Eur Respir J
1989, 2, 1015–1020

Scientific Meeting of the Contact Group "Respiratory Physiopathology" of the "National Fund for Scientific Research" of June 3, 1989 at the Catholic University of Leuven

Invited Lectures on: Inhalation pathology

Metal toxicity and the respiratory tract

B. Nemery
Universitair Ziekenhuizen, K.U.L. Leuven

This article is a review of the human pulmonary disorders which may result from exposure to inhaled metals. Since carbon and silicon are not metals, this review does not cover coal workers' pneumoconiosis, silicosis, asbestos-related diseases, or pneumoconioses caused by other silicates. The type of lung disease caused by metal compounds depends on the nature of the offending agent, its physico-chemical form, the dose, exposure conditions and host factors.

The fumes or gaseous forms of several metals (*e.g.* Cd, Mn, Hg, $Ni(CO)_4$, $ZnC1_2$, V_2O_5) may lead to acute chemical pneumonitis and pulmonary oedema or to acute tracheo-bronchitis. Metal fume fever, which may follow the inhalation of metal fumes (*e.g.* Zn, Cu and many others) is still a poorly understood influenza-like reaction, accompanied by an acute self-limited neutrophil alveolitis.

Chronic obstructive lung disease may result from occupational exposure to mineral dusts, including probably some metallic dusts, or from jobs involving the working of metal compounds such as welding. Exposure to cadmium has been demonstrated to be capable of leading to emphysema.

Bronchial asthma may be caused by complex platinum salts, nickel, chromium or cobalt, presumably on the basis of allergic sensitization. The cause of asthma in aluminium workers is unknown. It is remarkable that asthma induced by Ni or Cr is apparently infrequent, considering their potency and frequent involvements as dermal sensitizers.

Metallic dusts deposited in the lung may give rise to more or less marked pulmonary fibrosis and functional impairment, depending on the fibrogenic potential of the agent and on poorly understood host factors. Inhalation of iron compounds causes siderosis, a pneumoconiosis with little or no fibrosis. Hard metal lung disease is a fibrosis characterized by desquamative and giant cell interstitial pneumonitis and is probably caused by cobalt, since a similar disease has been observed in workers exposed to cobalt in the absence of tungsten carbide. Chronic beryllium disease is a fibrosis with sarcoid-like epitheloid granulomas and is presumably due to a cell-mediated immune response to beryllium. Such a mechanism may be responsible for pulmonary fibrosis occasionally found in subjects exposed to other metals (Al, Ti, rare earths).

The proportion of lung cancer attributable to occupation is around 15%, with exposure to metals being frequently incriminated. Underground mining of *e.g.*, uranium or iron is associated with a high incidence of lung cancer, as a result of exposure to radon. At least some forms of arsenic, chromium and nickel are well established lung carcinogens in humans. There is also evidence for increased lung cancer mortality in cadmium workers and in iron or steel workers. (Full paper to be published in Eur. Respir. J).

Interest of mineralogical analysis of biological samples in pneumoconiosis

P. de Vuyst
Hôpital Erasme, U.L.B., Bruxelles

The mineral dust lung burden can be evaluated through mineralogical analysis performed on lung tissue samples (surgery or autopsy) or on bronchoalveolar (BAL) fluid. Usually, digestion techniques are used to concentrate the

particles on a filter, free of organic material. This allows counting and provision of a quantitative analysis. The different methods used for analysis are optical and electron microscopy, energy-dispersive X-ray spectrometry and electron diffraction. Mineralogical analyses (MA) can be useful for the evaluation of dust retention, especially in cases with ill-defined occupational histories. In this regard, the counting of asbestos bodies (AB) in BAL appears to be a simple technique that can be applied to clinical routine. Together with other laboratories, we are trying to define a "normal mineralogical profile" of lung tissue and BAL. This is necessary for interpreting the presence of non fibrous mineral particles in such samples. The total number of particles, their sizes and shapes, the relative proportion of particle type, the frequency of occurrence of a type of particle (ubiquitous, frequent, rare), are all parameters to take into account. Electron microscopic studies should be limited to specific cases (medico-legal analyses, research).

The mineral dust lung burden depends on many factors: it is mainly caused by inhalation and deposition of exogenous particles from occupational environment (influenced by duration, intensity and end of exposure). Environmental (nature or pollution) and endogenous (Fe, Ca) particles also contribute to this burden. Clearance mechanisms (influenced by diseases and smoking) and dissolution processes, tend to eliminate dust. So, mineralogical analysis will provide information about the cumulated doses of retained particles at the moment of sampling. It is never a proof of disease but an element of diagnosis which must be integrated with the clinical, radiological and histological data.

Acid anhydrides and asthma

A.J. Newman Taylor
Brompton Hospital, London, U.K.

Acid anhydrides are low molecular weight reactive organic chemicals used in the manufacture of plasticisers and as curing agents for epoxy and alkyd resins. Several, including phthalic (PA), trimellitic (TMA), tetrachlorophthalic (TCPA) and maleic (MA), have been shown to cause asthma, characteristic of an acquired hypersensitivity response. Specific IgE from the serum of cases of anhydride induced asthma binds to anhydride-human serum albumin conjugates. Specific IgE and IgG_4 is associated with the development of asthma; specific IgG with exposure.

Inhalation testing with anhydrides, provokes asthmatic reactions; late asthmatic responses are associated with provoked increases in non specific airway responsiveness which can be identified at 3 h after exposure preceding and predicting the onset of the late response. Airway hyper-responsiveness and respiratory symptoms persist in a high proportion of cases despite avoidance of anhydride exposure for several years. In a group of patients with TCPA induced asthma, TCPA-HSA specific IgE declined exponentially with a t1/2 of one year. This compares with the t1/2 of IgE in serum of 2 to 3 days and implies continuing specific IgE secretion. It is interesting to speculate that the continuing immunological response and associated persisting airway hyperresponsiveness may be related to retained hapten in the body. The risk of developing specific IgE antibody and asthma to TCPA (and to platinum salts and several other causes of occupational asthma) is markedly increased in cigarette smokers.

Animal studies have shown a similar adjuvant effect of respiratory irritants, suggesting the effect of cigarette smoke is non specific. It seems likely to be a consequence of local damage to the bronchial epithelium. If so, this model has wide implications for the interaction of pollutants and inhalant allergens in the general environment, particularly children exposed to new antigens.

Reference: Newman Taylor A.J. Anhydrides and asthma. *Int Arch Allergy Appl Immun.* 1987, 82, 435–439.

Dyspnoea during exercise in normal subjects

A. Lachman, A. Sanna, R. Sergysels
Hôpital Universitaire St. Pierre, U.L.B. Bruxelles

In 10 normal subjects (24–25 years) during an incremental progressive exercise until maximal cardiac frequency, we measured the following parameters : ventilation and derivatives ($\dot{V}_E$, V_T, fr, V_T/T_I, T_I/TOT), gas exchange values ($\dot{V}O_2$, $\dot{V}CO_2$, ERO_2, $ERCO_2$), occlusion pressure (P 0.1) and dyspnoea, as assessed by a visual analogue score (VAS). All subjects experienced increasing dyspnoea in a near linear fashion starting in close relationship with the anaerobic threshold ($r=0.72$, $p<0.05$) evaluated with a non-invasive ventilatory technique.

Above the anaerobic threshold, VAS was significantly

correlated with $\dot{V}_E$ (r=0.91, p< 0.001), mean inspiratory flow (V_T/T_I) r=0.88, p<0.01), occlusion pressure (P 0.1) (r=0.85, p<0.05) and, finally, respiratory rate (r=0.80, p<0.05).

This suggests that in normal subjects a "dyspnoea threshold" appears when the extra $\dot{V}CO_2$ load above the anaerobic threshold leads to increasing demand on $\dot{V}_E$ and respiratory muscular activity.

Flow mechanics in healthy snorers and obstructive sleep apnoea patients

G. Liistro, D. Stanescu, C.L. Veriter, D. Rodenstein, G. Aubert-Tulkens
Clinique Universitaire St. Luc. U.C.L. Bruxelles

We measured inspiratory supraglottic resistance (Rsg) during sleep in 5 healthy heavy snorers (mean age±SD: 42.2±8.4yr and body mass index, BMI, 32.7±7.7 $kg \cdot m^{-2}$) and in 5 obstructive sleep apnoea patients (OSA, age 51±6 years, BMI, 34.8±4.2 $kg \cdot m^{-2}$). Supraglottic pressure was measured with a catheter and flow with a pneumotachograph fixed to a face mask. Thermistors placed in front of the nostrils and mouth showed that all the subjects breathed exclusively through the nose. The evolution of Rsg during inspiratory snoring was different in the 2 groups. In healthy subjects, Rsg either levelled off or slightly increased, reaching, on average, 17.6±9.7 $cmH_2O \cdot l^{-1} \cdot s^{-1}$ in OSA , Rsg progressively increased up to higher values (45.5±18.5 $cmH_2O \cdot l^{-1} \cdot s^{-1}$ p<0.01), followed by a sudden decrease. In OSA, the majority of snores occurred during the fall in Rsg by contrast, in healthy subjects, snoring began in all cases during a progressive rise of inspiratory Rsg. Snoring occurred in OSA either between or at the end of apnoeas and their characteristics were similar in both cases. In conclusion, snoring features appear to differ between OSA patients and healthy snorers. These differences may reflect the underlying pathophysiological process.

Broxaterol induced-effects on contractile properties of canine diaphragm *in vitro*

E. Derom, S. Janssens, G. Gurrieri, A. Longo, M. Decramer
Universitaire Ziekenhuizen K.U.L. Leuven en R.U.G. Gent and Zambon Group, Milano, Italy

Broxaterol (B) is a new, selective B_2-agonist. Since it is well documented that sympathomimetic amines and B_2-agonists alter contractile properties of skeletal muscle *in vivo* and *in vitro*, the aim of the present study was to investigate the effects of B at therapeutic (10 $ug \cdot l^{-1}$) and supra-therapeutic (100 $ug \cdot l^{-1}$) serum levels on canine diaphragm *in vitro*. Both concentrations caused a dose-dependent increase in force production at low stimulation frequencies. Twitch-tetanus ratio increased at both concentrations, reaching statistical significance at 100 $ug \cdot l^{-1}$ (0.28±0.04 *vs.* 0.33±0.05, ±18±10%, p<0.001). Force at 10 Hz thus increased by 4±9% (NS) at 10 $ug \cdot l^{-1}$, and by 31±25% (p<0.001) at 100 $ug \cdot l^{-1}$. Moreover, force at 25 Hz increased by 5±6% (p<0.05) at 10 $ug \cdot l^{-1}$, and by 14±10% (p<0.001) at 100 $ug \cdot l^{-1}$. Half-relaxation time decreased from 56±4 to 50±6 ms at 10 $ug \cdot l^{-1}$ (p < 0.05) and a similar tendency was present at 100 $ug \cdot l^{-1}$, although not statistically significant. Concomittantly, B resulted in a significantly more pronounced decrease in force output of the interpolated 100 Hz stimulations during the force-frequency curve. In a second series of experiments, bundles were fatigued by repetitive 25 Hz stimulations during 2 min. When B was then added to the bath in a concentration of 100 $ug \cdot l^{-1}$, it significantly increased force production by 14±13% after 30 min (p<0.001). and thus accelerated recovery of fatigue. We conclude that: 1. B increases force production at low stimulation frequencies in a dose-dependent way; 2. B promotes recovery from muscle fatigue; 3. since at therapeutic serum levels, small but significant inotropic effects are observed, B may be a potentially interesting drug in the treatment of respiratory failure; 4. B tends to promote the occurrence of muscle fatigue *in vitro*. *In vivo* this effect may be balanced by dilating effects on diaphragmatic vessels. The latter two effects require more *in vivo* studies.

Fenoterol inhalation causes hypokalaemia but not hypomagnesaemia in healthy volunteers

M. Noppen, W. Musch, W. Vincken, Y. Taeymans, F. Gorus, L. Corne
Academisch Ziekenhuis V.U.B. Brussels

Following parenteral administration of B_2-agonists both hypokalaemia and hypomagnesaemia have been described. Although inhalation of therapeutic doses of B_2-agonists has also been found to cause hypokalaemia, the effect of this mode of administration on plasma magnesium is still unknown.

The aim of the study was to determine whether inhalation of fenoterol in a dose sufficient to produce hypokalaemia, was accompanied by significant changes in plasma (Mgpl) and intraerythrocyte (MgIE) magnesium concentrations'. Ten healthy volunteers (8 male 2 female; aged 26±3 yrs) participated in the study. They inhaled 2 mg of nebulized fenoterol during 20 min in the semi-supine position. Plasma potassium (Kpl), Mgpl and MgIE were measured before fenoterol inhalation (t_0), at the end of the inhalation (t_1) and 15 min (t_2), 30 min (t_3), 60 min (t_4) 110 min and (t_5) after the inhalation. The results (fig. 1) show statistically significant and clinically important reductions in Kpl starting 15 min after the end of fenoterol inhalation (t_2) and persisting at least until (t_5). By contrast, no significant changes were noted in Mgpl and MgIE.

We conclude that B_2-adrenergic stimulation after inhalation of fenoterol in a dose capable of causing hypokalaemia, does not induce hypomagnesaemia up to 2 hours after the inhalation. Since it is thought that hypokalaemia and hypomagnesemia induced by B_2-adrenergic stimulation follow similar mechanisms, our findings indicate a different sensitivity of Mg^{++} and K^+ ions to B_2-adrenergic stimulation.

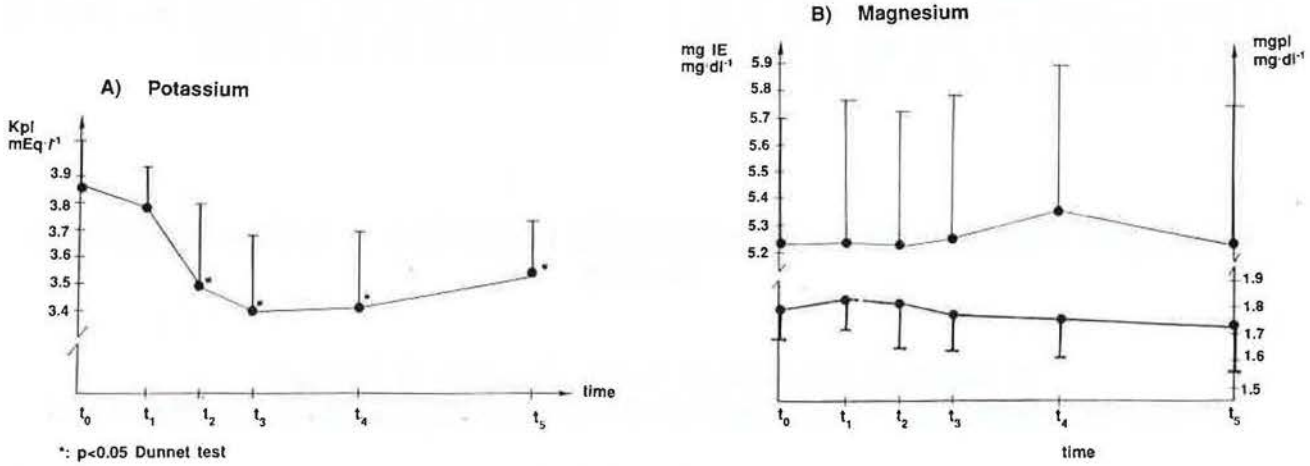

Fig. 1. – Potassium and magnesium plasma concentrations after inhaled fenoterol. to: start of study; t_1: end of inhalation of fenoterol; t_2: 15 mins after inhalation; t_3: 30 mins after inhalation; t_4: 60 mins after inhalation; t_5: 110 mins after inhalation. *: $p<0.05$ (Dunnet test); $\bar{x}\pm SD$ for each point. Plasma potassium (Kpl) showed significant changes. B. Intraerythrocyte (MgIE) — and plasma (Mgpl) — magnesium showed no significant change after inhalation.

Oxygen saturation during sleep at high altitude: influence of different drugs

C. van Schaardenburg, W. De Backer, M. Willemen, W. Wittesaele,
W. De Cock, M. Vreugde, P. Vermeire
Universitair Ziekenhuis U.I.A. Antwerpen

O_2 saturation (Sao_2) at high altitude, especially during sleep, reflects instability of breathing and/or periodic breathing (PB). PB depends on the degree of loop gain brought about by the activity of peripheral and central chemoreceptors. We studied the effect of different drugs on this control mechanism. Four normal volunteers were studied at the base camp of Mt. Everest (5350 m) during the Belgian winter expedition 1988. Sao_2 was measured continuously with the Minolta oximeter and data was stored by a personal computer on floppy disk.

Acclimatisation effects were studied by comparing data at the start and the end of the 32 day period at the base camp. The following drugs were administered at 5 day intervals to evaluate their effects on O_2 saturation during sleep: acetazolamide (Diamox) 750 mg, ketanserine (Sufrexal) 20 mg, triazolam (Halcion) 0.125 mg and nifedipine (Adalat) 10 mg. Sao_2 hypoxic periods (HP) (decrease in Sao_2 of at least 10% compared to running average value) are given below (Table 1).

There was no significant change in the number of HP. Compared to the results at time 0 all drugs except Adalat improve Sao_2. When the effect of acclimatisation (supposed to be linear) was taken into account, a significant change was observed only in the case for Sufrexal (Sao_2 corr = the improvement in Sao_2 induced by the drugs is diminished with the improvement in Sao_2 due to acclimatisation). In addition, we found no correlation between the hypoxic ventilatory response at sea level and the improvement of Sao_2 corr during high altitude sleep after Sufrexal administration. It is concluded that high altitude acclimatization improves Sao_2. Only Sufrexal improved Sao_2 in addition to the acclimatization effect, but its mode of action in mediating this effect remains to be elucidated.

Table. 1. – Effect of drugs on nocturnal oxygen saturation and hypoxic periods

	Placebo	Diamox	Halcion	Sufrexal	Adalat	Placebo
time day	0.0	5.5	10.3	16.3	19.2	32.0
Sao_2 %	77.7	79.8*	80.0*	82.4*	78.7	81.0**
	±1.7	±2.3	±1.4	±0.8	±0.3	±1.5
Sao_2 corr %	77.7	79.3	79.0	80.7*	76.6	77.7
	±1.7	±2.3	±1.4	±0.8	±0.1	±1.7
hypoxic periods	40.6	26.2	41.3	46.6	24.3	37.1
	±14.9	±12.4	±5.1	±10.2	±6.8	±9.1

Values are expressed as mean ± SE *: $p<0.05$ compared to time 0; **: $p<0.01$.

The effect of aerosolized SKF-104535-Z_2, a specific LTD_4 antagonist, on the bronchoconstrictor effect of LTD_4 in asthmatics

G.F. Joos, J.C. Kips, R.A. Pauwels, M.E. van der Straeten
Universitair Ziekenhuis R.U.G., Gent

Leukotriene D_4 (LTD_4) is a potent bronchoconstrictor and vasoactive mediator that has been implicated in the pathogenesis of bronchial asthma. We have studied the effect of SKF 104535-Z_2, a specific LTD_4 antagonist in animals and isolated human bronchi, on LTD_4-induced bronchoconstriction in asthmatic patients. Twelve mild asthmatics, (mean baseline (predicted normal) FEV_1±SEM: 86%±2.6 received on two separate days, a double-blind crossover study, 800 mcg SKF 104535-Z_2 or placebo *via* aerosol. Thirty minutes later, doubling concentrations of LTD_4 (0.08 to 80.00 mCM) were inhaled at intervals of 30 minutes. Specific airways conductance (sGaw) and forced expiratory volume in one second (FEV_1) were measured. On the placebo-day LTD_4 inhalation caused a concentration dependent bronchoconstriction. After inhalation of SKF 104535-Z_2 a small but significant increase in sGaw (0.107±0.013 to 0.128±0.012 cm $H_2O \cdot l^{-1} \cdot s^{-1}$) and FEV_1 (3.33±0.22 to 3.47±0.23 *l*) was observed. On the active treatment day, the dose-response curve for LTD_4 was significantly shifted to the right. Geometric mean PC_{20} (FEV_1) LTD_4 (mCM) was 11.9±2.8 on the placebo and 39.5±9.0 on the active treatment day ($p<0.01$). Geometric mean PC_{35} (sGaw) LTD_4 (mCM) was 16.6±7.2 on the placebo and 31.2±9.1 on the active treatment day ($p<0.05$).

We conclude that SKF 104535-Z_2 is able to antagonise the bronchoconstrictor effect of LTD_4 in asthmatics.

Domestic endotoxin exposure in asthma

O. Michel, B. Le Bon, J. Duchateau, F. Vertongen, R. Sergysels
Hôpital Universitaire St. Pierre, U.L.B. Bruxelles

In previous studies, we have shown that inhalation of endotoxin in bronchial challenge tests induces in asthmatics a significant bronchial obstruction associated with an increase of histamine bronchial reactivity. Endotoxin

is present in house dust (HD) at a concentration of 2.59 $ng \cdot mg^{-1}$ HD which is the same as in some occupational exposures.

In this study we show in 28 perennial asthmatics (20 HD mite allergic and 8 intrinsic) that exposure to high LPS level (> 5.6 ng·5 mg HD) is associated with a higher dyspnoeic score, a higher beta-$_2$-mimetic and oral daily methylprednisolone intake, a higher treatment score and a lower FEV_1/FVC, thus corresponding to more severe asthma. On the other hand, exposure to low or high HD mite antigen (evaluated by the guanine content of house dust) was not associated with the severity of asthma. We conclude that endotoxin exposure is one element modulating the severity of asthmatic disease.

Comparison of dynamic lung function indices during forced and quiet breathing in upper airways obstruction, asthma and emphysema

C.F. Melissant, J.A. van Noord, K.P. Van de Woestijne, M. Demedts
Universitaire Ziekenhuizen K.U.L., Leuven

We compared the dynamic lung function parameters in asthma (n=27), emphysema (n=20) and upper airways construction (UAO) (n=18) to determine whether different patterns of abnormalities could be found.

Forced expiration parameters were measured (FEV_1, PEF, MEF_{50}) as well as parameters during quiet breathing (Raw, Gaw, sGaw). In the three groups PEF was similar (about 60±20% predicted). The group with upper airways obstruction showed significantly larger FEV_1 (84% predicted *versus* 55% predicted in the other groups) and MEF_{50} (71% predicted *versus* 25% and 23% predicted in the other groups). Raw was greatest in asthma, 0.37±0.18 $kPa \cdot l^{-1} \cdot s^{-1}$ *versus* 0.24±0.13 in UAO and 0.22±0.10 in emphysema. Upper airways obstruction could be recognized by a significantly lower PEF/MEF_{50} ratio and a higher FEV_1/PEF ratio than in the other conditions (table 1.).

MEFV curves were no different between asthma and emphysema. A distinction between the latter group could be made by comparing airway patency during forced and quiet breathing, *i.e.* the MEF_{50}/Gaw-ratio. This ratio was significantly different for all three groups, having the lowest value in emphysema, 0.19±0.08 kPa compared with 0.44±0.23 kPa and 0.63±0.34 kPa in asthma and UAO respectively (table 1). Within the group with UAO, those with a variable intrathoracic obstruction showed the least difference with asthma and emphysema.

Table. 1. – Ratio of different dynamic lung function indices in upper airways obstruction (U), asthma (A) and emphysema (E)

Group	G U	G A	G E	Duncan grouping
n	18	27	20	
PEF/MEF_{50} % / %	0.88±0.26	2.87±1.29	3.07±1.05	U-AE
FEV_1/PEF $ml \cdot l^{-1} \cdot min^{-1}$	9.89±1.70	6.62±1.39	6.16±0.94	U-AE
MEF_{50}/Gaw kPa	0.63±0.34	0.44±0.23	0.19±0.08	U-A-E

n= number of subjects. Mean±SD.