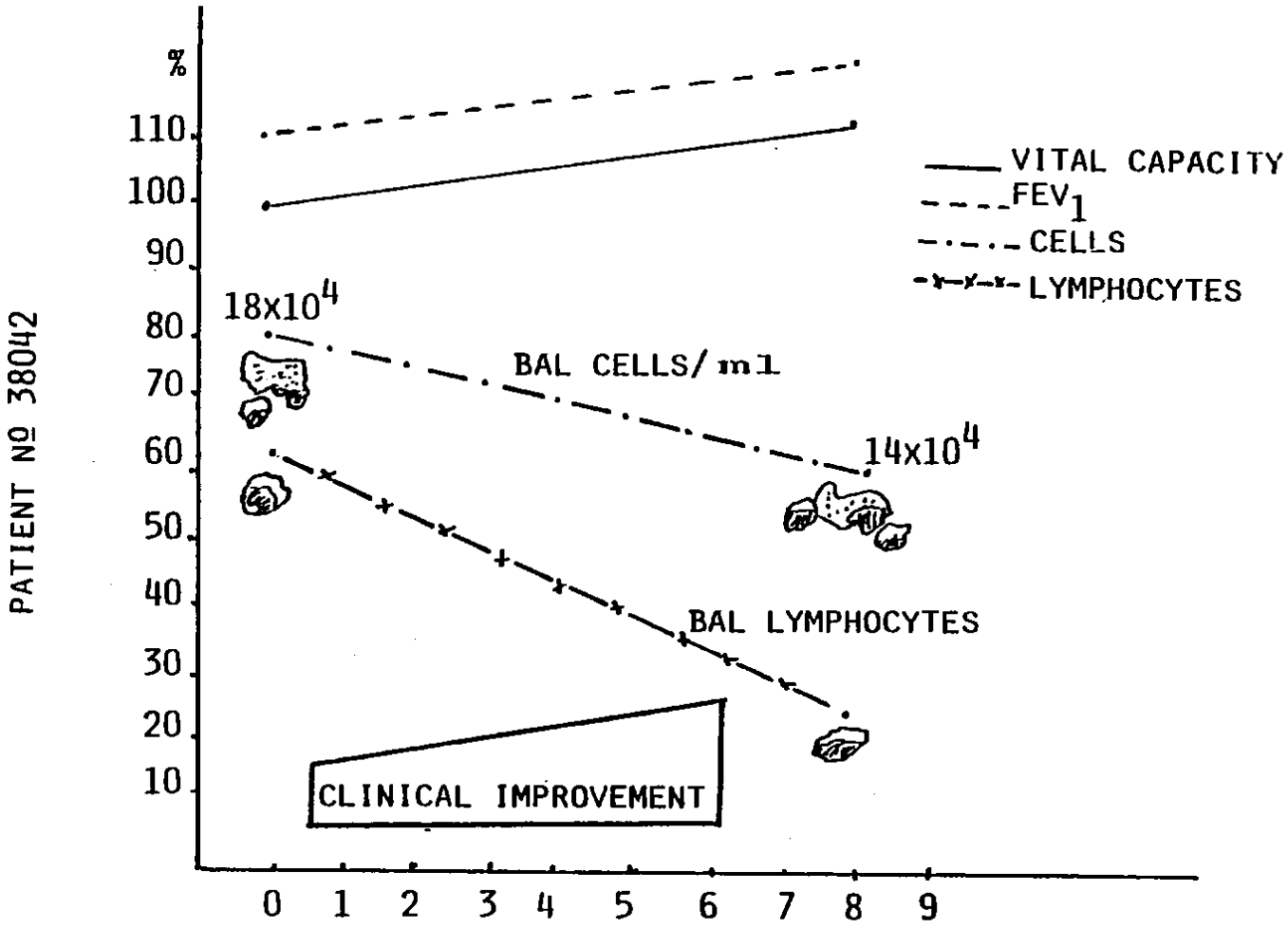


Table VIII



Thus when it is necessary to consider the use of corticosteroids the inhalatory therapy can represent an alternative or a complement to oral corticosteroids. This alternative becomes more important if one considers that inhaled corticosteroids rarely cause systemic side effects and do not reach immunosuppressive levels,[2] which is of a great interest in patients with susceptibility to infections such as the case of Silicosis.

Further studies will be necessary to define the real usefulness of Budesonide in the treatment of these patients, which are the parameters necessary to define when it can be used as the unique therapeutic measure, besides the evication from the aggressive noxious, and when it must be used as a complement to oral corticosteroids, permitting a significant dose reduction.

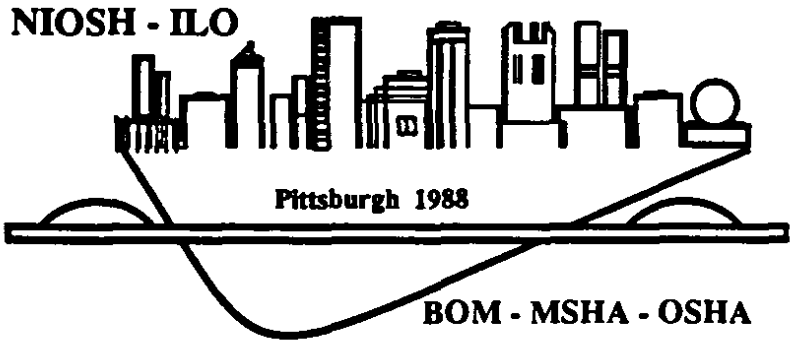
REFERENCES

1. Bernard, J., Gree, L.: Occupational Lung Diseases. Contemporary Issues in Pulmonary Diseases (1984).
2. Brooks, Stuart M., Kalica, Anthony, R.: Strategies for Elucidating the Relationship Between Occupational Exposures and Chronic Airflow Obstruction (NHLBI Workshop Summary). *Am. Rev. Resp. Dis.* 135:268-273 (1987).
3. Dunnil, M.S.: Pulmonary Pathology. Interstitial Lung Diseases. *Ed. Churchill Livingston*, pag. 487-529 (1987).
4. Haslam, P.L., Cromwell, O., Dewar, A., Turner-Warwick: Evidence of Increased Histamine Levels in Lung Lavage Fluids from Patients with Cryptogenic Fibrosing Alveolitis. *Clin. Exp. Immunol.* 44:587-593 (1981).
5. Hunninghake, G.W., Ganett, K.C., Richardson, H.B., Fantone, J.C., Ward, P.A., Rennard, S.I., Bitterman, P.B., Crystal, B.G.: Pathogenesis of the Granulomatous Lung Diseases. *Am. Rev. Resp. Dis.* 130:476-496 (1984).
6. Lugano, E.M., Dauber, J.H., Elias, J.A., Bashey, R.I., Jimenez, S.A., Daniele, R.P.: The Regulation of Lung Fibroblast Proliferation by Alveolar Macrophages in Experimental Silicosis. *Am. Rev. Resp. Dis.* 129:767-771 (1984).
7. Reynolds, H.Y., Chrétien, J.: Respiratory Tract Fluids: Analysis of Content and Contemporary Use in Understanding Lung Diseases. *Disease-a-Month. Year Book Medical Publishers, Inc.* Chicago, February, (1984).
8. Schwarz, M.I., King, T.E.: Interstitial Lung Disease. *B.C. Decker*, Inc., 63-110 (1988).
9. Selroos, O.: Use of Budesonide in the Treatment of Pulmonary Sarcoidosis. Advances in the Use of Inhaled Corticosteroids Symposium. *Excerpta Medica*, (1986).
10. Simões, M.H., Araújo, A.T., Arnoux, B., Palma-Carlos, A.G., Freitas e Costa, M., Benveniste, J.: The Release of Paf-acether and Lyso-Paf-acether Bronchoconstrictive Mediators by Alveolar Macrophages on Granulomatosis. Proceeding of the IV European Conference on Sarcoidosis and Other Granulomatous Disorders. *Ed. Blasi, Olivieri, Pezza*, pag. 229-234 (1983).
11. Taylor, A.Y.N.: The Lung and the Work Environment. Current Perspectives in the Immunology of Respiratory Disease. *Ed. A.B. Kay, Edward, Y. Greetz, Churchill Livingston*, pag. 128-142 (1988).

12. Teles de Araujo, A., Alfarroba, E., Freitas e Costa, M.: The Role of Monoclonal Antibodies in the Study of Chronic Inflammatory Diseases Induced by Dust Inhalatory. *Eur. Y. Resp. Dis. Supl.* 146:203-210 (1986).
13. Teles de Araujo, A., Mendes, A. Cristina, Monteiro, J.T., Freitas e Costa, M.: Characteristics of the Lymphocytary Alveolitis of Sarcoidosis and Mineral Dust Inhalation Induced Pulmonary Granulomatosis. *Sarcoidosis and Other Granulomatous Disorders.* 711-712 (1988).
14. Teles de Araujo, A., Reis Ferreira. J.M., Freitas e Costa. M., Benveniste. J.: Abnormalities of Lipid Composition of Bronchoalveolar Lavage (BAL) in Respiratory Diseases Induced by Dust Inhalation. Sarcoidosis and Other Granulomatous Disorders. *Ed. Elsevier Science Publishers,* 685-688 (1988).
15. Teles de Araujo, A., Valenca, J., Bugalho de Almeida, A., Freitas e Costa, M.: Release of Histamine by Cultures of Bronchoalveolar Adherent Cells, *Prog. Resp. Res.*, 19:35-42 (1985).
16. Tukrainen, P., Lahdensuo, A.: Effect of Inhaled Budesonide on Severe Steroid-Dependent Asthma. *Eur. J. Resp. Dis.* 70:239-244 (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*

I



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)

September 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 I