

Metal toxicity and the respiratory tract

B. Nemery

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ABSTRACT: The type of lung disease caused by metal compounds depends on the nature of the offending agent, its physicochemical form, the dose, exposure conditions and host factors. The fumes or gaseous forms of several metals, *e.g.* cadmium (Cd), manganese (Mn), mercury (Hg), nickel carbonyl (Ni(CO)₄), zinc chloride (ZnCl₂), vanadium pentoxide (V₂O₅), may lead to acute chemical pneumonitis and pulmonary oedema or to acute tracheobronchitis. Metal fume fever, which may follow the inhalation of metal fumes *e.g.* zinc (Zn), copper (Cu) and many others, is a poorly understood influenza-like reaction, accompanied by an acute self-limiting 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 may lead 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 nickel (Ni) or chromium (Cr) is apparently infrequent, considering their potency and frequent involvement as dermal sensitizers. Metallic dusts deposited in the lung may give rise to 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 the pulmonary fibrosis occasionally found in subjects exposed to other metals *e.g.* aluminium (Al), titanium (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.

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Laboratory of Lung Toxicology, Division of Pneumology and Dept of Occupational Medicine, K. U. Leuven, Leuven, Belgium.

Correspondence: B. Nemery, Laboratorium Longtoxicologie, Kapucijnenvoer 35, B-3000 Leuven, Belgium.

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For centuries metals have been known to be capable of causing human diseases, including pulmonary disease [1-8]. Elements may be defined as metals on the basis of their physical or chemical properties, but these definitions do not allow a sharp distinction to be made between metals and non-metals, because a number of elements, *e.g.* arsenic (As), bismuth (Bi), germanium (Ge), antimony (Sb), selenium (Se) and tellurium (Te), often called metalloids, share properties of both. From a *toxicological* viewpoint, a metal can be defined as "an element which under biologically significant conditions may react by losing one or more electrons to form cations" [9].

For the purposes of this review we may consider that metal-induced lung diseases are those lung disorders caused by mineral compounds other than carbon and

silicon. This review will, therefore, not deal with coal workers pneumoconiosis, silicosis (caused by crystalline free silica or SiO₂), asbestos-related disease (caused by some fibrous silicates) or pneumoconioses caused by other silicates such as talc, mica, kaolin etc., although silicates are associated with various cations including aluminium (Al), magnesium (Mg) or iron (Fe). These "classical" pneumoconioses constitute the majority of lung diseases due to mineral dusts and they have been extensively studied and reviewed.

In contrast, lung diseases caused by mineral compounds other than carbon or silicon probably concern fewer individuals, who often work in small industries with generally poor characterization of exposure. Consequently, lung disorders caused by metals have been less well studied and this may pose problems for occupational

physicians who need to prevent such disorders and for pulmonary physicians who have to diagnose and treat them.

The present review focuses on human data, rather than on information obtained from animal or *in vitro* experimentation. Information which is available in standard texts [6-8] has been taken as such, whereas more recent acquisitions are emphasized and referred to more specifically. As usual, studies showing disease have been given more attention than "negative" studies. This survey will not consider routes of exposure other than inhalation, although the lungs may be affected *via* the blood by metal containing drugs or chemicals, *e.g.* gold salts.

General toxicity of metals [9]

People are rarely exposed to the pure metallic form (zero oxidation state) of metals or metalloids, but more usually to oxides (or other binary metal compounds, such as sulphides, halides, hydrides, carbides, etc.) or to multielement compounds, mainly salts. Metals, most notably transition metals, can also form co-ordination complexes with various ligands *e.g.* ammonia (NH₃), carbon monoxide (CO), cyanogen (CN⁻), organic nitrogen or sulphur molecules. Some metals may also form organometallic compounds in which the metal is bound to the carbon atom of an organic group. The chemical form of a metal, also called metal speciation, and the resulting physicochemical properties have important consequences in terms of toxicokinetics and biological effects.

Thus, the biological availability and absorption of metals will be greatly influenced by their solubility in water and lipids, but more importantly by their actual solubility in biological fluids, which contain a variety of organic ligands. For instance, the more insoluble the metal compound deposited in the airways, the more likely that it will be cleared by the mucociliary escalator. Conversely, soluble salts will readily dissociate, thus facilitating their transport as metal ions into lung cells or into the blood circulation.

The strong attraction between metal ions and organic ligands situated within tissue molecules results in the binding of the metal ion to those molecules. This underlies a number of the biological effects and toxic actions of metals:

1) Some metals *e.g.* iron (Fe), copper (Cu), manganese (Mn), cobalt (Co), zinc (Zn), chromium (Cr) are essential as coenzymes for many enzymes. Dysfunction in these enzymatic processes may, therefore, result from deficiency states, but also from overwhelming by very high doses of the essential metal or through substitution and mimicry of essential ions by inappropriate compounds.

2) The transport and accumulation of metals is often the result of their ability to interact with ligands. Transferrin, ferritin, albumin and ceruloplasmin are the main transport or storage proteins for Fe and Cu and their abundance probably constitutes a safeguard against the toxicity of free iron and copper ions [10, 11]. Cadmium

and other metals bind to metallothionein, a low-molecular weight protein rich in sulphhydryl (SH) groups. This process also plays a role in the defence against cadmium, but it eventually leads to the retention and progressive accumulation of cadmium in various tissues, including probably the pulmonary tissue [12].

3) The interaction of metals with functional groups on macromolecules is an important mechanism for their toxicity and their carcinogenicity [13, 14]. Thus, several metal ions react avidly with free SH groups, thereby possibly inhibiting active centres of enzymes, coenzymes or membrane bound receptors. Direct interaction of metals with deoxyribonucleic acid (DNA) is one of the possible mechanisms for metal carcinogenesis (as well as for the chemotherapeutic effects of some metal complexes).

4) Another toxicologically relevant consequence of metal binding to proteins is the possible acquisition of antigenicity. Thus platinum, chromium, nickel and cobalt are sensitizers probably by mechanisms similar to those of other reactive organic molecules of low molecular weight which may function as haptens.

The biological activity and toxicity of some metals is also greatly influenced by their ability to change their oxidation state by oxidation (loss of electrons) and reduction (gain of electrons). Transition metals are electronically stable in more than one oxidation state. As a result of this property, transition metals play important roles in catalysing biological oxidation reactions. Of the transition metals, iron and to a lesser extent copper have been extensively studied because of their implication in many pulmonary and non-pulmonary disease processes by virtue of their ability to enhance the production of toxic free-radical species of oxygen [10, 11, 15]. In pulmonary toxicology, free-radical oxygen toxicity, which seems always to involve metal catalysis [16, 17], is considered to be a mechanism for the effects of hyperoxia [18], paraquat [19], nitrofurantoin [20] and asbestos [22]. However, inhaled metals have so far received rather less attention in this respect.

Pulmonary disorders due to metal exposure

General remarks

Before discussing the various lung disorders caused by metals it is worth emphasizing some important points:

1. *The respiratory system is not necessarily the only, or the principal, target for the toxicity of metal compounds, even when their entry to the body is by inhalation.* Thus, the chronic inhalation of lead, mercury or manganese may lead to systemic effects, such as neurological damage, without leading to serious respiratory damage. Other metals, such as cadmium, are capable of causing both lung and kidney alterations, probably depending in part upon the route of exposure. It is, therefore, important to be aware of possible extra-pulmonary manifestations in metal toxicology.

On the other hand, from a scientific point of view, non-toxicity in the lung may be toxicologically as

rele vant as frank toxicity, since the absence of serious pulmonary injury by inhaled metallic compounds having significant toxicity for other organ systems may reveal the existence of an effective defence mechanism within the lungs (even if this mechanism is obviously not the sole basis for the existence of selective targets for toxicity).

2. *Lung disease found in people who are occupationally exposed to metals is not necessarily due to these metals.* The most obvious example is the presence of smoking-related lung disease in industrial workers. On the other hand, cigarette smoking often obscures, or interferes with, the possible occupational origin of chronic obstructive pulmonary disease or lung cancer in the individual patient. Other examples of mixed exposures to metals and non-metals concern silicosis and asbestos-related lung disease in iron or other metal foundries. In metal smelting, cutting or burning, as well as during welding, toxic gases are produced in addition to metal oxides. In these instances sulphur dioxide (SO₂), ozone (O₃), or nitrogen dioxide (NO₂) and other volatile compounds released from the pyrolysis of coating materials or solvents and degreasers, rather than the metals themselves, may be responsible for acute or chronic airway or lung disease. Organic compounds are also present in metal industries, e.g. isocyanate asthma has been described by several groups in iron and steel plants, in processes where synthetic resin binders are used [23–26].

3. *Exposure to metals is not confined to workers involved in metal mining or metallurgy.* Metal compounds are indeed used in almost every sector of industry and even in agriculture. Thus, cobalt-induced fibrosing alveolitis and bronchial asthma have been described in diamond polishers who used cobalt-containing polishing discs [27, 28]. Dental technicians are at risk of pneumoconiosis [29, 30]. Several processes in the electronics industry involve the use of metals or metalloids, e.g. gallium, germanium, the toxicology of which is often poorly known. Numerous metal compounds are used as pigments in the paint industry, as catalysts in the chemical industry, or as additives in the plastics industry, where they have not so far been reported to cause much respiratory disease. However, to give an example of an *a priori* unsuspected use of metals, a case of asthma to cobalt was recently diagnosed in a man working in the animal feed industry, where he was involved in the addition of cobalt sulphate to the feed (used for the prevention of cobalt deficiency in cattle) [31] (Dr E. Stevens, personal communication, unpublished).

4. *Significant exposure to metals is not confined to the work environment.* Hobbies and domestic activities may lead to significant exposure. A classical example of para-occupational exposure is that of berylliosis in housewives and family contacts of beryllium-workers who brought factory-dust to their homes [32].

From these introductory considerations we may conclude that the pulmonary physician should always remember that metal exposure is ubiquitous. When taking

the patient's history it is, therefore, not sufficient to fill in the entry relative to occupation with a single job title to either demonstrate or exclude occupational exposure to metals. In some cases a more thorough enquiry with a plant physician, an occupational hygienist or toxicologist will be necessary.

The pulmonary disorders due to inhaled metallic compounds are quite diverse. Two approaches may be adopted to describe them. Either the metals can be listed and their possible pulmonary effects enumerated [33], or different disease entities can be grouped and their possible metal etiologies discussed [34]. For this review we have chosen the second option, but the main toxicity of the individual metals is given in a summary form in table 1.

Acute toxic effects: chemical pneumonitis and bronchitis, metal fume fever

Exposure to high concentrations of the fumes of several metals can lead to acute pulmonary manifestations, the outcome of which can range from complete recovery to death depending on the agent involved.

Chemical pneumonitis and bronchitis. The most severe form of acute pulmonary damage is chemical pneumonitis which classically follows the inhalation of cadmium fumes [7]. Cadmium is present in several areas of metallurgy; from a practical point of view, the important points to be aware of in relation to the risk of cadmium pneumonitis are: 1) that cadmium oxides may be liberated from the welding or burning of cadmium-containing alloys [35] or from the smelting of zinc or lead [36], which often contain significant levels of contaminating cadmium; and 2) that exposure to toxic levels of cadmium fumes does not necessarily lead to immediate respiratory symptoms. Indeed respiratory distress is usually delayed for several hours until severe non-cardiogenic pulmonary oedema develops [7].

The inhalation of other metallic compounds can also cause acute pulmonary damage. Past literature [7], and recent reports of accidental and non-accidental exposures show that exposure to fumes or dusts containing beryllium, cobalt, manganese, mercury [37, 38], nickel carbonyl [Ni(CO)₄] [39], and osmium are capable of causing chemical pneumonitis or acute airway irritation. Cases of adult respiratory distress syndrome have recently been reported in military or civilian personnel accidentally exposed to smoke bombs which liberate zinc chloride (ZnCl₂) [40, 41]. Antimony trichloride (SbCl₃) and pentachloride (SbCl₅) [7], zirconium tetrachloride (ZrCl₄) [7], titanium tetrachloride (TiCl₄) [42] and uranium hexafluoride (UF₆) [43] may also lead to inhalation injury (presumably as a result of damage by the halide ion, rather than by the metal ion). Lithium hydride (LiH) and phosphine (PH₃) have also been reported to cause pulmonary oedema [7].

It is worth mentioning that the inhalation of the hydride forms of arsenic (arsine, AsH₃) or antimony (stibine, SbH₃) can also be lethal as a result of fulminant

Table 1. – Summary of pulmonary toxicity of metals

	Exposures and uses*	Acute toxicity	Airways***†	Lung parenchyma***	Lung cancer†***	Extra-pulmonary toxicity††	Comments
Aluminium Al	Bauxite, cryolite, electrical engineering, transport & building industry, packaging, abrasives		Potroom asthma, bronchial hyperreactivity, (fluorides?, some salts), COLD	Fibrosis (rare), (aluminosis), [granulomatous fibrosis], [alveolar proteinosis]		CNS	Pulmonary disease rare considering extensive use
Antimony Sb	Alloys (with Sn, Pb, Cu), chemical & textile industry, pigments, ceramics, glass	Pneumonitis (SbCl ₃ , SbCl ₅), haemolysis (SbH ₃)		Benign pneumoconiosis, (antimoniosis)	Possible	Heart	Often concomitant exposure to As
Arsenic As	Smelting of Cu, Pb, gold (Au), Zn, Co, glass, pigments, tanning, pesticides, alloys	Metal fume fever, haemolysis (AsH ₃)	Nasal septum perforation		Definite	Skin, PNS, C-V system, blood	
Barium Ba	Alloys, paints, glass, ceramics			Benign pneumoconiosis, (baritosis)		Heart	
Beryllium Be	Alloys (with Cu), ceramics, electronics, nuclear, space, aircraft, dental technicians, metal reclaiming	Pneumonitis, metal fume fever		Granulomatous fibrosis, (chronic beryllium disease, berylliosis)	Suspect	Skin	Cell-mediated immune response, LTT in BAL lymphocytes
Cadmium Cd	In association with Zn & Pb alloys, electroplating, batteries, pigments, plastics, welding electrodes & silver solders, cigarettes	Pneumonitis, metal fume fever	COLD	Emphysema, (fibrosis in animals)	Suspect	Kidney	Cumulative metal (in man & environment)
Chromium Cr	Alloys (stainless steel), chrome plating, pigments, refractory bricks, tanning, welding		Allergic asthma (rare?) nasal septum perforation	Definite (CrVI)		Contact dermatitis (frequent)	Strong sensitizer
Cobalt Co	Alloys, hard metal (with WC), diamond polishing, magnets, pigments, catalysts, animal feed	Pneumonitis, metal fume fever	Allergic asthma, COLD	Fibrosing alveolitis, ("hard metal lung disease", "cobalt-lung")	Possible	Heart, contact dermatitis	Giant cells in BAL

Table 1. 2

	Exposures and uses*	Acute toxicity	Airways***†	Lung parenchyma****	Lung cancer†****	Extra-pulmonary toxicity††	Comments
Copper Cu	Electrical equipment, alloys (brass=Cu+Zn, bronze=Cu+Sn), pesticides, pigments	Metal fume fever		"Vineyard sprayers' lung"		Skin	Cu smelters: As, SO ₂
Gold Au	Jewellery, therapeutic			(Pneumonitis with gold salt therapy)		Skin	Gold refining: Hg
Iron Fe	Mining, steel	Metal fume fever	COLD	Benign pneumoconiosis, (siderosis)	Iron ore mines (radon?), foundries (PAH ?)		Concomitant SiO ₂ , asbestos, catalysis of Fenton reaction (oxygen free radicals)
Lanthanons (rare earths) Cerium Ce,	Photoengraving, glass			Fibrosis, (rare earth pneumoconiosis, cerium pneumoconiosis)			
Lead Pb	Lead smelting, alloys, batteries, pigments, paints, welding, petrol (alkyllead)	Metal fume fever				G-I tract, CNS, PNS, kidney, blood	Contamination with Cd, environmental concern
Lithium Li	Alloys, ceramics, electronics, catalysts	Pneumonitis (LiH)					
Magnesium Mg	Alloys	Metal fume fever					
Manganese Mn	Steel, alloys, batteries, pigments, welding, chemical industry, metal slags (fertilizer)	Pneumonitis, metal fume fever	COLD	Pneumonia		CNS	Methylcyclopentadienyl manganese tricarbonyl (MMT) lung damage in animals
Mercury Hg	Chlor-alkali industry, electrical, paints, measuring, pesticides, drugs, dentists, gold & silver refining	Pneumonitis, metal fume fever				CNS, kidney, contact dermatitis	Saturation of air with Hg rapidly achieved, environmental concern
Nickel Ni	Alloys, nickel plating, coins, batteries, electronics, catalysts, cheap jewellery	Metal fume fever, pneumonitis [Ni(CO) ₄]	Allergic asthma (rare)		Definite (mainly low solubility comp.), also nasal cancer	Contact dermatitis (frequent)	Strong sensitizer
Platinum Pt	Catalyst, photography, jewellery, chemotherapeutic agent		Allergic rhinitis and asthma (complex halide salts)			Contact dermatitis	Anaphylactic shock following treatment with cisplatin drug

Table 1.3

Exposures and uses*	Acute toxicity	Airways***†	Lung parenchyma***	Lung cancer†***	Extra-pulmonary toxicity††	Comments
Osmium Os	Electron microscopy	Bronchitis, pneumonitis				
Selenium Se	Byproduct of Cu refining, alloys, pigments, electronics, rubber, glass	Pneumonitis				Garlic odour breath, (also with tellurium)
Silver Ag	Alloys, soldering, photography, catalyst, jewellery				Discoloration of skin and mucosae (argyria)	
Tin Sn	Tin plating, alloys, welding	Metal fume fever	Benign pneumoconiosis	(stannosis)		
Titanium Ti	Alloys, white pigment (TiO ₂)	Pneumonitis (TiCl ₄)	COLD?	[granulomatous pneumonitis]		Usually considered to be inert
Tungsten W	Hard metal (WC+Co+other metals), cutting, drilling, polishing tools		Probably not directly involved in hard metal lung disease			
Uranium U	Nuclear fuel	Pneumonitis (UF ₆)		Definite	Kidney	
Vanadium V	Steel, alloys, catalyst, pigments, present in fuel ash & metal slags	Tracheobronchitis, (boilermaker's bronchitis)	Bronchial hyperreactivity		Green tongue, metallic taste	
Zinc Zn	Alloys, brass, galvanizing, pigments, pesticides, ZnCl ₂ (smoke bombs)	Metal fume fever, pneumonitis (ZnCl ₂)		[Asthma? (galvanized steel welding)]		Contamination with Cd
Zirconium Zr	Alloys, nuclear, industry, pigments, catalysts, abrasives	Pneumonitis (ZrCl ₄)	Benign pneumoconiosis		Skin granulomas	Pulmonary granulomas in animals

This summary is compiled from general sources [3-7] and is intended only for use as a quick reference. Not all species of a metal cause the indicated disorder, the reader is referred to the text and original references for a complete description of exposure conditions and diseases. Metals not indicated in the table have not been associated with respiratory disease in humans. *: only typical or noteworthy uses are indicated; **: in general, chronic excessive exposure to mineral dust may lead to industrial bronchitis and possibly chronic obstructive lung disease (COLD); †: high temperature treatments of metals during refinery, smelting, cutting or welding may lead to exposure to toxic gases and/or carcinogenic organic compounds; ***: underground mining of metal ores may lead to exposure to free silica and/or radon daughters; ††: only some selected target-organs are indicated, particularly when relevant to chronic exposure by inhalation. C-V system: cardio-vascular system; G-I tract: gastro-intestinal tract; PNS: peripheral nervous system; CNS: central nervous system; LTT: lymphocyte transformation test; BAL: bronchoalveolar lavage. Diseases in square brackets [] concern isolated case reports.

haemolysis, which may sometimes manifest itself initially as dyspnoea.

Chemical pneumonitis has often been said not to lead to sequelae, however, this is certainly not a rule and in several case reports various chronic pulmonary manifestations, such as fibrosis, bronchial lesions or airway hyperreactivity were shown to follow the acute episode [35, 37, 38, 42-44].

Acute tracheobronchitis with persisting bronchial hyperreactivity [45] can be caused by exposure to vanadium pentoxide (V_2O_5), a significant risk associated with the cleaning of oil tanks ("boilermaker's bronchitis") [46, 47]. Exposure to chromic acid during chrome-plating leads to upper airway lesions, particularly nasal septal ulceration and perforation, which, in a recent study, was found in an astonishing two thirds of subjects exposed to moderately high peak levels of Cr [48].

Metal fume fever. A more benign condition following exposure to high concentrations of metal fumes, particularly but not exclusively zinc oxide, is metal fume fever [49, 50]. This condition, of which there are several synonyms [7], is an influenza-like or malaria-like reaction consisting of fever, chills and malaise with relatively mild respiratory symptoms, and classically little or no X-ray or functional abnormalities, although this is not always the case [51, 52]. The symptoms, often accompanied by a sweet metallic taste in the mouth, usually begin at home a few hours after a heavy exposure to metal oxides, e.g. after welding in a confined space, and they then subside spontaneously. Leucocytosis is present during the acute illness. A recent report of bronchoalveolar lavage findings in a case of zinc fume fever showed marked neutrophil infiltration, and appropriately posed the question of how such spectacular inflammatory events remain so self-limited [53]. A strange feature of this syndrome is the occurrence of tolerance: symptoms only appear when exposure takes place after a period of days without exposure and they do not appear on subsequent days.

The exact pathogenesis of metal fume fever is poorly understood. In some instances allergic mechanisms may be involved [54], but then metal fume fever may be a misnomer or may be superimposed on bronchial asthma or hypersensitivity pneumonitis [55]. There is a striking resemblance between metal fume fever and the organic dust toxic syndrome, which occurs after heavy exposure to organic dust contaminated with micro-organisms [56]. Both syndromes have a similar clinical course with fever, leucocytosis, acute transient neutrophilic alveolitis [57] and occurrence of tolerance. These similarities indicate common pathogenic mechanisms.

With appropriate environmental control measures, cases of metal fume fever are fortunately not common any more, but the disease has certainly not disappeared and is presumably often overlooked as a simple viral infection. Metal fume fever is said not to lead to sequelae, but this has not been adequately investigated.

Chronic obstructive lung disease

There is no doubt that the main exogenous cause of chronic obstructive lung disease and emphysema in the general population is cigarette smoking [58]. However, clinically important airflow limitation occurs in less than 15% of smokers [59]. In our opinion, this concept underscores two important points with regard to occupational factors. Firstly, since the basis for the susceptibility to cigarette smoke is still largely unknown, there is no *a priori* reason why subjects who are (or would be) particularly susceptible to smoking-induced lung and airway disease, will not be equally susceptible to respiratory insults from the occupational environment, including metallic compounds which are capable of causing tissue destruction and inflammation. Secondly, even for environmental substances which would carry a risk similar to that of cigarette smoking (*i.e.* affecting "only" 15% of the exposed subjects) the chances of conclusively demonstrating such a risk are small because of: i) the relatively small number of subjects exposed; ii) the complexity of the exposures (in terms of their nature as well as their intensity and duration); iii) the high prevalence of smoking, particularly in industrial populations [60]; and iv) selection factors collectively known as "the healthy worker effect" [61].

Despite these methodological difficulties, several recent studies have shown that occupational factors may cause not only symptoms of industrial bronchitis, but also loss of ventilatory function, which may be of similar magnitude to that associated with cigarette smoking [61]. This view, however, is not universally accepted and the issue of the real impact of occupational exposures on ventilatory function is still controversial [62-64]. In practice, it remains impossible to determine the contribution of occupation in the causation of chronic obstructive lung disease in the individual smoking patient.

The mainly longitudinal studies that have led to the conclusion that significant airflow limitation may result from dust exposure, have essentially involved coal miners [65-67], grain dust exposed workers [68] or workers exposed to poorly defined "industrial dust, fumes or gases" [69]. No such studies have been performed with workers exposed to specific metallic compounds and the available information, therefore, mainly stems from less powerful cross-sectional observations.

The as yet somewhat controversial issue of whether chronic cadmium fume inhalation leads to pulmonary emphysema [70, 71] has recently been settled by the results of a study of a large group ($n=101$) of workers and ex-workers from a cadmium alloy factory in England [72]. This study showed a clear excess of functional (ventilatory function and diffusing capacity) and radiological signs of emphysema in the exposed subjects compared to appropriate controls. The causal role of cadmium was strengthened by the existence of a positive relationship between effects and dose, with the latter being estimated both by past hygiene measurements and by the internal (liver) cadmium burden. Moreover, the significance of these findings has been borne out by the demonstration of an increased mortality from

non-malignant respiratory disease in cadmium-exposed workers [73, 74]. The mechanisms for cadmium-induced emphysema are not elucidated. Animal studies suggest that fibrosis, rather than alveolar wall destruction, precede the development of emphysematous lesions [75-77].

Cross-sectional studies have also suggested an increased prevalence of chronic bronchitis and a loss of ventilatory function, sometimes mainly of forced vital capacity (FVC), associated with chronic exposure to **beryllium** [78], **aluminium** [79, 80], **cobalt** (or **hard metal**) [81-83], **manganese** [84], or **titanium dioxide** (TiO_2) [85], apparently independently from the overt forms of other respiratory diseases seen with some of these metals (see below). However, other surveys of workers exposed to these compounds do not always reach the same conclusions [86-89], possibly because of differences in total dust, in concomitant exposures, or in population characteristics and study designs.

Studies of the effect on ventilatory function in groups such as "steel workers" [58, 90-92] or "metal welders" [64, 93-101] have been largely negative, inconclusive or showing only small effects, despite the generally consistent finding of increases in the prevalence of chronic bronchitis, defined by questionnaire. However, for the methodological reasons alluded to above, one should not conclude that there are no specific work processes within these broad categories which entail a risk of significant obstructive respiratory impairment in susceptible subjects.

Bronchial asthma

Several metals are known to be capable of causing bronchial asthma [102-105]. The complex halide salts of **platinum** (Pt) provide a unique example of a situation where a very considerable proportion of exposed subjects may become sensitized [102]. There is good evidence for an immunoglobulin E (IgE)-mediated mechanism in platinum salt asthma [102, 106, 107]. However, the determination of Pt-specific antibodies by radio-allergosorbent test (RAST) is less sensitive than skin testing in the clinical diagnosis of Pt-hypersensitivity, possibly because of a frequent increase in total IgE [107].

Other metals reported to cause asthma, mostly in case reports, are **nickel** [108-111], **chromium** [112, 113] and **cobalt** [28, 87, 114-118]. There is evidence for specific (IgE) antibody formation against protein-conjugates of nickel (Ni) [109, 110, 119] and cobalt (Co) [118, 120, 121], thus, suggesting that asthmatic reactions to these metals also result from an IgE-induced response. In a recent report [122] of asthma in subjects welding galvanized metal, sensitization to zinc was suggested; however, the possible presence of other metals such as Co, which can be present in galvanized metal [31], was not addressed. The causative agent of asthma ("potroom-asthma") and bronchial hyperreactivity in **aluminium** smelters (or other workers exposed to aluminium salts) [126, 127] is not known; the condition is not felt to be due to allergic mechanisms, but rather to an inflammatory reaction to irritation by fluorides.

In view of the widespread use of Ni, Cr and Co and the occurrence of respiratory exposure in many occupational settings, it is remarkable that these metals are so rarely incriminated as causing occupational asthma, particularly when it is realized that they are well known by dermatologists for their potential to cause dermal sensitization [128, 129]. Contact dermatitis caused by Cr is indeed the most prevalent occupational dermatitis in men, and Ni is the most prevalent contact allergen in women (probably because of exposure to jewellery), with cobalt-allergy frequently being associated. It should be remembered that epidemiological investigations conducted after the discovery of a single case of occupational asthma have generally disclosed the existence of many more cases [130]; the relative rarity of respiratory rather than dermal manifestations of metal sensitization may, therefore, result in part from underdiagnosis and underreporting. However, it is unlikely that this is the only explanation; differences related to route of exposure and mechanisms of sensitization must be involved. Contact dermatitis is not an IgE-mediated type of allergy, but a "cellular" allergy [131]. It is noteworthy that, at least in the case of cobalt, a condition more usually considered to be cell-mediated [132], such as alveolitis [27, 116], and asthma combined with alveolitis [133], has been described. The apparent absence of correlation between respiratory and dermal manifestations of occupational allergy to metals is a subject that should merit further epidemiological and experimental research.

It is not known whether the general features of occupational asthma caused by small molecular weight compounds also apply to metal-induced asthma, but it is fair to assume that this is so. In this case, there is probably no relationship between a background of atopy and the occurrence of occupational respiratory allergy to metals [103-105, 134, 135]. Cigarette smoking [136] or exposure to other irritants such as ozone [137] may well prove to be a more important determinant (in interaction with atopy) for the occurrence of asthma in the allergen-exposed individual (although the converse seems to hold for occupational asthma due to isocyanates, which is probably not IgE-mediated) [138].

Another recent concept, which has emerged consistently from follow-up studies of occupational asthma from various causes, is the need for a rapid and total removal from exposure of symptomatic people in order to prevent permanent asthma [139, 140]. It is reasonable to adopt the same attitude in metal-induced asthma, although the ubiquity of some of the metals involved may well make total avoidance of exposure very difficult to achieve in practice.

Interstitial lung disorders

Metallic dusts deposited in the lungs may give rise to more or less marked pulmonary fibrosis, depending on the intrinsic properties and amount of the inhaled agent, as well as on hitherto poorly understood host factors. The fibrogenic potential of inhaled substances is presumably determined by their ability to interfere with

the pulmonary immuno-inflammatory system, either directly, *e.g. via* effects on alveolar macrophages, or indirectly, *e.g. via* injury to epithelial cells. In other words, as in other forms of interstitial lung disease, the fibrotic process is probably dependent on the occurrence of alveolitis with an abnormal release of mediators by some cells [140, 141]. It must be recognized, however, that the exact pathogenic mechanisms of lung fibrosis, whether caused by metals or by other agents, have not been elucidated despite intense research efforts.

Within the conceptual framework that continued pulmonary injury and/or inflammation ultimately lead to fibrosis, the metal pneumoconioses may be categorized into three broad categories: 1) "benign" pneumoconioses with little or no fibrosis, *e.g.* siderosis; 2) pneumoconioses with features of diffuse interstitial pneumonitis *e.g.* hard-metal lung disease; and 3) pneumoconioses with sarcoid-like epithelioid granuloma formation *e.g.* berylliosis.

1. *Pneumoconioses without fibrosis.* Of the "benign" pneumoconioses the most frequent and best studied is siderosis, which is caused by the inhalation of iron compounds [6, 7, 33].

Occupational exposure to iron occurs during iron mining and related operations, during iron refining and at various stages in steelmaking, during welding, cutting and abrading of iron-containing materials, as well as during the manufacture or use of iron-containing abrasives (such as emery).

Siderosis is a "radiological disorder" in that it manifests itself by the presence of small, very radio-dense opacities with uniform distribution throughout the lungs, but without formation of conglomerates. With cessation of exposure the radiographic opacities may gradually disappear. Pure siderosis is not associated with respiratory symptoms or functional impairment, and does not predispose to tuberculosis. However, it is important to realize that exposure to silica or asbestos is not uncommon in many jobs that involve exposure to iron, thus giving rise to mixed dust fibrosis or to asbestosis, which do have associated morbidity and complications. Moreover, the view that the symptomatic interstitial fibrosis, which is sometimes found in welders (welder's pneumoconiosis), is simply siderosis with coexisting silicosis has recently been challenged on the grounds that the pulmonary silicon content of such cases did not differ from that of control lungs [142].

Other rare "benign" pneumoconioses include those caused by tin (stannosis), barium (baritosis), antimony [143, 144] and possibly zirconium [7].

2. *Hard-metal lung disease and "cobalt-lung".* The condition known as hard-metal lung disease has been the subject of renewed interest in recent years, particularly with regard to the causative role of cobalt [145-147]. **Hard-metal or cemented tungsten carbide (WC)** is found in tools used for high speed cutting, drilling, grinding or polishing of other metals or hard materials. In a minority of workers involved in the manufacture or utilization of these tools, bronchial asthma and diffuse

pulmonary fibrosis have been described in various areas of the world [81, 88, 114-116, 148-153]. On the basis of relatively crude animal data [154] showing little toxicity from the main constituent of hard-metal, *i.e.* tungsten carbide, the consensus is that tungsten carbide is not the agent responsible for the fibrosis, but that it is more probably due to the binding agent, *i.e.* cobalt.

The pneumonitis is often of the desquamative type, and in the subacute forms it appears to be mainly characterized by the presence of multinucleated giant cells (to the extent that the proposal was made that giant cell interstitial pneumonitis (GIP) may be pathognomonic for hard-metal exposure) [155]. The aetiological role of cobalt in giant cell interstitial pneumonitis has been strongly supported by the observation of several cases of a disease identical to hard-metal lung disease in diamond polishers, who used polishing discs made with microdiamonds (not tungsten carbide) cemented with cobalt [27, 156]. The term cobalt-lung has, therefore, been proposed [27].

The mechanisms for the pulmonary toxicity of cobalt have not yet been discovered [121, 146]. Unlike the classical pneumoconioses in which the lung burden of dust seems to be the predominant factor in causing the disease (even if host factors do play a role in these diseases also), several features of cobalt-lung suggest some form of hypersensitivity or host idiosyncrasy, perhaps analogous to the situation observed with beryllium (see below). Indeed for both beryllium and cobalt the dose-response relationship is not straightforward: on the one hand the attack rate of the disease appears to be determined by the dose of exposure, but on the other hand, within similarly exposed workforces only a small minority of sometimes very young subjects, with relatively little cumulative exposure, are affected [27]. The known dermal sensitizing potential of cobalt and the existence of cobalt-asthma suggest immunological hypersensitivity to cobalt as causing the fibrosing alveolitis. However, this is by no means proven, and other options must be envisaged, such as oxygen free-radical mediated toxicity resulting from the ability of cobalt to promote the Fenton reaction [156].

In view of the widespread use of cobalt in alloys, magnets, special corrosion resistant steels, pigments, plastics and many other applications [31] it is very important to discover the determinants of the toxicity of this metal, both with regard to the chemical or physical form of cobalt compounds that are "intrinsically" harmful, and the extent to which host or other factors may render cobalt toxic. It is indeed remarkable that no lung fibrosis has been reported in workers involved in the mining or refining of cobalt [157], except perhaps for four cases which arose before World War II in a German factory making cobalt carbonate [158].

Cobalt does not appear to be implicated, at least not in the same way as in the previous fibroses, in the causation of dental technician's pneumoconiosis, which may arise from excessive exposure to dust produced from the machining of vitallium, an alloy consisting of chromium-cobalt-molybdenum [159]. Histologically this fibrosis is manifested by dense interstitial fibrosis around dust deposits, without giant cells. Vitallium dust is, however,

not the sole dust to which dental technicians may be exposed, and other agents such as alginate [160], beryllium, hard-metal and silica may also cause lung disease in these workers [29, 30, 161, 162].

3. Interstitial lung disease with granuloma formation. Berylliosis or chronic beryllium disease is well known for its striking histological and clinical resemblance to sarcoidosis. The clinical, epidemiological and experimental aspects of the disease have recently been reviewed [163-165]. Apart from the extraction and primary refining industry, beryllium exposure is an occupational risk in many sectors of modern technological industries, such as aircraft and aerospace, electronics, computers and communications, where beryllium may be found in alloys (often with copper) or in ceramics. However, it is important to realize that scrap metal refiners [166], non-ferrous metal welders, dental technicians, laboratory maintenance or transport workers may also be exposed to an often unsuspected, but significant, risk.

The differential diagnosis between chronic beryllium disease and other interstitial lung disease, mainly sarcoidosis, rests essentially on the proof of exposure, which may be difficult to obtain solely on the basis of the occupational history. The finding of beryllium in biological samples confirms ongoing (urine) and sometimes past exposure (lung tissue, lymph nodes). Specific blast transformation test of lymphocytes (LTT) in response to culture with beryllium appears to be highly specific, but not very sensitive in peripheral blood lymphocytes, although recent data suggest a great improvement in sensitivity in lymphocytes from the bronchoalveolar lavage [167].

This and other experimental evidence strongly suggest that beryllium triggers a cell-mediated immune response, thereby explaining the low incidence and high variability in time of onset of disease in exposed workers. However, the chemical and physical forms of beryllium probably also play a role, which remains to be clarified.

It is possible that beryllium is not the sole metal involved in causing sarcoid-like lung disease. Zirconium may cause granulomas in human skin, but has not been associated with granulomatous or fibrotic lung disease in man [168]. Titanium, otherwise considered as virtually non-toxic, has been suggested as an aetiological agent in a case of granulomatous lung disease on the basis of the presence of metallic particulates containing titanium in the lung granulomas and of a positive blood LTT to titanium chloride, and not to the other metals tested, including beryllium [169]. On the basis of similar reasoning, aluminium exposure has also been suggested to have led to sarcoid-like lung granulomatosis in a patient who had apparently not been exposed to beryllium [170]. These cases confirm that an occupational exposure (also to silicates, such as talc) should always be considered in cases of "sarcoidosis".

Exposure to rare earth metals (or lanthanides), of which cerium is the most abundant element, has also been associated with interstitial fibrosis in a small number of subjects [171-175]. Rare earths are essential

components of carbon arc lamps used for photoengraving, and the majority of cases of this pneumoconiosis have been described in photoengravers. Rare earths are also used in the fabrication and polishing of glass. One histological report [171] mentions the presence of granulomatous interstitial alterations, although this is not mentioned in the other available pathological descriptions of cerium-pneumoconiosis [175].

The authors of a recent report [170] posed the interesting question as to whether aluminium-induced pulmonary fibrosis or "aluminium-lung" may present in its early stage as a granulomatous lung disease. The very existence of aluminium-lung has been the subject of considerable controversy [176, 177]. Indeed, in view of the extensive industrial use of aluminium, lung disease caused by exposure to this metal is very uncommon. On reviewing past literature, DINMAN [176] concluded that fibrosis only occurred: 1) in workers who were heavily exposed to submicron-sized aluminium plates lubricated with an easily removed lubricant during the production of fireworks and explosives; and 2) in workers involved in the smelting of bauxite for the production of corundum abrasive (Shaver's disease), but who were perhaps also exposed to crystalline silica. However, isolated cases of alveolar proteinosis [178] or fibrosis in aluminium welders or polishers [170, 179-181] do not entirely corroborate this conclusion. The physical characteristics of the aluminium particles, notably their surface area, or even their possibly fibrous nature [182], have been suggested as important determinants of their bioreactivity and hence fibrogenicity.

Although the synthetic abrasive silicon carbide (SiC) or carborundum is not a metallic compound - in contrast to some other abrasives, such as corundum (Al_2O_3) or emery (corundum with iron oxides) - it is worth mentioning that respiratory disease, including pneumoconiosis with fibrosis, has been associated with exposure to SiC, during its manufacture or use [183-185].

Lung cancer

Several metallic compounds are proven lung carcinogens in humans; they include radioactive metals (and their decay products) and non-radioactive metals [186-189].

The increased incidence of lung cancer observed in uranium miners has been causally linked with the inhalation of radon daughters [190]. However, the underground mining of other compounds may also be associated with significant exposure to radioactivity, if there is insufficient ventilation of the radon which leaks from igneous rocks [191]. This factor has been implicated in the higher incidence of lung cancer seen in various groups of mineworkers, such as Swedish iron ore miners [192], although it does not seem to play a role in the similarly increased lung cancer incidence of French iron ore miners [193]. The role of domestic radon gas exposure in the causation of bronchial cancer is the subject of intense research [194].

Epidemiological and experimental studies have clearly established the carcinogenic risk of exposure to arsenic,

chrome and nickel, at least to some of their chemical forms [186–189, 195]. Thus, the relationship of arsenic to increased lung cancer risk in copper smelting workers is unequivocal. This is also the case for other occupational exposures to arsenic, such as the manufacture or spraying of arsenical pesticides [196–197]. A greatly increased risk of lung cancer has also been demonstrated for workers in the primary chromate production and in the chromate pigment industry [186–189, 198–201]. Epidemiological studies of the carcinogenic risk of exposure to chromium during metal plating or during stainless steel welding have been considered inconclusive. However, the exposure in these jobs is to the carcinogenic form of chromium, *i.e.* hexavalent chromium, and there are several recent studies showing an increased lung cancer mortality in welders or platers [202–206]. Occupational exposure to nickel in nickel smelters and refineries is also unequivocally associated with an increase in cancer of the lung and the nasal sinuses [207–208]. Again the situation in nickel-using industries is less clear, but a cancer hazard has not been excluded.

There are also epidemiological or experimental indications that **antimony, beryllium, cadmium, cobalt** and **iron**, or occupations associated with these metals are carcinogenic for the human lung [186–189]. Thus, studies of iron and steel foundry workers have consistently found an increased risk of lung cancer, but this may be due to the emission of polycyclic aromatic hydrocarbons as pyrolysis products of organic materials used [209, 210]. An increased mortality from lung cancer attributable to cadmium has also been shown in some [74, 211, 212], but not all [213–215], recent studies of cadmium exposed workers.

Clearly the study of occupational exposures in the causation of lung cancer is hampered by the effect of cigarette smoking, which has been found to act in any fashion from less than additive to multiplicative with occupational exposure, depending on the agent, but also on characteristics of the study population [191, 216]. Since there are no indications that specific histological types of lung cancer are associated with any specific environmental carcinogen [217–219], it is not possible to attribute a particular lung cancer to a particular aetiology.

Various studies have shown that the proportion of lung cancer attributable to occupation is far from negligible, being around 15%, but possibly up to 47%, in some populations [205, 206, 220–224].

In all of these studies, most of the incriminated exposures are related to asbestos, underground mining, and metals or metal industries. It is therefore worthwhile, even in the individual patient with lung cancer, to thoroughly search the past occupational history for exposure to carcinogens rather than to limit the aetiological "investigation" to cigarette smoking. Not only can this have implication in terms of compensation, where legislation provides for such compensation, but it may also help to discover or further strengthen the role of hitherto unproven carcinogenic exposures, particularly when clusters of cancers are found.

Conclusions and perspectives

This review attempts to show that the toxic effects of metallic compounds may be manifested in almost any form of pulmonary disease. The most important step towards uncovering a possible occupational or environmental cause for an illness in the individual patient is a careful and complete history taking. Inquiring about present and past jobs and understanding the patient's occupational history generally require a good knowledge of existing or past work practices. To link this with possible pulmonary disorders, it is essential for the practising physician to possess, and frequently consult, standard textbooks on occupational disease and to complement this with some awareness of the relevant contemporary literature. However, the recognition of occupational disease may in addition sometimes require an alertness for "strange" occurrences and some degree of scepticism against "idiopathic" or "intrinsic" origins. This attitude must always be backed by elementary scientific principles of toxicology and epidemiology.

Obviously further clinical, radiological, functional, pathological and other investigations will usually be needed to characterize the disease and its progression. Various immunological assays may be helpful for evaluating immunologically mediated lung disease, including that caused by metals, although these tests are generally still to be regarded "as adjuncts to clinical diagnosis, and not as independent proof of causation or of diagnosis" [225]. When hypersensitivity is suspected, bronchial challenge testing may be justified [226].

Bronchoalveolar lavage (BAL) is increasingly used, mainly in the assessment of interstitial lung diseases [227]. BÉGIN [228] has recently advocated the use of this technique in the pneumoconioses in order to eliminate other causes of lung disease, to document mineral dust exposure, to support other clinical information, and to investigate the biological mechanisms of these diseases. With regard to metal toxicity, no systematic studies have as yet appeared concerning the profile of inflammatory cells in BAL, although case reports have mentioned the use of this technique. Besides the proportions of inflammatory cell types, other features may be of possible diagnostic value, such as the presence of multinucleated giant cells. The latter were found in BAL from subjects with cobalt-related fibrosing alveolitis [27]. Analysis of mediators of inflammation and fibrosis [229], cellular subtypes and responsiveness of lymphocytes to *in vitro* challenge [167] are all potentially useful. The toxic effects of metallic compounds on pulmonary alveolar macrophages are also being investigated, but so far macrophages from laboratory animals have mainly been used.

Documentation of exposure to metals may be obtained from the analysis of metal concentrations in blood or urine taken for biological monitoring [230]. In addition, elemental analysis may be carried out on BAL, on biopsy tissue or on autopsy material. Both macroanalytical (or bulk) and microanalytical techniques may be applied [231–233]. The former are destructive techniques which allow the detection, quantitation and/or characterization

of crystalline structure of inorganic elements. The latter techniques allow *in situ* analysis of individual cells and particles. Several microanalytical techniques exist [231], but the one which has been most widely applied, mainly in silicosis and asbestos-related lung disease, is that based on the analysis of X-rays emitted from elements following their bombardment with electrons: energy dispersive X-ray analysis (EDXA). This analysis may be coupled to scanning or transmission electron microscopy. One of the disadvantages of this technique in the field of pulmonary metal-toxicity, is that it does not allow the detection of beryllium. The latter metal can, however, be detected by electron energy loss spectrometry (EELS) [234] and laser microprobe mass analysis (LAMMA) [235].

A potential danger of indiscriminate use of these techniques is that the finding of metallic elements in certain disease states may be unduly associated with a causative role of these elements [236]. Only properly conducted studies, including experimental studies, will prevent such erroneous conclusions being drawn, although case reports will continue to be helpful in suggesting possible associations and stimulating further research.

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References

1. Sakula A. – Ramazzini's de Morbis Artificum and occupational lung disease. *Br J Dis Chest*, 1983, 77, 349–361.
2. Bisetti AA. – Bernardino Ramazzini and occupational lung medicine. *Ann NY Acad Sci*, 1988, 534, 1029–1037.
3. Friberg L, Nordberg GF, Vouk VB, (eds). – *In: Handbook on the toxicology of metals. Vol I and Vol II. 2nd Edn. Elsevier, North-Holland, 1986.*
4. Lauwerys RR. – *In: Toxicologie industrielle et intoxications professionnelles. 2nd Edn. Masson, Paris, 1982, p. 462.*
5. Hammond PB, Beliles RP. – Metals. *In: Casarett and Doull's toxicology. The basic science of poisons. 2nd Edn. J. Doull, C.D. Klaassen and M.O. Amdur eds, MacMillan, New York, 1980, pp. 409–467.*
6. Rom WN, (ed.). – *In: Environmental and occupational medicine. Little, Brown and Co., Boston, 1983, p.1015.*
7. Parkes WR. – *In: Occupational lung disorders. 2nd Edn, Butterworths, London, 1982, p. 529.*
8. Morgan WKC, Seaton A. – *In: Occupational lung diseases. Saunders, Philadelphia, 1975, p. 391.*
9. Vouk V. – General chemistry of metals. Chp 2. *In: Handbook on the toxicology of metals. Vol. I. General aspects. L. Friberg, G.F. Nordberg and V.B. Vouk eds, Elsevier, North-Holland, 1986, pp. 15–35.*
10. Halliwell B, Gutteridge JMC. – Oxygen toxicity, oxygen radicals, transition metals and disease. *Biochem J*, 1984, 219, 1–14.
11. Halliwell B, Gutteridge JMC. – Oxygen free radicals and iron in relation to biology and medicine: some problems and concepts. *Arch Biochem Biophys*, 1986, 246, 501–514.
12. Hart BA. – Cellular and biochemical response of the rat lung to repeated inhalation of cadmium. *Toxicol Appl Pharmacol*, 1986, 82, 281–291.
13. Martell AE. – Chemistry and metabolism of metals relevant to their carcinogenicity. *Environ Health Perspect*, 1981, 40, 27–34.
14. Jennette KW. – The role of metals in carcinogenesis: biochemistry and metabolism. *Environ Health Perspect*, 1981, 40, 233–252.
15. Slater TF. – Free-radical mechanisms in tissue injury. *Biochem J*, 1984, 222, 1–15.
16. Aust SD, Morehouse LA, Thomas CE. – Role of metals in oxygen radical reactions. *J Free Rad Biol Med*, 1985, 1, 3–25.
17. Halliwell B, Gutteridge JMC. – Free radicals and antioxidant protection: mechanisms and significance in toxicity and disease. *Human Toxicol*, 1988, 7, 7–13.
18. Freeman BA, Crapo JD. – Hyperoxia increases oxygen radical production in rat lungs and lung mitochondria. *J Biol Chem*, 1981, 256, 10986–10992.
19. Smith LL. – Mechanism of paraquat toxicity in lung and its relevance to treatment. *Human Toxicol*, 1987, 6, 31–36.
20. Martin WJ. – Nitrofurantoin: evidence for the oxidant injury of lung parenchymal cells. *Am Rev Respir Dis*, 1983, 127, 482–486.
21. Cooper JAD, White DA, Matthay RA. – Drug-induced pulmonary disease. Part 1: Cytotoxic drugs. *Am Rev Respir Dis*, 1986, 133, 321–340.
22. Goodlick LA, Kane AB. – Role of reactive oxygen metabolites in crocidolite asbestos toxicity to mouse macrophages. *Cancer Res*, 1986, 46, 5558–5566.
23. Zammit-Tabona M, Sherkin M, Kijek K, Chan H, Chan-Yeung M. – Asthma caused by diphenylmethane diisocyanate in foundry workers. *Am Rev Respir Dis*, 1983, 128, 226–230.
24. Venables KM, Dally MB, Burge PS, Pickering CAC, Newman-Taylor AJ. – Occupational asthma in a steel coating plant. *Br J Ind Med*, 1985, 42, 517–524.
25. Johnson A, Chan-Yeung M, Maclean L, Atkins E, Dybuncio A, Cheng F, Enarson O. – Respiratory abnormalities among workers in an iron and steel foundry. *Br J Ind Med*, 1985, 42, 94–100.
26. Low I, Mitchell C. – Respiratory disease in foundry workers. *Br J Ind Med*, 1985, 42, 101–115.
27. Demedts M, Gheysens B, Nagels J, Verbeken E, Lauwerys J, Van Den Eeckhout A, Lahaye D, Gyselén A. – Cobalt lung in diamond polishers. *Am Rev Respir Dis*, 1984, 130, 130–135.
28. Gheysens B, Auwerx J, Van Den Eeckhout A, Demedts M. – Cobalt-induced bronchial asthma in diamond polishers. *Chest*, 1985, 88, 740–744.
29. Anonymous. – Lung disease in dental laboratory technicians. *Lancet*, 1985, i, 1200–1201.
30. Rom WN, Lockey JE, Jeffrey LS, Lee JS, Kimball AG, Bang KM, Leaman H, Johns RE Jr, Perrota D, Gibbons HL. – Pneumoconiosis and exposure of dental laboratory technicians. *Am J Public Health*, 1984, 74, 1252–1257.
31. Donaldson JD, Clark SJ, Grimes SM. – Cobalt in chemicals. (The monograph series). Cobalt Development Institute Slough, UK, 1986.
32. Knishkowsky B, Baker EL. – Transmission of occupational disease to family contacts. *Am J Ind Med*, 1986, 9, 543–550.
33. Brooks SM. – Lung disorders resulting from the inhalation of metals. *Clin Chest Med*, 1981, 2, 235–254.
34. Anonymous. – Metals and the lung. *Lancet*, 1984, ii, 903–904.
35. Barnhart S, Rosenstock L. – Cadmium chemical pneumonitis. *Chest*, 1984, 86, 789–791.
36. Taylor A, Jackson MA, Burston J, Lee HA. – Poisoning with cadmium fumes after smelting lead. *Br Med J*, 1984, 288, 1270–1271.
37. Liles R, Miller A, Lerman Y. – Acute mercury poisoning

- with severe chronic pulmonary manifestations. *Chest*, 1985, 88, 306-309.
38. Levin M, Jacob J, Polos PG. - Acute mercury poisoning and mercurial pneumonitis from gold ore purification. *Chest*, 1988, 94, 554-556.
39. Zhicheng S. - Acute nickel carbonyl poisoning: a report of 179 cases. *Br J Ind Med*, 1986, 43, 422-424.
40. Matarese SL, Matthews JL. - Zinc chloride (smoke bomb) inhalational lung injury. *Chest*, 1988, 89, 308-309.
41. Hjortsø E, Qvist J, Bud MI, Thomsen JL, Andersen JB, Wiberg-Jorgensen F, Jensen NK, Jones R, Reid LM, Zapol WM. - ARDS after accidental inhalation of zinc chloride smoke. *Intensive Care Med*, 1988, 14, 17-24.
42. Park T, Di Benedetto R, Morgan K, Colmers R, Sherman E. - Diffuse endobronchial polyposis following a titanium tetrachloride inhalation injury. *Am Rev Respir Dis*, 1984, 130, 315-317.
43. Brooks SM, Weiss MA, Bernstein IL. - Reactive airways dysfunction syndrome (RADS). Persistent asthma syndrome after high level irritant exposures. *Chest*, 1985, 88, 376-384.
44. Townshend RM. - Acute cadmium pneumonitis: a 17 year follow-up. *Br J Ind Med*, 1982, 39, 411-412.
45. Musk AW, Tees JG. - Asthma caused by occupational exposure to vanadium compounds. *Med J Aust*, 1982, 1, 183-184.
46. Lees REM. - Changes in lung function after exposure to vanadium compounds in fuel oil ash. *Br J Ind Med*, 1980, 37, 253-256.
47. Levy BS, Hoffman L, Gottsegen S. - Boilermakers bronchitis. Respiratory tract irritation associated with vanadium pentoxide exposure during oil-to-coal conversion of a power plant. *J Occup Med*, 1984, 26, 567-570.
48. Lindberg E, Hedenstierna G. - Chrome plating: symptoms, findings in the upper airways, and effects on lung function. *Arch Environ Health*, 1983, 38, 367-374.
49. Mueller EJ, Seger DL. - Metal fume fever: a review. *J Emerg Med*, 1985, 2, 271-274.
50. Armstrong CW, Moore LW, Hackler RL, Miller GB Jr, Stroube RB. - An outbreak of metal fume fever. Diagnostic use of urinary copper and zinc determinations. *J Occup Med*, 1983, 25, 886-888.
51. Brown JJ. - Zinc fume fever. *Br J Radiol*, 1988, 61, 327-329.
52. Johnson JS, Kilburn KH. - Cadmium induced metal fume fever: results of inhalation challenge. *Am J Ind Med*, 1983, 4, 533-540.
53. Vogelmeier C, Konig G, Bencze K, Fruhmann G. - Pulmonary involvement in zinc fume fever. *Chest*, 1987, 92, 946-948.
54. Farrell FJ. - Angioedema and urticaria as acute and late phase reactions to zinc fume exposure, with associated metal fume fever-like symptoms. *Am J Ind Med*, 1987, 12, 331-337.
55. Kawane H, Soejima R, Umeki S, Niki Y, Malo JL. - Metal fume fever and asthma (letters). *Chest*, 1988, 93, 1116-1117.
56. May JJ, Stallones L, Darrow D, Pratt DS. - Organic dust toxicity (pulmonary mycotoxicosis) associated with silo unloading. *Thorax*, 1986, 41, 919-923.
57. Lecours R, Laviolette M, Cormier Y. - Bronchoalveolar lavage in pulmonary mycotoxicosis (organic dust toxic syndrome). *Thorax*, 1986, 41, 924-926.
58. Elmes PC. - Relative importance of cigarette smoking in occupational lung disease. *Br J Ind Med*, 1981, 38, 1-13.
59. Fletcher Ch, Peto R, Tinker C, Speizer FF. - In: The natural history of chronic bronchitis and emphysema. An eight year study of early chronic obstructive lung disease in working men in London. Oxford University Press, 1976, p. 272.
60. Covey LS, Wynder EL. - Smoking habits and occupational status. *J Occup Med*, 1981, 23, 537-542.
61. Becklake MR. - Chronic airflow limitation: its relationship to work in dusty occupations. *Chest*, 1985, 88, 608-617.
62. Barnhart S. - Occupational bronchitis: a marker for irritant exposure. *Semin Respir Med*, 1986, 7, 249-256.
63. Morgan WKC. - On dust, disability, and death. *Am Rev Respir Dis*, 1986, 134, 639-641.
64. Department of Health and Social Security. - Bronchitis and emphysema. HMSO, London, 1988.
65. Soutar CA. - Update on lung disease in coalminers (Editorial). *Br J Ind Med*, 1987, 44, 145-148.
66. Marine WM, Gurr D, Jacobsen M. - Clinically important respiratory effects of dust exposure and smoking in British coal-miners. *Am Rev Respir Dis*, 1988, 137, 106-112.
67. Nemery B, Veriter C, Brasseur L, Frans A. - Impairment of ventilatory function and pulmonary gas exchange in non-smoking coalminers. *Lancet*, 1987, ii, 1427-1430.
68. Enarson DA, Vedal S, Chan-Yeung M. - Rapid decline in FEV₁ in grain handlers: relation to level of dust exposure. *Am Rev Respir Dis*, 1985, 132, 814-817.
69. Kauffmann F, Drouet D, Lellouch J, Brille D. - Occupational exposure and 12-year spirometric changes among Paris area workers. *Br J Ind Med*, 1982, 39, 221-232.
70. Bernard A, Lauwerys R. - Effects of cadmium exposure in humans. In: Cadmium. Handbook of Experimental Pharmacology, Vol 80. E.C. Foulkes ed., Springer Verlag, Berlin, 1986, pp. 135-177.
71. Edling C, Elinder CG, Randma E. - Lung function in workers using cadmium containing solders. *Br J Ind Med*, 1986, 43, 657-662.
72. Davison AG, Newman Taylor AJ, Darbyshire J, Chettle DR, Gutherie CJG, O'Malley D, Mason HJ, Fayers PM, Venables KM, Pickering CAC, Franklin D, Scott MC, Holden H, Wright AL, Gompertz D. - Cadmium fume inhalation and emphysema. *Lancet*, 1988, i, 663-667.
73. Armstrong BG, Kazantzis G. - Prostatic cancer and chronic respiratory and renal disease in British cadmium workers: a case control study. *Br J Ind Med*, 1985, 42, 540-545.
74. Kazantzis G, Lam TH, Sullivan KR. - Mortality of cadmium-exposed workers. *Scand J Work Environ Health*, 1988, 14, 220-223.
75. Niewoehner DE, Hoidal JR. - Lung fibrosis and emphysema: divergent responses to a common injury. *Science*, 1982, 217, 359-360.
76. Martin FM, Witschi HP. - Cadmium-induced lung injury: cell kinetics and long-term effects. *Toxicol Appl Pharmacol*, 1985, 80, 215-227.
77. Snider GL, Lucey EC, Faris B, Jung-Legg Y, Stone PJ, Franzblau C. - Cadmium chloride-induced airspace enlargement with interstitial pulmonary fibrosis is not associated with the destruction of lung elastin. Implications for the pathogenesis of human emphysema. *Am Rev Respir Dis*, 1988, 137, 918-923.
78. Kriebel D, Sprince NL, Eisen EA, Greaves IA, Feldman HA, Greene RE. - Beryllium exposure and pulmonary function. A cross-sectional study of beryllium workers. *Br J Ind Med*, 1988, 45, 167-173.
79. Chan-Yeung M, Wong R, Maclean L, Tan F, Schulzer M, Enarson D, Martin A, Dennis R, Grzybowski S. - Epidemiologic health study of workers in an aluminium smelter in British Columbia. *Am Rev Respir Dis*, 1983, 127, 465-469.
80. Townsend MC, Enterline PE, Sussman NB, Bonney TB, Rippey LL. - Pulmonary function in relation to total dust

- exposure at a bauxite refinery and alumina-based chemical products plant. *Am Rev Respir Dis*, 1985, 132, 1174-1180.
81. Sprince NL, Chamberlin RI, Hales CA, Weber AL, Kazemi H. - Respiratory disease in tungsten carbide production workers. *Chest*, 1984, 86, 549-557.
82. Kusaka Y, Ichikawa Y, Shirakawa T, Goto S. - Effect of hard metal dust on ventilatory function. *Br J Ind Med*, 1986, 43, 486-489.
83. Nemery B, Roosels D, Lahaye D, Casier P, Demedts M. - Cross-sectional survey of lung function and assessment of cobalt exposure in diamond polishers (abstract). *Am Rev Respir Dis*, 1988, 137 (2), 96.
84. Roels H, Lauwerys R, Genet P, Sarhan MJ, de Fays M, Hanotiau I, Buchet JP. - Epidemiological survey among workers exposed to manganese: effects on lung, central nervous system, and some biological indices. *Am J Ind Med*, 1988, 11, 307-327.
85. Garabrant DH, Fine LJ, Oliver C, Bernstein L, Peters JM. - Abnormalities of pulmonary function and pleural disease among titanium metal production workers. *Scand J Work Environ Health*, 1987, 13, 47-51.
86. Cotes JE, Gilson JC, McKerron CB, Oldham PD. - A long-term follow-up of workers exposed to beryllium. *Br J Ind Med*, 1983, 40, 13-21.
87. Roto P. - Asthma, symptoms of chronic bronchitis and ventilatory capacity among cobalt and zinc production workers. *Scand J Work Environ Health*, 1980, 6 (Suppl. 1), 49.
88. Sprince NL, Oliver LC, Eisen EA, Greene RE, Chamberlin RI. - Cobalt exposure and lung disease in tungsten carbide workers: a cross-sectional study of current workers. *Am Rev Respir Dis*, 1988, 138, 1220-1226.
89. Chen JL, Fayerweather WE. - Epidemiologic study of workers exposed to titanium dioxide. *J Occup Med*, 1988, 30, 937-942.
90. Deutsche Forschungsgemeinschaft (H. Valentin and U. Smidt). - Research report: chronic bronchitis and occupational dust exposure. Harald Boldt Verlag KG, Boppard, 1978.
91. Nemery B, Moavero NE, Mawet M, Kivits A, Brasseur L, Stanescu D. - Etude de la symptomatologie et de la fonction pulmonaire chez des sidérurgistes. *Rev Inst Hyg Mines (Hasselt)*, 1981, 36, 198-218.
92. Nemery B, Van Leemputten R, Goemaere E, Veriter C, Brasseur L. - Lung function measurements over 21 days shift-work in steelworkers from a strandcasting department. *Br J Ind Med*, 1985, 42, 601-611.
93. Oxhøj H, Bake B, Wedel H, Wilhelmsen L. - Effects of electric arc welding on ventilatory lung function. *Arch Environ Health*, 1979, 34, 211-217.
94. Akbarkhanzadeh F. - Long-term effects of welding fumes upon respiratory symptoms and pulmonary function. *J Occup Med*, 1980, 22, 337-341.
95. Keimig DG, Pomrehn PR, Burmeister LF. - Respiratory symptoms and pulmonary function in welders of mild steel: a cross-sectional study. *Am J Ind Med*, 1983, 4, 489-499.
96. Mur JM, Cavelier C, Meyer-Bisch C, Pham QT, Masset JC. - Etude de la fonction pulmonaire de soudeurs à l'arc. Résultats d'une enquête dans une entreprise de construction de véhicules industriels. *Respiration*, 1983, 44, 50-57.
97. Mur JM, Teculescu D, Pham QT, Gaertner M, Massin N, Meyer-Bisch C, Moulin JJ, Diebold F, Pierre F, Meuroy-Poncelet B, Muller J. - Lung function and clinical findings in a cross-sectional study of arc welders. An epidemiological study. *Int Arch Occup Environ Health*, 1985, 57, 1-17.
98. Sjögren B, Ulfvarson U. - Respiratory symptoms and pulmonary function among welders working with aluminium, stainless steel and railroad tracks. *Scand J Work Environ Health*, 1985, 11, 27-32.
99. Stern RM, Berlin A, Fletcher A, Hemminki K, Jarvisalo J, Peto J. - International conference on health hazards and biological effects of welding fumes and gases. Summary report. *Int Arch Occup Environ Health*, 1986, 57, 237-246.
100. Lockey JE, Schenker MB. - Current issues in occupational lung disease. (Symposium). *Am Rev Respir Dis*, 1988, 138, 1047-1049.
101. Sjögren B. - Effects of gases and particles in welding and soldering. In: Occupational medicine. Principles and practical applications (2nd Edn). C. Zenz ed., Year Book Medical Publ., Chicago-London, 1988, pp. 1053-1060.
102. Pepys J. - Occupational asthma: an overview. *J Occup Med*, 1982, 24, 534-538.
103. Davies RJ, Blainey AD. - Occupational asthma: classification and clinical aspects. *Semin Respir Med*, 1984, 5, 229-239.
104. Chan-Yeung M, Lam S. - Occupational asthma. *Am Rev Respir Dis*, 1986, 133, 686-703.
105. Moller DR, Baughman R, Murlas C, Brooks SM. - New directions in occupational asthma caused by small molecular weight compounds. *Semin Respir Med*, 1987, 7, 225-239.
106. Biagini RE, Bernstein IL, Gallagher JS, Moorman WJ, Brooks S, Gann PH. - The diversity of reaginic immune responses to platinum and palladium metallic salts. *J Allergy Clin Immunol*, 1985, 76, 794-802.
107. Murdoch RD, Pepys J, Hughes EG. - IgE antibody responses to platinum group metals: a large scale refinery survey. *Br J Ind Med*, 1986, 43, 37-43.
108. Block GY, Yeung M. - Asthma induced by nickel. *J Am Med Assoc*, 1982, 247, 1600-1602.
109. Malo J, Cartier A, Doepner M, Nieboer E, Evans S, Dolovich J. - Occupational asthma caused by nickel sulfate. *J Allergy Clin Immunol*, 1982, 69, 55-59.
110. Novey HS, Habib M, Wells ID. - Asthma and IgE antibodies induced by chromium and nickel salts. *J Allergy Clin Immunol*, 1983, 72, 407-412.
111. Davies JE. - Occupational asthma caused by nickel salts. *J Soc Occup Med*, 1986, 36, 29-31.
112. Keskinen H, Kalliomaki PL, Alanko K. - Occupational asthma due to stainless steel welding fumes. *Clin Allergy*, 1980, 10, 151-159.
113. Moller DR, Brooks SM, Bernstein DI, Cassidy K, Enrione M, Bernstein IL. - Delayed anaphylactoid reaction in a worker exposed to chromium. *J Allergy Clin Immunol*, 1986, 77, 45-46.
114. Scherrer M, Maillard JM. - Hartmetall-Pneumopathien. *Schweiz Med Wschr*, 1982, 112, 198-207.
115. Hartmann A, Wuthrich B, Bolognini G. - Berufsbedingte Lungenkrankheiten bei der Hartmetallproduktion und-bearbeitung. Ein allergisches Geschehen? *Schweiz Med Wschr*, 1982, 112, 1137-1141.
116. Davison AG, Haslam PL, Corrin B, Coutts H, Dewar A, Riding WD, Studdy PR, Newman Taylor AJ. - Interstitial lung disease and asthma in hard-metal workers: bronchoalveolar lavage, ultrastructural, and analytical findings and results of bronchial provocation tests. *Thorax*, 1983, 38, 119-128.
117. Kusaka Y, Yokoyama K, Sera Y, Yamamoto S, Sone S, Kyono H, Shirakawa T, Goto S. - Respiratory diseases in hard metal workers: an occupational hygiene study in a factory. *Br J Ind Med*, 1986, 43, 474-485.
118. Shirakawa T, Kusaka Y, Fujimura N, Goto S, Kato M, Heki S, Morimoto K. - Occupational asthma from cobalt sensitivity in workers exposed to hard metal dust. *Chest*, 1989, 95, 29-37.
119. Dolovich J, Evans SL, Nieboer E. - Occupational asthma from nickel sensitivity: I. Human serum albumin in the antigenic determinant. *Br J Ind Med*, 1984, 41, 51-55.
120. Shirakawa T, Kusaka Y, Fujimura N, Goto S, Morimoto

- K. - The existence of specific antibodies to cobalt in hard metal asthma. *Clin Allergy*, 1988, 18, 451-460.
121. Demedts M, Ceuppens JL. - Respiratory diseases from hard metal or cobalt exposure. Solving the enigma. (Editorial). *Chest*, 1989, 95, 2-3.
122. Malo JL, Cartier A. - Occupational asthma due to fumes of galvanized metal. *Chest*, 1987, 92, 375-377.
123. Field GB. - Pulmonary function in aluminum smelters. *Thorax*, 1984, 39, 743-751.
124. Šarić M, Godnić-Cvar J, Gomzi M, Štilinović L. - The role of atopy in potroom workers' asthma. *Am J Ind Med*, 1986, 9, 239-242.
125. Wergeland E, Lund E, Waage JE. - Respiratory dysfunction after potroom asthma. *Am J Ind Med*, 1987, 11, 627-636.
126. Simonsson BG, Sjöberg A, Rolf C, Haeger-Aronson B. - Acute and long-term airway hyperreactivity in aluminium-salt exposed workers with nocturnal asthma. *Eur J Respir Dis*, 1985, 66, 105-118.
127. Hjortsberg U, Nise G, Ørbaek P, Sjøes-Petersen U, Arborelius M Jr. - Bronchial asthma due to exposure to potassium aluminum tetrafluoride. (Letter). *Scand J Work Environ Health*, 1986, 12, 223.
128. Dooms-Goossens A, Ceuterick A, Vanmaele N, Degreef N. - Follow-up study of patients with contact dermatitis caused by chromates, nickel, and cobalt. *Dermatologica*, 1980, 166, 249-260.
129. Fisher AA. - Dermatitis and discoloration from metals. In: Contact Dermatitis. 3rd Edn. Lea & Febiger, Philadelphia, 1986, pp. 710-744.
130. Burge PS. - Problems in the diagnosis of occupational asthma. *Br J Dis Chest*, 1987, 81, 105-115.
131. Breatnach SM, Katz SI. - Cell-mediated immunity in cutaneous disease. *Hum Pathol*, 1986, 17, 161-167.
132. Daniele RP. - Cell-mediated immunity in pulmonary disease. *Hum Pathol*, 1986, 17, 154-160.
133. Van Cutsem EJ, Ceuppens JL, Lacquet LM, Demedts M. - Combined asthma and alveolitis induced by cobalt in a diamond polisher. *Eur J Respir Dis*, 1987, 70, 54-61.
134. Terr AI. - The atopic worker. *Clin Rev Allergy*, 1986, 4, 267-288.
135. Venables KM. - Epidemiology and the prevention of occupational asthma. *Br J Ind Med*, 1987, 44, 73-75.
136. Venables KM, Topping MD, Howe W, Luczynska CM, Hawkins R, Newman Taylor AJ. - Interaction of smoking and atopy in producing specific IgE antibody against a hapten protein conjugate. *Br Med J*, 1985, 290, 201-204.
137. Biagini RE, Moorman WJ, Lewis TR, Berstein IL. - Ozone enhancement of platinum asthma in a primate model. *Am Rev Respir Dis*, 1986, 134, 719-725.
138. Mapp CE, Boschetto P, Dal Vecchio L, Maestrelli P, Fabbri LM. - Occupational asthma due to isocyanates. *Eur Respir J*, 1988, 1, 273-279.
139. Chan-Yeung M. - Occupational asthma update. *Chest*, 1988, 93, 407-411.
140. Crystal RG, Gadek JE, Ferrans VJ, Fulmer JD, Line BR, Hunninghake GW. - Interstitial lung disease: current concepts of pathogenesis, staging and therapy. *Am J Med*, 1981, 70, 542-568.
141. Snider GL. - Interstitial pulmonary fibrosis - which cell is the culprit. *Am Rev Respir Dis*, 1983, 127, 535-539.
142. Funahashi A, Schlueter DP, Pintar K, Bemis EL, Siegesmund KA. - Welders' pneumoconiosis: tissue elemental microanalysis by energy dispersive X-ray analysis. *Br J Ind Med*, 1988, 45, 14-18.
143. Dagueneil J, Gaucher P, Dumortier L, Geraut C, Moignetau C, Ligot J, Boiteau HL, Guichet J, Leseac'h C. - Antimoniose pulmonaire. *Arch Mal Prof*, 1979, 40, 110-112.
144. Potkonjak V, Pavlovich M. - Antimoniosis: a particular form of pneumoconiosis. I. Etiology, clinical and X-ray findings. *Int Arch Occup Environ Health*, 1983, 51, 199-207.
145. National Institute of Occupational Safety and Health (NIOSH). - Criteria for controlling occupational exposure to cobalt. U.S. Department of health and human services. Publ no. 82-107, CDC-NIOSH, 1981.
146. Cullen MR. - Respiratory diseases from hard metal exposures. A continuing enigma. *Chest*, 1984, 86, 513-514.
147. Balmes JR. - Respiratory effects of hard-metal dust exposure. *State of the Art Rev Occup Med*, 1987, 2, 327-344.
148. Sjögren I, Hillerdal G, Andersson A, Zetterström O. - Hard metal lung disease: importance of cobalt in coolants. *Thorax*, 1980, 35, 653-659.
149. Meyer D, Stoeckel C, Geist T, Le Bouffant L, Roegel E. - A propos de trois nouveaux cas de fibrose pulmonaire chez des affûteurs d'outils renforcés en carbure de tungstène. *Poumon-Coeur*, 1981, 37, 165-175.
150. Hartung M, Valentin H. - Lungenfibrose durch Hartmetallstäube. *Zbl Bakt Hyg I Abt Orig B*, 1983, 177, 237-250.
151. Hartung M. - Lungenfibrosen bei Hartmetallschleifern. Bedeutung der Cobaltwirkung. Schriftenreihe des Hauptverbandes der gewerblichen Berufsgenossenschaften C.V. Sankt Augustin, 1986.
152. Anttila S, Sutinen S, Paananen M, Kreuz KE, Sivonen SJ, Grekula A, Alapieti T. - Hard-metal lung disease: a clinical, histological, ultrastructural and X-ray microanalytical study. *Eur J Respir Dis*, 1986, 69, 83-94.
153. Rizzato G, Locicero G, Barberis M, Torre M, Pietra R, Sabbioni E. - Trace of metal exposure in hard metal lung disease. *Chest*, 1986, 90, 101-106.
154. Schepers GWH. - The biological action of particulate cobalt metal, tantalum oxide, cobalt oxide, tungsten metal, tungsten carbide and carbon, tungsten carbide and cobalt. *Am Arch Ind Health*, 1955, 12, 121-146.
155. Abraham JL. - Lung pathology in 22 cases of giant cell interstitial pneumonia (GIP) suggests GIP is pathognomonic of cobalt (hard metal) disease. (Abstract). *Chest*, 1987, 91, 312.
156. Nemery B, Nagels J, Verbeke E, Dinsdale D, Demedts M. - Rapidly fatal progression of cobalt-lung in a diamond polisher. Possible involvement of an oxygen free-radical mechanism. *Am Rev Respir Dis*, 1990, in press.
157. Morgan LG. - A study into the health and mortality of men exposed to cobalt and oxides. *J Soc Occup Med*, 1983, 33, 181-186.
158. Reinl W, Schnellbacher F, Rahm G. - Lungenfibrosen und entzündliche Lungenerkrankungen nach Einwirkung von Kobaltkontaktmasse. *Zbl Arbeitsmed*, 1979, 12, 318-325.
159. De Vuyst P, Van de Weyer R, Decoster A, Marchandise FX, Dumortier P, Ketelbant P, Jedwab J, Yernault JC. - Dental technician's pneumoconiosis. A report of two cases. *Am Rev Respir Dis*, 1986, 133, 316-320.
160. Loewen GM, Weiner D, McMahon J. - Pneumoconiosis in an elderly dentist. *Chest*, 1988, 93, 1312-1313.
161. Carles P, Fabre J, Pujol M, Duprez A, Bollinelli R. - Pneumoconioses complexes chez les prothésistes dentaires. *Poumon-Coeur*, 1978, 34, 189-192.
162. Morgenroth K, Kronenberger H, Tuengerthal S, Schneider M, Meyer-Sydow J, Reimann H, Kroidl RF, Anthor M. - Histologische Lungenbefunde bei Pneumokoniosen von Zahn Technikern. *Prax Klin Pneumol*, 1981, 35, 670-673.
163. Eisenbud M, Lisson J. - Epidemiological aspects of beryllium-induced non malignant lung disease: a 30 year update. *J Occup Med*, 1983, 25, 196-202.
164. Cullen MR, Cherniack MG, Kominsky JR. - Chronic

- beryllium disease in the United States. *Semin Respir Med*, 1987, 7, 203-209.
165. Kriebel D, Brain JD, Sprince NL, Kazemi H. - The pulmonary toxicity of beryllium. *Am Rev Respir Dis*, 1988, 137, 464-473.
166. Cullen MR, Kominsky JR, Rossman MD, Cherniack MG, Rankin JA, Balmes JR, Kern JA, Daniele RP, Palmer L, Naegel GP. - Chronic beryllium disease in a precious metal refinery. Clinical epidemiologic and immunologic evidence for continuing risk from exposure to low level beryllium fume. *Am Rev Respir Dis*, 1987, 135, 201-208.
167. Rossman MD, Kern JA, Elias JA, Cullen MR, Epstein PE, Preuss OP, Markham TN, Daniele RP. - Proliferative response of bronchoalveolar lymphocytes to beryllium. A test for chronic beryllium disease. *Ann Intern Med*, 1988, 108, 687-693.
168. Hadji Michael OC, Brubaker RE. - Evaluation of an occupational respiratory exposure to a zirconium-containing dust. *J Occup Med*, 1986, 23, 543-547.
169. Redline S, Barna BP, Tomaszewski JF Jr, Abraham JL. - Granulomatous disease associated with pulmonary deposition of titanium. *Br J Ind Med*, 1986, 43, 652-656.
170. Devuyt P, Dumortier P, Schandené L, Estenne M, Verhest A, Yernault JC. - Sarcoidlike lung granulomatosis induced by aluminium dust. *Am Rev Respir Dis*, 1987, 135, 493-497.
171. Husain MH, Dick JA, Kaplan YS. - Rare-earth pneumoconiosis. *J Soc Occup Med*, 1980, 30, 15-19.
172. Sinico M, Le Bouffant L, Paillas J, Fabre M, Trincard MD. - Pneumoconiose due au cérium. Documents anatomopathologiques. *Arch Mal Prof*, 1982, 43, 249-252.
173. Vocaturo G, Colombo F, Zanoni M, Rodi F, Sabbioni E, Pietra R. - Human exposure to heavy metals. Rare earth pneumoconiosis in occupational workers. *Chest*, 1983, 83, 780-783.
174. Sulotto F, Romano C, Berra A, Botta GC, Rubino GF, Sabbioni E, Pietra R. - Rare-earth pneumoconiosis: a new case. *Am J Ind Med*, 1986, 9, 567-575.
175. Vogt P, Spycher MA, Rüttner JR. - Pneumokoniose durch "seltene Erden" (Cer-Pneumokoniose). *Schweiz Med Wschr*, 1986, 116, 1303-1308.
176. Dinman BD. - Aluminum in the lung: the pyropowder conundrum. *J Occup Med*, 1987, 29, 869-876.
177. Dinman BD. - Alumina-related pulmonary disease. *J Occup Med*, 1988, 30, 328-335.
178. Miller RR, Churg AM, Hutcheon M, Lam S. - Pulmonary alveolar proteinosis and aluminum dust exposure. *Am Rev Respir Dis*, 1984, 130, 312-314.
179. Vallyathan V, Bergeron WN, Robichaux PA, Craighead JE. - Pulmonary fibrosis in an aluminum arc welder. *Chest*, 1982, 81, 372-374.
180. Herbert A, Sterling G, Abraham J, Corrin B. - Desquamative interstitial pneumonia in an aluminum welder. *Human Pathol*, 1982, 13, 694-699.
181. De Vuyst P, Dumortier P, Rickaert F, Van de Weyer R, Lenclud C, Yernault JC. - Occupational lung fibrosis in an aluminium polisher. *Eur J Respir Dis*, 1986, 68, 131-140.
182. Gilks B, Churg A. - Aluminum-induced pulmonary fibrosis: do fibers play a role? *Am Rev Respir Dis*, 1987, 136, 176-179.
183. Wegman DH, Eisen EA. - Causes of death among employees of a synthetic abrasive product manufacturing company. *J Occup Med*, 1981, 23, 748-754.
184. Peters JM, Smith TJ, Bernstein L, Wright WE, Hammond SK. - Pulmonary effects of exposures in silicon carbide manufacturing. *Br J Ind Med*, 1984, 41, 109-115.
185. Funahashi A, Schlueter DP, Pintar K, Siegesmund KA, Mandel GS, Mandel NS. - Pneumoconiosis in workers exposed to silicon carbide. *Am Rev Respir Dis*, 1984, 129, 635-640.
186. Doll R. - Problems of epidemiological evidence. *Environ Health Perspect*, 1981, 40, 11-20.
187. Cone JE. - Occupational lung cancer. *State of the Art Rev Occup Med*, 1987, 2, 273-295.
188. International Agency for Research on Cancer (IARC). - IARC Monographs on the evaluation of carcinogenic risks to humans. Overall evaluations of carcinogenicity: an updating of IARC Monographs Volumes 1 to 42. Supplement 7 IARC, Lyon, 1987.
189. Norseth T. - Metal carcinogenesis. *Ann NY Acad Sci*, 1988, 534, 377-386.
190. Samet JM, Kutvirt DM, Waxweiler RJ, Key CR. - Uranium mining and lung cancer in Navajo men. *N Engl J Med*, 1984, 310, 1481-1484.
191. Archer VE. - Lung cancer risks of underground miners: cohort and case-control studies. *Yale J Biol Med*, 1988, 61, 183-194.
192. Radford EP, Renard StC KG. - Lung cancer in Swedish iron miners exposed to low doses of radon daughters. *N Engl J Med*, 1984, 310, 1485-1494.
193. Mur JM, Meyer-Bisch C, Pham QT, Massin N, Moulin JJ, Cavellier C, Sadoul P. - Risk of lung cancer among iron ore miners: a proportional mortality study of 1,075 deceased miners in Lorraine, France. *J Occup Med*, 1987, 29, 762-768.
194. Samet JM, Marbury MC, Spengler JD. - Health effects and sources of indoor pollution. Part 2. *Am Rev Respir Dis*, 1988, 137, 221-242.
195. Peters JM, Thomas D, Falk H, Oberdörster G, Smith TJ. - Contribution of metals to respiratory cancer. *Environ Health Perspect*, 1986, 70, 71-83.
196. Lee-Feldstein A. - Cumulative exposure to arsenic and its relationship to respiratory cancer among copper smelter employees. *J Occup Med*, 1986, 28, 296-302.
197. Sobel W, Bond GG, Baldwin CL, Ducommun DJ. - An update of respiratory cancer and occupational exposure to arsenicals. *Am J Ind Med*, 1988, 13, 263-270.
198. Norseth T. - The carcinogenicity of chromium and its salts. *Br J Ind Med*, 1986, 43, 649-651.
199. Satoh K, Fukuza Y, Torii K, Katsuno N. - Epidemiological study of workers engaged in the manufacture of chromium compounds. *J Occup Med*, 1982, 23, 835-838.
200. Langård S, Vigander T. - Occurrence of lung cancer in workers producing chromium pigments. *Br J Ind Med*, 1983, 4, 71-74.
201. Davies JM. - Lung cancer mortality among workers making lead chromate and zinc chromate pigments at three English factories. *Br J Ind Med*, 1984, 41, 158-169.
202. Beaumont JJ, Weiss NS. - Lung cancer among welders. *J Occup Med*, 1981, 23, 839-844.
203. Becker N, Claude J, Frentzel-Beyme R. - Cancer of arc welders exposed to fumes containing chromium and nickel. *Scand J Work Environ Health*, 1985, 11, 75-82.
204. Sorahan T, Burges DCL, Waterhouse JAH. - A mortality study of nickel/chromium platers. *Br J Ind Med*, 1987, 44, 250-258.
205. Lerchen ML, Wiggins CL, Samet JM. - Lung cancer and occupation in New Mexico. *JNCI*, 1987, 79, 639-645.
206. Ronco G, Ciccone G, Mirabelli D, Troia B, Vineis P. - Occupation and lung cancer in two industrialized areas of Northern Italy. *Int J Cancer*, 1988, 41, 354-358.
207. Grandjean P, Anderson O, Nielsen GD. - Carcinogenicity of occupational nickel exposures: an evaluation of the epidemiological evidence. *Am J Ind Med*, 1988, 13, 193-210.
208. Kaldor J, Peto J, Easton D, Doll R, Hermon C, Morgan L. - Models for respiratory cancer in nickel refinery workers. *JNCI* 1986, 77, 841-848.
209. Fletcher AC, Ades A. - Lung cancer mortality in a

- cohort of English foundry workers. *Scand J Work Environ Health*, 1984, 10, 7-16.
210. Silverstein M, Maizlich N, Park R, Silverstein B, Brodsky L, Mirer F. - Mortality among ferrous foundry workers. *Am J Ind Med*, 1986, 10, 27-43.
211. Elinder CG, Kjellstrom T, Hogstedt C, Anderson K, Span G. - Cancer mortality of cadmium workers. *Br J Ind Med*, 1985, 42, 651-655.
212. Thun MT, Schnorr TM, Smith AB, Halperin WE, Lemen RA. - Mortality among a cohort of US cadmium production workers. An update. *JNCI*, 1985, 74, 325-333.
213. Sorahan T. - Mortality from lung cancer among a cohort of nickel cadmium battery workers: 1946-1984. *Br J Ind Med*, 1987, 44, 803-809.
214. Ades AE, Kazantzis G. - Lung cancer in a non-ferrous smelter: the role of cadmium. *Br J Ind Med*, 1988, 45, 435-442.
215. Oberdörster G. - Airborne cadmium and carcinogenesis of the respiratory tract. *Scand J Work Environ Health*, 1986, 12, 523-527.
216. Steenland K, Thun M. - Interaction between tobacco smoking and occupational exposures in the causation of lung cancer. *J Occup Med*, 1986, 28, 110-118.
217. Ives JC, Buffler PA, Greenberg SD. - Environmental associations and histopathologic patterns of carcinoma of the lung: the challenge and dilemma in epidemiologic studies. *Am Rev Respir Dis*, 1983, 128, 195-209.
218. Pershagen G, Bergman F, Klominek J, Damber L, Wall S. - Histological types of lung cancer among smelter workers exposed to arsenic. *Br J Ind Med*, 1987, 44, 454-458.
219. Tokudome S, Haratake J, Horie A, Era S, Fujii H, Kawachi J, Miyamoto Y, Suko S, Tokunaga M, Tsuji K, Ikeda M. - Histologic types of lung cancers among male Japanese copper smelter workers. *Am J Ind Med*, 1988, 14, 137-143.
220. Doll R, Peto R. - The causes of cancer: quantitative estimates of avoidable risks of cancer in the US today. *JNCI*, 1981, 66, 1191-1308.
221. Kjuus H, Langård S, Skjaerven R. - A case-referent study of lung cancer, occupational exposures and smoking. III. Etiologic fraction of occupational exposures. *Scand J Work Environ Health*, 1986, 12, 210-215.
222. Kvale G, Bjelke E, Heuch I. - Occupational exposure and lung cancer risk. *Int J Cancer*, 1986, 37, 185-193.
223. Damber LA, Larsson LG. - Occupation and male lung cancer: a case-control study in northern Sweden. *Br J Ind Med*, 1987, 44, 446-453.
224. Simonato L, Vineis P, Fletcher AC. - Estimates of the proportion of lung cancer attributable to occupational exposure. *Carcinogenesis*, 1988, 9, 1159-1165.
225. Newman L, Storey E, Kreiss K. - Immunologic evaluation of occupation lung disease. *State of the Art Rev Occup Med*, 1987, 2, 345-372.
226. Newman Taylor AJ, Davies RJ. - Inhalation challenge testing. In: Occupational lung diseases. Lung Biology in Health and Disease. Vol. 18. H. Weill and M. Turner-Warwick eds, Dekker, New York, Basel, 1981, pp. 143-167.
227. Reynolds HY. - Bronchoalveolar lavage (State of the art). *Am Rev Respir Dis*, 1987, 135, 250-263.
228. Bégin RO. - Bronchoalveolar lavage in the pneumoconioses. Who needs it? *Chest*, 1988, 94, 454.
229. Rom WN, Bitterman PB, Rennard SI, Cantin A, Crystal RG. - Characterization of the lower respiratory tract inflammation of non-smoking individuals with interstitial lung disease associated with chronic inhalation of inorganic dust. *Am Rev Respir Dis*, 1987, 136, 1429-1434.
230. Lauwerys RR. - Biological monitoring of metals: an overview. In: Genotoxic and carcinogenic metals: environmental and occupational occurrence and exposure. Vol XI in Advances in Modern Environmental Toxicology. L. Fishbein, A. Furst and M.A. Mehlman eds, Princeton Scientific Publ., 1987, pp. 265-278.
231. Abraham JL. - Recent advances in pneumoconiosis: the pathologist's role in etiologic diagnosis. In: The lung. Structure, function and disease. W.M. Thurlbeck and M.R. Abell eds, Williams & Wilkins, Baltimore, 1978, pp. 96-137.
232. Roggli VL, Ingram P, Linton RW, Gutknecht WF, Mastin P, Shelburne JD. - New techniques for imaging and analyzing lung tissue. *Environ Health Perspect*, 1984, 56, 163-183.
233. Johnson NF, Haslam PL, Dewar A, Newman Taylor AJ, Turner-Warwick M. - Identification of inorganic dust particles in bronchoalveolar lavage macrophages by energy dispersive X-ray microanalysis. *Arch Environ Health*, 1986, 41, 133-144.
234. Dinsdale D, Bourdillon AJ. - The ultrastructural localisation of beryllium in biological samples by electron energy-loss spectrometry. *Exp Mol Pathol*, 1982, 36, 396-402.
235. Jones Williams W, Kelland D. - New aid for diagnosing chronic beryllium disease (CBD): laser ion mass analysis (LIMA). *J Clin Pathol*, 1986, 39, 900-901.
236. Langer AM. - Mineral dust and pulmonary lesions: etiological link or epiphenomenon. *Am J Ind Med*, 1984, 6, 169-171.

Toxicité des métaux et appareil respiratoire. B. Nemery.

RÉSUMÉ: Le type d'affection pulmonaire causée par les composés métalliques dépend de la nature de l'agent inhalé, de sa forme physico-chimique, de la dose, des conditions d'exposition, et de facteurs liés à l'hôte. Les fumées ou formes gazeuses de différents métaux (par exemple Cd, Mn, Hg, Ni (CO)₄, ZnCl₂, V₂O₅) peuvent entraîner une pneumonie chimique aiguë, avec œdème pulmonaire ou de la trachéo-bronchite aiguë. La fièvre des fumées de métaux, qui peut résulter de l'inhalation de fumées métalliques, par exemple Zn, Cu et beaucoup d'autres, est une réaction pseudo-grippale encore mal comprise et accompagnée d'une alvéolite aiguë à neutrophiles autolimitative. Des pneumopathies chroniques obstructives peuvent résulter de l'exposition professionnelle aux poussières de minéraux, et probablement de certaines poussières de métaux, ou encore de travaux comportant la manipulation de composés métalliques comme par exemple lors du soudage. L'exposition au cadmium est capable d'entraîner de l'emphysème. L'asthme bronchique peut être provoqué par des sels complexes de platine, le nickel, le chrome ou le cobalt, sans doute sur la base d'une sensibilisation allergique. La cause de l'asthme chez les travailleurs de l'aluminium n'est pas connue. Il est remarquable que l'asthme induit par le Ni ou le Cr soit apparemment peu fréquent, si l'on considère leur puissance en tant que sensibilisateurs cutanés. Les poussières de métaux peuvent donner lieu à une fibrose pulmonaire plus ou moins marquée, et à des troubles fonctionnels selon le fibrogène potentiel fibrogène de l'agent et de facteurs de l'hôte encore mal compris. L'inhalation de composés de fer provoque de la sidérose, une pneumoconiose qui ne provoque que peu ou pas de fibrose. La pneumopathie des métaux durs est une fibrose caractérisée par une pneumonie interstitielle desquamative et à cellules géantes, et est probablement due au cobalt, puisqu'une pathologie similaire a été observée chez les travailleurs exposés au cobalt en l'absence de carbure de tungstène. La béryllose est une fibrose avec granulomes épithélioïdes semblable à la sarcoïdose et est probablement due à une réponse immunitaire de type cellulaire à l'égard du béryllium. Un mécanisme similaire pourrait être responsable de la fibrose pulmonaire, rencontrée occasionnellement chez les sujets exposés à d'autres métaux (Al, Ti, terres rares). La proportion des cancers pulmonaires d'origine professionnelle, est de l'ordre

de 15%, et l'exposition à des métaux est fréquemment incriminée. Le travail au fond de la mine d'uranium ou de fer, est associé à une incidence élevée de cancer du poumon, par suite de l'exposition au radon. Au moins certaines formes d'arsenic, de chrome et de nickel, sont des carcinogènes

pulmonaires bien démontrés chez l'homme. Il existe également une augmentation de la mortalité par cancer du poumon chez les travailleurs du cadmium et chez les travailleurs du fer et de l'acier.

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