Metal-Induced Lung Disease: Lessons from Japan’s Experience

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Abstract: Metal-Induced Lung Disease: Lessons from Japan’s Experience: Yukinori KUSAKA, et al. Department of Environmental Health, School of Medicine, Fukui Medical University—Metals inducing occupational respiratory diseases, e.g. metal fever, acute and chronic pneumonia, asthma, bronchitis, chronic obstructive lung disease, pulmonary fibrosis and lung cancer are described. The metals mentioned are the following: aluminum, antimony, arsenic, barium, beryllium, cadmium, chromium, cobalt, copper, iron, lithium, manganese, mercury, nickel, platinum, rhodium, rare earth metals, titanium, uranium, vanadium, welding, zinc, zirconium. With respect to these metals, mechanism of the disease, disease statistics, case reports, diagnostic methods, patho-physiology of the disease, and preventive measures including occupational exposure limits are also described. Experience in Japan on these issues is given in detail. (J Occup Health 2001; 43: 1–23)

Key words: Metal, Lung disease, Occupational, Toxicity, Pneumoconiosis, Pneumonia, Bronchitis, Asthma, Lung cancer, Pulmonary fibrosis

Buddha, Jipang and Meiji revolution in Japan

Since ancient times, inorganic mercury has been used as an amalgam by which mixtures of metals are plated or coated. The “Nara Daibutsu”, Great Buddha Statue in the oldest capital city, was plated with gold by using mercury amalgam and it was reported that, during this process, workers inhaled high levels of mercury fumes, resulting in poisoning.

In the middle of the Edo Era lasting from early in the 1600 to the middle of the 1800, gold mines were opened. Refined gold was then exported through China and the Netherlands to Europe, and Japan came to be known for its gold trade and named Jipang, meaning Golden Hope Island. Marco Polo, who tried to reach the Golden Hope Island by boat, in fact discovered a sea route from West Europe to India.

Pneumoconiosis and associated respiratory failure was well known among gold miners, and was named “Yoroke” which means severe cardiopulmonary failure. It was said that on the Sado Island, which had the biggest gold mine, since miners died young, their wives often remarried to a total of up to seven husbands.

Japan experienced the Meiji Civil Revolution in 1868 followed by an industrial revolution and then westernization. In the middle of the 1930, pneumoconiosis was legally recognized as a compensatable disease and a prevention code for silicosis was introduced among miners.

After the Second World War, the Government’s efforts were focused on recognition of and compensation for various occupational diseases. The Silicosis Law was therefore passed in 1960, particularly for miners in copper, iron and coal mines suffering from silicosis and silicotuberculosis.

In the meantime along with the growth of the Japanese economy cases of occupational lung diseases increased, including pneumoconiosis from agents other than silica and metal. Asbestosis, for instance, arose in Japan and there was a need for workers exposed to asbestos to be supervised and compensated. Therefore, along with advances in knowledge of pneumoconiosis in other industries, the Pneumoconiosis Law was passed in 1978.

The pneumoconiosis law

This Law covers asbestosis and other types of pneumoconiosis such as siderosis and mixed dust pneumoconiosis.

Under this Law, dusty types of work are listed in which workers may develop pneumoconiosis. Some types of dusty work where exposure to metal aerosols take place have also been designated under the Pneumoconiosis Law (Table 1).

According to the Law, employers responsible for these types of work should provide employees with periodic
health examinations including chest x-rays. The Pneumoconiosis Law has designated its own standard chest x-rays, and its coding system is according to the ILO classification scheme.

It is recommended that once a worker’s chest radiograph is judged by the Local Pneumoconiosis Panel designated by the Bureau for Labour Standard, Ministry of Labour, to show pneumoconiotic changes, he or she should have a health examination annually. Severe cases of pneumoconiosis associated with large opacities of type C or with severe pulmonary dysfunction are compensated. Other pulmonary conditions such as tuberculosis and bronchitis secondary to pneumoconiosis are also subject to compensation for treatment and disability.

**Special Ordinance on Specified Hazardous Metals**

Apart from the Pneumoconiosis Law, there are regulations to protect against metal-related lung toxicity. Among them the Special Ordinance on Specified Hazardous Substances deals with metal-related lung cancer, metal fume fever, airway syndrome including perforation of the nasal septum, bronchial irritation, bronchial asthma and bronchitis due to exposure to metals (Table 2).

According to this Ordinance, workers under these circumstances shall be subject to health supervision, and health examinations targeting specific respiratory disorders. At the same time, the working environment in which these metals are handled shall be monitored in terms of metal levels in general air samples and evaluated by comparing the levels with administrative limits designated by the government according to the Working Environment Measurement Law.

Diagnostic criteria for classification of occupational diseases including metal-related lung diseases are open to public scrutiny through governmental codes, and litigation has taken place over these criteria.

Governmental statistics are only limited to lung diseases related to metals in terms of exposed population size, kinds of industries, and prevalence: Table 3 shows the prevalence of these diseases recognized among currently exposed workers. There may be negative case report bias.

**Disease recognition codes under the practice and enforcement ordinance of labour standards law on metals**

With respect to other metals, not covered by the
Pneumoconiosis Law or the Ordinance on Specified Hazardous Substances, there are Disease Recognition Codes under the Practice and Enforcement Ordinance of the Labour Standards Law, defining occupational causation (Table 4)\(^2\). Workers exposed to these metals are not under health supervision specific to relevant disorders but, once workers develop the relevant disease, workers or their relatives can claim compensation for disability and for treatment costs. The Practice Code has recently been raised so that employers must inform employees about the state of knowledge of hazardous metals in their workplace and potential health effects. This can be done by occupational health personnel during periodic health checks, mainly for age-related and lifestyle-related diseases, which employers are compelled to provide.

Furthermore, any metals which have not been designated by the Pneumoconiosis Law, the Ordinance, or the Codes can theoretically be subjected to recognition as causing occupational lung diseases and compensation, if patients or their physicians appeal to the Labour Standard Bureau of the Ministry of Labour. This depends on the physicians’ knowledge of the diseases.

### Statistics of recognized metal-related lung diseases

Little has been known of the numbers of cases of metal-related lung diseases legally recognized in Japan. Japan’s Ministry of Labour reported the data accumulated during 1977 and 1999: 159 chromium-related lung cancers and 75 arsenic-related lung cancers or skin cancers. There were no cases with nickel-related lung cancer during 1994 and 1999.

### Exposure standards in Japan

At the same time the Japan Society for Occupational Health (JSOH)\(^6\) has recommended occupational exposure

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**Table 2.** Metals causing occupational lung diseases designated by Ordinance on Prevention of Hazards due to Specified Chemical Substances with reference to administrative levels (mg/m\(^3\)) assigned by Working Environment Measurement Law

<table>
<thead>
<tr>
<th>Metal</th>
<th>Administrative level (mg/m(^3))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkyl mercury compound</td>
<td>0.01 (as Hg)</td>
</tr>
<tr>
<td>Arsenic trioxide</td>
<td>0.5</td>
</tr>
<tr>
<td>Beryllium</td>
<td>0.002 (as Be)</td>
</tr>
<tr>
<td>Cadmium</td>
<td>0.05</td>
</tr>
<tr>
<td>Chromic acid and its salts, dichromate</td>
<td>0.1 (as Cr)</td>
</tr>
<tr>
<td>Vanadium pentoxide</td>
<td>0.03 (as V)</td>
</tr>
<tr>
<td>Nickel carbonyl</td>
<td>ND</td>
</tr>
<tr>
<td>Manganese</td>
<td>2.5 (as Mn)</td>
</tr>
<tr>
<td>Mercury and its inorganic compounds</td>
<td>0.05 (as Hg)</td>
</tr>
</tbody>
</table>

*Not determined.

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**Table 3.** Numbers of workers undergoing special medical examinations by type of worker covered (1993)

<table>
<thead>
<tr>
<th>Metal</th>
<th>Number of workplaces conducting examination</th>
<th>Number of workers examined</th>
<th>Number of workers with positive findings</th>
<th>Rate of positive findings to total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beryllium</td>
<td>53</td>
<td>913</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Alkyl mercury compounds</td>
<td>30</td>
<td>117</td>
<td>2</td>
<td>1.7</td>
</tr>
<tr>
<td>Cadmium</td>
<td>338</td>
<td>6644</td>
<td>64</td>
<td>1.0</td>
</tr>
<tr>
<td>Chromic acid</td>
<td>2548</td>
<td>26674</td>
<td>238</td>
<td>0.9</td>
</tr>
<tr>
<td>Vanadium pentoxide</td>
<td>157</td>
<td>2102</td>
<td>4</td>
<td>0.2</td>
</tr>
<tr>
<td>Arsenic trioxide</td>
<td>174</td>
<td>2759</td>
<td>20</td>
<td>0.7</td>
</tr>
<tr>
<td>Mercury</td>
<td>303</td>
<td>3492</td>
<td>92</td>
<td>2.6</td>
</tr>
<tr>
<td>Nickel carbonyl</td>
<td>7</td>
<td>495</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Manganese</td>
<td>776</td>
<td>12958</td>
<td>42</td>
<td>0.3</td>
</tr>
</tbody>
</table>
limits (OELs) for various chemical substances over several decades. Recommendations with explanatory documentation have been made on the basis of global scientific knowledge and have been regularly renewed whenever new data have become available. Table 5 shows the metals for which the JSOH has made recommendations, the OELs with reference to target organs including the respiratory systems and to classes of carcinogenicity.

Epidemiology of metal-related lung diseases: Overviews of overseas and Japanese literature

For centuries metals have been known to be capable of causing human diseases, including pulmonary diseases. 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.” Thus some of the so-called metalloids, e.g. Arsenic (As) and Antimony (Sb), are included in the subjects for this review. Although silicates such as talc, mica, and kaolin are associated with various cations including aluminium (Al), magnesium (Mg), and iron (Fe), these minerals causing “classical” pneumoconioses, the majority of occupational lung diseases, are excluded.

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 has been taken as such, whereas more recent acquisitions appearing up to 1997 are emphasized and referred to more specifically.

Further, we have reviewed all papers published up to 1997 in Japan as well as other countries. The search for this literature covered the period between 1935 and 1997. Sensitizing metals such as beryllium, chromium, nickel, cobalt and hard metal, platinum, rhodium, mercury, zirconium and gold were included in a review article by one of the authors. Case reports, reports on epidemiological studies, and reports on the mechanism of metal-related lung diseases have been reviewed by one of the authors. From them, reports of interest for occupational chest medicine were included in the present review.

Aluminium

Cross-sectional studies have suggested an increased prevalence of chronic bronchitis and a loss of ventilatory function, mainly forced vital capacity (FVC), in association with chronic exposure to aluminium. These are apparently independent of the overt forms of other respiratory diseases seen with some of these metals in steel or from welding. The underlying mechanism is not fully clarified.

The causative agent of asthma (“potroom-asthma”) and bronchial hyper-reactivity in aluminium smelters (or other workers exposed to aluminium salts) is not known. The condition is not considered to be due to allergic mechanisms, but rather to an inflammatory response to irritation by fluorides, in view of the close relationship between the levels of fluoride exposure and work-related asthmatic symptoms observed.

A recent report has confirmed the presence of aluminium potroom asthma by means of a positive response in workplace challenge.

Aluminium exposure has been suggested to have led to sarcoid-like lung granulomatosis in a patient who had apparently not been exposed to beryllium. These cases confirm that an occupational exposure (also to silicates, such as talc) should always be considered in cases of “sarcoidosis”.

The recent report by Devuyst et al. posed the interesting question as to whether aluminium-induced pulmonary fibrosis or “aluminum 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. Indeed, in view of the extensive industrial use of aluminium, lung disease caused by exposure to this metal has been questionable. On reviewing past literature, Dinman concluded that fibrosis only occurred: 1) in workers who were heavily exposed to submicron-sized particles from aluminium plates lubricated with an easily removed lubricant during the production of fireworks and Explosives; and 2) in workers involved in the melting of bauxite for the production of corundum abrasive (Shaver’s disease), but who were perhaps also exposed to crystalline silica. Nevertheless, isolated cases of alveolar proteinosis or fibrosis in aluminium welders or polishers do not...
entirely corroborate this conclusion. The physical characteristics of the aluminium particles, notably their surface area, or even their possibly fibrous nature, have been suggested as important determinants of their bioreactivity and hence fibrogenicity.

Mixed dust pneumoconiosis is derived from silicates with low free silica and other mineral content. Mixed dust pneumoconiotic foci are typically stellate lesions with slight to moderate fibrosis. In histopathological data obtained in Japan, aluminium-related pulmonary fibrosis has been described as mixed dust pneumoconiosis accompanied with interstitial pneumonitis.

As stated previously, pulmonary fibrosis related to aluminium and/or aluminium oxides has been designated as pneumoconiosis by the Pneumoconiosis Law in Japan. It is possible that case reports included individuals with so-called Shaver’s disease whose typical pathological findings were compatible with granulomatous lung disease, but to date Shaver’s disease has been neither reported in Japan nor designated as a recognized disease.

**Antimony**

Antimony trichloride (SbCl₃) and pentachloride (SbCl₅) may lead to inhalation injury, presumably as a result of damage caused by the halide ion, rather than by the metal ion. It is worth mentioning that the inhalation of the hydride forms of antimony (stibine, SbH₃) can also be lethal as a result of fulminant haemolysis, which

<table>
<thead>
<tr>
<th>Metal</th>
<th>OEL (mg/m³)</th>
<th>Target organs or pulmonary manifestation</th>
<th>Class of carcinogenicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arsenic trioxide</td>
<td>0.5 (as As)</td>
<td>Systemic toxicity</td>
<td>1</td>
</tr>
<tr>
<td>Beryllium and compounds</td>
<td>0.002 (as Be)</td>
<td>Acute berylliosis</td>
<td>2A</td>
</tr>
<tr>
<td>Cadmium and compounds</td>
<td>0.05 (as Cr)</td>
<td>Renal disorder</td>
<td>1</td>
</tr>
<tr>
<td>Chromium and compounds</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chromium metal</td>
<td>0.5 (as Cr)</td>
<td>Nasal disorder</td>
<td></td>
</tr>
<tr>
<td>Chromium (III) compounds</td>
<td>0.5</td>
<td>Nasal disorder</td>
<td></td>
</tr>
<tr>
<td>Chromium (VI) compounds</td>
<td>0.05</td>
<td>Lung cancer</td>
<td>1</td>
</tr>
<tr>
<td>Certain Chromium (VI) compounds</td>
<td>0.01</td>
<td>Lung cancer</td>
<td>1</td>
</tr>
<tr>
<td>Cobalt and compounds</td>
<td>0.05 (as Co)</td>
<td>Pulmonary fibrosis</td>
<td>2B</td>
</tr>
<tr>
<td>Manganese and compounds</td>
<td>0.3 (as Mn for respirable fraction)</td>
<td>Neurological disease</td>
<td></td>
</tr>
<tr>
<td>Mercury and compounds</td>
<td>0.05 (as Hg)</td>
<td>Neurological disease</td>
<td></td>
</tr>
<tr>
<td>Nickel</td>
<td>1</td>
<td>Lung cancer</td>
<td>2B</td>
</tr>
<tr>
<td>Nickel carbonyl</td>
<td>0.007</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selenium and compounds</td>
<td>0.1</td>
<td>Acute pneumonia</td>
<td></td>
</tr>
<tr>
<td>Silver and compounds</td>
<td>0.01 (as Ag)</td>
<td>Skin disease</td>
<td></td>
</tr>
<tr>
<td>Vanadium compounds</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vanadium oxide fume</td>
<td>0.1</td>
<td>Asthmatic bronchitis</td>
<td></td>
</tr>
<tr>
<td>Vanadium oxide dust</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferrovanadium dust</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zinc oxide fume</td>
<td>5</td>
<td>Metal fever</td>
<td></td>
</tr>
<tr>
<td>Alumina, aluminum</td>
<td>0.5 for respirable fraction</td>
<td>Pulmonary fibrosis</td>
<td></td>
</tr>
<tr>
<td>Iron oxide</td>
<td>1 for respirable fraction</td>
<td>2.0 for total portion</td>
<td>Pneumoconiosis</td>
</tr>
<tr>
<td>Titanium oxide</td>
<td>1 for respirable fraction</td>
<td>4 for total portion</td>
<td>Pneumoconiosis</td>
</tr>
<tr>
<td>Zinc oxide</td>
<td>1 for respirable fraction</td>
<td>4 for total portion</td>
<td>Pneumoconiosis</td>
</tr>
</tbody>
</table>
sometimes manifests itself initially as dyspnoea\textsuperscript{32}. This is not the case for insoluble antimony trioxide.

Antimony is known to cause “benign” pneumoconiosis\textsuperscript{33, 44}.

**Arsenic**

It is worth mentioning that the inhalation of the gaseous hydride forms of arsenic (arsine, AsH\textsubscript{3}) can also be lethal due to the mechanism of fulminant hemolysis\textsuperscript{45, 46}.

Epidemiological and experimental studies have established the carcinogenic risk of exposure to inorganic arsenic compounds\textsuperscript{47–51}. In recent years lung cancer, at an odds ratio as high as 15.2, was reported for arsenic exposed populations\textsuperscript{52}. In another study, SMR as high as 3.73 was found in both a case-control study and a cohort study made by the same authors\textsuperscript{53, 54}. A recent review of occupational lung carcinogens has reported relative risks of lung cancer due to arsenic with reference to the number of exposed workers\textsuperscript{55}.

This is also the case for other occupational exposures to arsenic, such as in the manufacture or spraying of arsenic pesticides\textsuperscript{56, 57}. By contrast, no excess lung cancer was noted in the study by Enterline et al.\textsuperscript{39} for smelters whose exposures were estimated to be at the current OSHA level, 10 \( \mu \text{g/m}^3 \).

In Japan, several areas with arsenic mines and refineries have been recognized as environmentally-polluted sites according to Law for Prevention of Public Pollution. Both workers and residents have been found there to be victims of arsenic. It was reported, for example, that the residents in an area producing the most arsenic in Japan also had lung cancer highly associated with skin cancer\textsuperscript{59, 60}.

**Barium**

Baritosis, a benign pneumoconiosis, has been associated with exposure to barium\textsuperscript{12–14}.

**Beryllium**

Past literature\textsuperscript{15} on accidental and non-accidental exposures shows that exposure to fumes or dusts containing beryllium is capable of causing chemical pneumonitis or acute airway irritation. A cross-sectional study has also suggested an increased prevalence of chronic bronchitis and loss of ventilatory function, mainly forced vital capacity (FVC), in association with chronic berylliosis\textsuperscript{61}, although another study did not reach the same conclusion\textsuperscript{62}.

Berylliosis or chronic beryllium disease (CBD) 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\textsuperscript{63–65}. Apart from the extraction and primary refining industry, beryllium exposure is an occupational risk in many sectors of modern 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\textsuperscript{66}, non-ferrous metal welders, dental technicians, laboratory maintenance or transport workers may also be exposed to an often unsuspected but significant risk. Contacts with beryllium-workers who brought factory-dust to their homes caused a classical para-occupational example of chronic berylliosis\textsuperscript{67}.

The differential diagnosis between chronic beryllium disease and other interstitial lung diseases, mainly sarcoidosis, rests essentially on the proof of exposure, which may be difficult to obtain solely on the basis of occupational history. The finding of beryllium in biological samples confirms present (urine) and sometimes past exposure (lung tissue, lymph nodes)\textsuperscript{68}. 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 bronchoalveolar lavage\textsuperscript{69}. Saltini et al.\textsuperscript{70} showed that major histocompatibility complex class II antigens and functional interleukin 2 receptors were necessary for CD4+ lung T cells from patients with chronic beryllium disease to proliferate in vitro in response to stimulation by beryllium.

This and other experimental evidence strongly suggest that beryllium triggers a cell-mediated immune response, thereby explaining the low incidence and high variation in the time of onset of disease in exposed workers. Moreover, an HLA-DPB1 (HLA-DPB1 glutamate 69) allele was suggested to be closely associated with chronic beryllium disease\textsuperscript{71}.

This marker could be useful in screening for those workers who should be monitored for evidence of sensitization or disease. However, the chemical and physical forms of beryllium probably also play a role, and this remains to be clarified.

The Japanese literature on CBD including the first report by Izumi et al.\textsuperscript{72} was reviewed by one of the authors\textsuperscript{39}.

Compared to other developed countries, Japan has experienced fewer cases (n=25) with CBD; five of these died from complications of CBD including pulmonary infection and pulmonary failure. A reason for the low number of cases is believed to be the genetic background\textsuperscript{73}. All of these cases dealt with beryllium oxide (BeO) which is said to be less toxic or potent in sensitization than beryllium salts.

According to the regulations in Japan as well as the U.S.A., workers handling beryllium alloy containing Be at less than 3% are not subjected to periodic health examinations. Moreover, beryllium-copper alloy has been recognized as being less potent in initiating CBD than
BeO but in recent reports in Japan, Be-Co alloy with Be content less than 3% caused CBD in two cases\(^73, 74\). The findings and test results including blood-Be-LTT for these cases matched the criteria of the U.S.A. Beryllium Case Registry\(^75\).

Follow-up studies have revealed that individuals with chronic beryllium disease have a higher incidence of lung cancer than the general population\(^76\). A thorough review article\(^77\) has recently been published on the carcinogenesis of beryllium, which is now assigned to category 1 by IARC\(^49\).

**Cadmium**

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 defense against cadmium, but it eventually leads to the retention and progressive accumulation of cadmium in various tissues including probably the lungs\(^78\). Cadmium is capable of causing both lung and kidney changes, probably depending in part on the route of exposure.

The most severe form of acute pulmonary damage is chemical pneumonitis which classically follows the inhalation of cadmium fumes\(^13\). Cadmium is present in several areas of metallurgy. From a practical viewpoint, it is important to be aware that risks in relation to cadmium pneumonitis are: 1) that liberation of cadmium oxides from welding, silver brazing, or burning of cadmium-containing alloys\(^79\) or from the smelting of lead\(^80\), which often contain significant levels of cadmium; 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\(^13\). A follow-up study\(^81\) showed that cadmium chemical pneumonitis leads to pulmonary fibrosis.

For instance in Japan, there have been reported cases of acute interstitial pneumonitis resulting from inhalation of cadmium fumes at high levels\(^82-85\). One report\(^81\) contained data on airborne concentrations of a number of metals generated during welding.

Symptoms suddenly developed several hours after burning cadmium alloys (Fig. 1), presenting with fever, dry cough, general malaise and so on. One day after onset, diffuse shadows were seen on chest x-rays (Fig. 2) and lung biopsy specimens revealed interstitial pneumonitis with infiltration of lymphocytes and eosinophils [Personal communications from Professor R. Tokunaga].

Exposure to cadmium also relates to metal fume fever, a malaria-like or influenza-like reaction consisting of fever, chills, and malaise, sometimes associated with X-ray abnormalities\(^86\).

The as yet controversial issue of whether chronic cadmium fume inhalation leads to pulmonary emphysema\(^87, 88\) has recently been settled by the results of a study of a large group (n=101) of workers and ex-workers from a cadmium factory in England\(^89\). 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. Evidence of a causal role for cadmium was strengthened by the existence of a positive exposure/response relationship with exposure being estimated from both past hygiene measurements and the internal (liver) cadmium burden. Moreover, the significance of these findings has been borne out by the demonstration of increased mortality from non-malignant
respiratory disease in cadmium-exposed workers\textsuperscript{90, 91}. The mechanism of cadmium-induced emphysema is still not elucidated. Animal studies suggested that fibrosis, rather than alveolar wall destruction, precede the development of emphysematous lesions\textsuperscript{92-94}.

There are also epidemiological and experimental indications that cadmium is carcinogenic in the human lung\textsuperscript{47-50}. Increased mortality from lung cancer attributable to cadmium has been shown in some\textsuperscript{91, 95, 96}, but not all studies of cadmium exposed workers\textsuperscript{97-99}. A recent review on occupational lung carcinogens has reported relative risks of lung cancer due to cadmium with reference to exposed workers in a number of industries\textsuperscript{53}.

**Chromium**

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\textsuperscript{100}.

Chromium is reported to cause asthma in chromium plating workers, mostly in case reports\textsuperscript{101, 102}. Shirakawa et al.\textsuperscript{103} demonstrated the existence of a specific IgE antibody to chromium-human serum conjugate in a 50-yr-old male engaged in metal plating.

The assay for the type I immediate reaction in combination with a bronchial provocation test is expected to clarify the basic mechanism underlying chromium-related lung sensitization.

Simultaneous exposure to sensitizing metals (Ni and Cr) takes place in electroplating and the question of a cross reaction between the two metals or simultaneous sensitization to the metals has been debated\textsuperscript{104}.

Epidemiological and experimental studies have clearly established the carcinogenic risk from exposure to chromium, in some of its chemical forms. A greatly increased risk of lung cancer has also been demonstrated for workers in primary chromate production and in the chromate pigment industry\textsuperscript{47-51, 55, 105-108}.

In Japan lung cancer was observed to occur in a significantly greater proportion of chromate workers than in the Japanese general population\textsuperscript{106, 109}.

Ishikawa et al.\textsuperscript{110} demonstrated that lung cancer from chromate tends to develop on the bronchial bifurcations in association with increased deposition at that site. Bronchial dysplasia also occurs at this site, and mucous cells express the p53 oncogene product, often followed by squamous cell lung cancer. This latter finding may support the dysplasia-carcinoma sequence theory.

There are several recent studies showing increased lung cancer mortality in welders and platers\textsuperscript{111-115}. The exposure in these jobs is probably to the carcinogenic form of chromium, i.e. hexavalent chromium\textsuperscript{116}, although a recent report suggested the potential for insoluble (trivalent) chromium to cause lung cancer\textsuperscript{117}. Epidemiological studies of the carcinogenic risk of exposure to chromium during metal plating or during stainless steel welding have been considered inconclusive.

**Cobalt**

Cobalt (Co) is an essential metal in many coenzymes and enzymes. Dysfunction in enzymatic processes, e.g. megalocytic anemia, may, therefore, result from Co deficiency. However, high doses of the essential metal may cause substitution and mimicry as inappropriate compounds.

Another toxicologically relevant consequence of cobalt binding to proteins is the acquisition of antigenicity, so that cobalt sensitizes probably by mechanisms similar to those of other reactive low molecular weight molecules and metals which may function as haptons.

The biological activity and toxicity of some metals is also greatly influenced by their ability to change their redox state by loss or 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 catalyzing 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\textsuperscript{118-120}. In pulmonary toxicology, free-radical oxygen toxicity, which seems always to involve metal catalysis\textsuperscript{121, 122}, is considered to be a mechanism for the effects of hyperoxia\textsuperscript{123}, paraquat\textsuperscript{124}, nitrofurantoin\textsuperscript{125} and asbestos\textsuperscript{126}. Cobalt performs all of these activities, and cobalt accumulated in the lungs enhances hyperoxia by this mechanism\textsuperscript{127}.

Cross-sectional studies have suggested an increased prevalence of chronic bronchitis and a loss of ventilatory function associated with chronic exposure to cobalt\textsuperscript{128, 129}.

Cobalt cause asthma\textsuperscript{130-136} with evidence of the formation of specific (IgE) antibodies to protein-conjugates of cobalt (Co)\textsuperscript{136-138}, suggesting that asthmatic reaction to the metal involves an IgE-mediated response. Among workers exposed to hard metal containing either cobalt or nickel as a binding matrix, cobalt-induced bronchial asthma and nickel-induced asthma are prevalent\textsuperscript{139}. Immunological mechanisms include immediate type (IgE-mediated) and cellular hypersensitivity\textsuperscript{138, 139}, and questions relating to the cross reactivity between the two metals versus simultaneous sensitization to the metals has been debated. In addition to sensitization to cobalt, atopy reflected in positive antibodies to common environmental antigens has been shown to be an independent risk factor for asthma among hard metal workers.

Airborne cobalt levels below the current standard limit
for cobalt were shown to carry increased risk. A case of asthmatic sensitization to cobalt was recently diagnosed in a man working in the animal feed industry. This individual was involved in the addition of cobalt sulphate to the feed used for the prevention of cobalt deficiency in cattle (Dr. E. Stevens, personal communication, unpublished).

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. Hard-metal or cemented tungsten carbide (WC) is found in tools used for high-speed cutting, drilling, grinding and 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 reported in various parts of the world. On the basis of relatively crude animal data 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. Indeed it has been proposed that giant cell interstitial pneumonitis (GIP) may be pathognomonic for hard-metal exposure. 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 cobalt. The term cobalt-lung has therefore been proposed. The mechanism of the pulmonary toxicity of cobalt has not yet been elucidated. 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 also play a role in these diseases), several features of cobalt-lung suggest some form of hypersensitivity or host idiosyncrasy, perhaps analogous to the situation observed with beryllium. 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 extent 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. The known dermal sensitizing potential of cobalt and the existence of cobalt-asthma suggest that hypersensitivity to cobalt may cause the fibrosing alveolitis. Conditions more usually considered to be cell-mediated, such as alveolitis, and asthma combined with alveolitis, have been reported. However, this is by no means proven, and other options must be considered, such as oxygen free-radical mediated toxicity resulting from the ability of cobalt to promote the Fenton reaction.

In view of the widespread use of cobalt in alloys, magnets, special corrosion resistant steels, pigments, plastics and many other applications it is important to discover the determinants of the toxicity of this metal. Both the chemical and physical forms of cobalt compounds that are “intrinsically” harmful, and the extent to which host or other factors may render cobalt toxic require investigation. It is indeed remarkable that no lung fibrosis has been reported in workers involved in the mining or refining of cobalt, with the exception of four cases seen before World War II in a Germany factory making cobalt carbonate.

Japan is now the third largest producer of hard metal tools in the world. An article by one of the authors reviewing all the Japanese literature on hard metal-related broncho-pulmonary diseases, demonstrated the prevalence of hard metal asthma to be 5.3%.

Apart from interstitial pulmonary fibrosis probably secondary to interstitial pneumonitis, cases of mixed-dust pneumoconiosis have been demonstrated to be due to a mixture of tungsten carbide dusts and grinding wheel dusts.

This finding is consistent with a report from Switzerland where imported hard metal tools are ground for reuse.

There are also epidemiological and experimental indications that cobalt may be carcinogenic in the human lung. Cobalt is a 2A carcinogen according to the IARC criteria. In Germany, cobalt is listed as one of the carcinogenic substances for which 5 mg/m³ is the maximum acceptable concentration.

**Dental technician pneumoconiosis**

Dental technicians are at risk of pneumoconiosis, as shown in Fig. 3. Intensive monitoring data on airborne dusts at dental technology workplaces have been described by Fukuzawa: some toxic metals including cobalt, chromium, and nickel, and mineral dusts including asbestos and silicates were shown to be present. Some dental pneumoconiosis may arise from excessive exposure to dust produced by the machining of vitallium, an alloy consisting of chromium-cobalt-molybdenum. 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, beryllium, hard-metal and silica may also cause lung disease in these workers.

Dr. Nanbu et al. including one of the authors, Kusaka, reported a technician who presented with interstitial pneumonitis of giant cell type (GIP) (Histopathological findings not shown, HRCT images shown in Fig. 4). This case showed a positive lymphocyte stimulation test with...
cobalt (stimulation index, SI; 4.1) (Fig. 5), while the same lymphocytes from the peripheral blood reacted positively to purified protein derivative of tuberculin (SI 7.4) [Dr. Nanbu and Dr. Kusaka, personal communication]. This evidence might raise the possibility that some dental technicians pneumoconiosis is compatible with cobalt lung which has been designated as interstitial pneumonitis for diamond polishers using cobalt discs\textsuperscript{155}.

Copper

Copper (Cu) is also an essential metal for coenzymes and enzymes. The transport and accumulation of copper is often the result of its ability to interact with ligands such albumin, and ceruloplasmin whose abundance probably constitutes a safeguard against the toxicity of free copper ion\textsuperscript{118}.

Copper is a transition metal which plays an important role in catalyzing biological oxidation reactions. Copper has been studied because of its implication in many pulmonary disease processes by virtue of its ability to enhance the production of toxic free-radical species of oxygen\textsuperscript{118}. In pulmonary toxicology, free-radical oxygen toxicity, seems always to involve metal catalysis\textsuperscript{121, 122}. However, inhaled metals have so far received rather little attention in this connection.

A more benign condition following exposure to high concentrations of copper fume is metal fume fever\textsuperscript{172, 173}. This condition is described more precisely in the section on zinc.

In Japan increased mortality from lung cancer has been reported from a cohort study associated with a net case control study at copper finery plants\textsuperscript{174, 175}. The proportion of Kreyberg group I among these cases with lung cancer was significantly larger than that in the population-based
cancer registries in Japan\(^{176}\). These findings suggested that squamous and small cell carcinoma was prominent and appeared to be environmentally related to bronchogenic carcinomas.

Workers engaged in refining copper ores are exposed to arsenic at the same time. The carcinogenicity of arsenic has been clearly established in epidemiological and experimental studies\(^{47–51, 55}\). Thus, the relationship of arsenic to increased risks of lung cancer in copper smelting workers is unequivocal.

**Iron**

Iron is another transition metal involved in catalyzing biological redox reactions. Studies on implication of iron and copper in many pulmonary disease processes have focused on their ability to enhance the production of toxic free-radical species of oxygen\(^{118–120}\). In pulmonary toxicology, free-radical oxygen toxicity seems always to involve metal catalysis\(^{111, 122}\).

Iron is an essential as a coenzyme for many enzymes. Transferrin, ferritin, and albumin are the main transport or storage proteins for iron, and their abundance probably constitutes a safeguard against the toxicity of free iron\(^{118, 119}\).

Occupational exposure to iron occurs during iron mining and related operations, during iron refining and at various stages in steel making. Exposure also occurs during welding, cutting and abrading of iron-containing materials, as well as during the manufacture or use of iron-containing abrasives (such as emery). Studies of the effects of iron exposure on ventilatory function in groups such as “steel workers”\(^{177–180}\) or “metal welders”\(^{181–189}\) have been largely negative, inconclusive or showing only small effects, despite the generally consistent finding of increases in the prevalence of chronic bronchitis, as founded by means of questionnaires. Nevertheless, 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.

Of the “benign” pneumoconioses the most frequent and best studied is siderosis, which is caused by the inhalation of iron compounds\(^{12, 13, 16}\). 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 asbestosis is not uncommon in many jobs that involve exposure to iron, thus giving rise to mixed dust fibrosis or to asbestosis, and these two conditions do have associated morbidity and complications. Moreover, the view that the symptomatic interstitial fibrosis which is sometimes found in welders (welders’ pneumoconiosis), is simply siderosis with existing silicosis has recently been challenged on the grounds that the pulmonary silicon content in such cases did not differ from that in control lungs\(^{190}\).

There are epidemiological and experimental indications that iron, or occupations associated with iron exposure may be carcinogenic for the human lung\(^{47–50}\). Increased risk of cancer and mortality have been definitely shown in epidemiological studies to be associated with exposure to steel welding\(^{192, 193}\). These studies of iron and steel foundry workers have consistently shown 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\(^{194, 195}\).

**Lead**

Lead is known to be toxic for many organs. Although it is absorbed mainly by inhalation into the body, there have been very rare reports on respiratory disorders due to the exposure to lead. Lead miners probably associated with silicosis were shown to accumulate lead in the lungs\(^{196}\). A cohort study of lead smelter workers in Sweden described increased incidence of lung cancer among them, with dose-response relationships\(^{197}\). The carcinogenicity of lead, however, has not been confirmed yet.

**Lithium**

Lithium hydride (LiH) and phosphine (PH\(_3\)) have been reported to cause pulmonary oedema\(^{13}\).

**Manganese**

Manganese (Mn) is essential as a coenzyme for many enzymes. Exposure to high concentrations of the fumes of manganese can lead to acute pulmonary manifestations, the outcome of which can range from complete recovery to death, depending on the agent involved.

Past literature\(^{13}\) on accidental and non-accidental exposure shows that exposure to fumes or dusts containing manganese is capable of causing chemical pneumonitis or acute airway irritation.

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 manganese\(^{198}\). Apparently these conditions arise independently or due to the other overt forms of respiratory disease seen with some of these metals.

**Mercury**

Past literature\(^{13}\) and recent reports of accidental and non-accidental environmental exposure show that
exposure to fumes or dusts containing mercury\textsuperscript{199–202} is capable of causing chemical pneumonitis or acute airway irritation. Skin absorption of mercury has been shown to be involved in the induction of systemic diseases including pulmonary manifestations\textsuperscript{202}.

**Nickel**

Past literature\textsuperscript{13} and a recent report of accidental and non-accidental exposure show that exposure to fumes or dusts containing nickel carbonyl [Ni(CO)\textsubscript{4}]\textsuperscript{203} is capable of causing chemical pneumonitis or acute airway irritation.

One of the toxicologically relevant consequences of metal binding to proteins is the possible acquisition of antigenicity, i.e. haptenization. As stated above with respect to hard metal disease, nickel and cobalt, which both belong to element group IV, cause asthma, mediated by type I allergic reaction of the bronchial tree.

Nickel has been known to cause asthma mostly in case reports\textsuperscript{204–208}. There is evidence of formation of specific (IgE) antibodies to protein-conjugates of nickel (Ni)\textsuperscript{205, 206, 208}, suggesting that asthmatic reaction to these metals also results from an IgE-mediated response. Exposure to Ni, Cr, or Co takes place in occupational settings such as hard metal industries and electroplating\textsuperscript{104, 139}. Cross reactivity between the two metals and simultaneous sensitization to the metals has been debated. It has also been pointed out that occupational asthma related to exposure to these metals occurs within the current exposure limits\textsuperscript{104, 138, 140, 161}.

New evidence has recently appeared from Japan on the potential of nickel to provoke eosinophilic pneumonia\textsuperscript{209}. In this case, nickel fumes were inhaled during a training course for welding and after a couple hours the pneumonia confirmed by BAL developed. A provocation test with nickel sulphate solution caused a recurrence of the pneumonia. Evidence of a positive provocation test suggests underlying hypersensitivity to nickel. To date, reports on eosinophilic pneumonia related to Ni, Cr, or Co takes place in occupational settings such as hard metal industries and electroplating\textsuperscript{104, 139}. Cross reactivity between the two metals and simultaneous sensitization to the metals has been debated. It has also been pointed out that occupational asthma related to exposure to these metals occurs within the current exposure limits\textsuperscript{104, 138, 140, 161}.

Another hypothesis on the role of nickel is in catalyzing biological oxidation reactions in the exposed lung. Like iron and copper which cause pulmonary disease processes by virtue of their ability to enhance the production of toxic free-radical species of oxygen\textsuperscript{118–120}, nickel may exert toxicity by the same mechanism.

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\textsuperscript{213, 214}. The interaction of metals including nickel with functional groups on macromolecules is an important mechanism for their toxicity and their carcinogenicity\textsuperscript{216, 217}. Several metal ions react strongly 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 of metal carcinogenesis as well as of the chemotherapeutic effects of some metal complexes.

**Platinum**

Platinum sensitizes probably by mechanisms similar to those of other small reactive organic molecules, i.e. haptenisation.

In recent review articles\textsuperscript{218–221} platinum is clearly shown to cause bronchial asthma. The complex halide salts of platinum (Pt) provide a unique example of a situation in which a very considerable proportion of exposed subjects may become sensitized\textsuperscript{18}. There is good evidence for an immunoglobulin E (IgE)-mediated mechanism in platinum salt asthma\textsuperscript{218, 222, 223}. Nevertheless, the detection of Pt-specific antibodies by radioallergosorbent test (RAST) is less sensitive than skin testing in the clinical diagnosis of Pt-hypersensitivity, possibly because of a frequent increase in total IgE\textsuperscript{225}. Smoking and atopy have been demonstrated to be predictors of platinum asthma like cobalt asthma\textsuperscript{224–226}.

Exposure to other irritants such as ozone may well prove to be a more important determinant in interaction with atopy in the occurrence of allergic platinum asthma\textsuperscript{227}.

Shima et al.\textsuperscript{228} reported asthma cases in association with the production of platinum-alloy sensors at Japanese factories.

**Rare earth metals**

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\textsuperscript{209–233}. Rare earth metals are essential compounds of carbon arc lamps used for photoengraving, and the majority of cases of this pneumoconiosis have been described in photoengravers. Rare earth metals are also used in the fabrication and polishing of glass. One histological report\textsuperscript{229} mentions the presence of granulomatous interstitial alterations, although this is not mentioned in the other available pathological descriptions of cerium-pneumoconiosis\textsuperscript{233}.

**Rhodium**

Rhodium, belonging to the same element group as...
platinum, has been assumed to be as potent as platinum in terms of bronchial and skin sensitization. A report from Japan suggested a role of rhodium in the sensitization of workers who handled rhodium replacing platinum as a plating agent\textsuperscript{241}.

**Titanium**

Titanium tetrachloride (TiCl\textsubscript{4})\textsuperscript{235} may lead to inhalation injury presumably as a result of damage caused by the halide ion, rather than by the metal ion.

Cross-sectional studies have suggested an increased prevalence of chronic bronchitis and a loss of ventilatory function associated with chronic exposure to titanium dioxide\textsuperscript{236, 237}.

Titanium, otherwise considered as virtually non-toxic, has been suggested as an aetiological agent in a case of granulomatous lung disease. This was based on the presence of metallic particulates containing titanium in lung granulomas and of a positive blood LTT to titanium chloride, and not to other metals tested, including beryllium\textsuperscript{238}.

Similar histological findings including granulomatous abnormalities, slight focal fibrosis, alveolar septal thickening, and interstitial infiltration with lymphocytes, were reported in one Japanese case with occupational exposure to organic titanium (tetra-butyl-titanium). The element analysis with electron x-ray dispersive analysis detected the presence of organic titanium compound in a fibrotic lung\textsuperscript{239}.

**Uranium**

Uranium hexafluoride (UF\textsubscript{6})\textsuperscript{240} may also cause pulmonary injury after inhalation possibly as a result of damage caused by the halide ion, rather than by the metal ion.

**Vanadium**

Acute tracheobronchitis with persisting bronchial hyper-reactivity\textsuperscript{241} can be caused by exposure to vanadium pentoxide (V\textsubscript{2}O\textsubscript{5}), a significant risk associated with the cleaning of oil tanks (“boilermaker’s bronchitis”)\textsuperscript{242, 243}.

**Welding**

Chronic obstructive lung disease may result from welding. Studies of the effect on ventilatory function in groups such as metal welders\textsuperscript{181–190} have been largely negative, inconclusive or showing only small effects, despite the generally consistent finding of an increase in the prevalence of chronic bronchitis, defined by a 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.

There are several recent studies showing increased lung cancer mortality in welders\textsuperscript{111, 112}. Epidemiological studies of the carcinogenic risk in exposure to chromium during stainless steel welding have been considered inconclusive.

**Zinc**

Zinc (Zn) is an essential metal in coenzymes and enzymes. Deficiency states may therefore cause problems but also high doses of the essential metal caused by substitution and mimicry of essential ions by inappropriate compounds.

Cases of adult respiratory distress syndrome have recently been reported in military and civilian personnel accidentally exposed to smoke bombs which liberate zinc chloride (ZnCl\textsubscript{2})\textsuperscript{244, 245}.

A more benign condition after exposure to high concentrations of metal fumes such as those of copper, manganese, zinc, and cadmium, is metal fume fever\textsuperscript{172, 173}. Among these metals, zinc is the best known causative agent for metal fumes because of wide application in various industries. This condition, of which there are several symptoms\textsuperscript{13}, 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\textsuperscript{246}. 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 stages of the 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\textsuperscript{247}. 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\textsuperscript{248}, but then metal fume fever may be a misnomer or it may be superimposed on bronchial asthma or hypersensitivity pneumonitis\textsuperscript{249}. 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\textsuperscript{250}. Both syndromes have a similar clinical course with fever, leucocytosis, acute transient neutrophilic alveolitis\textsuperscript{251} and occurrence of tolerance. Their similarities indicate common pathogenic mechanisms.

With appropriate environmental control measure, 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 to not lead to sequelae, but this has not been adequately investigated. In recent reports of asthma in subjects welding galvanized metal, sensitization to zinc was suggested; but the possible presence of other metals such as Co, which can be present in galvanized metal, was not investigated. Another suggestion of hypersensitivity to zinc is from a recent report on hypersensitivity pneumonitis in a smelter exposed to zinc fumes. These reports still show a lack of a specific allergic mechanism in zinc mediated lung injury.

Zirconium

Zirconium tetrachloride may lead to inhalation injury, presumably as a result of damage caused by the halide ion rather than by the metal ion. Zirconium may cause granulomas in human skin, but has not been associated with granulomatous or fibrotic lung disease in human subjects.

Summary

The metals causing occupational respiratory diseases are listed in Table 6 with reference to disease entities.

Carcinogenicity of metals is defined according to IARC criteria.

Diagnosis, treatment and prevention

—Research perspectives—

Diagnosis of metal-related occupational pulmonary diseases, as with other occupational diseases, is dependent on the level of knowledge of the physician who first sees the patient. Knowledge leads to recognition. Careful inquiry into occupational history is the first step in making a correct diagnosis.

Respiratory symptoms are not pathognomonic for the metal-related pulmonary diseases. As stated above, metal fume fever is easily overlooked because it is so much like influenza or the common cold. The presence of work-related asthmatic symptoms is a guide to diagnosis. However, their absence does not necessarily deny occupational origin, because failure to remove relevant workers with occupational hypersensitivity from the work leads to persistent and fixed bronchial obstruction.

Pulmonary image techniques are again not specific to each disease entity. Histopathological diagnosis of autopsy and biopsy is useful for interstitial lung diseases.

Table 6. Occupational respiratory diseases related to inhalation of metals

<table>
<thead>
<tr>
<th>Metal</th>
<th>Respiratory disease</th>
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<tbody>
<tr>
<td>Aluminium (Al)</td>
<td>Asthma, Granulomatous fibrosis (Shaver’s disease)</td>
</tr>
<tr>
<td>Antimony (Sb)</td>
<td>Acute pneumonitis, Pneumoconiosis</td>
</tr>
<tr>
<td>Arsenic (As)</td>
<td>Lung cancer, Acute pneumonitis (AsH₃)</td>
</tr>
<tr>
<td>Barium (Ba)</td>
<td>Pneumoconiosis</td>
</tr>
<tr>
<td>Beryllium (Be)</td>
<td>Acute pneumonitis, Chronic beryllium disease, Lung cancer</td>
</tr>
<tr>
<td>Cadmium (Cd)</td>
<td>Acute pneumonitis, Metal fume fever, Emphysema, Lung cancer</td>
</tr>
<tr>
<td>Chromium (Cr)</td>
<td>Nasal septal perforation, Asthma, Lung cancer</td>
</tr>
<tr>
<td>Cobalt (Co)</td>
<td>Chronic bronchitis, Asthma, Interstitial pneumonitis (Hard-metal lung disease, Cobalt lung)</td>
</tr>
<tr>
<td>Copper (Cu)</td>
<td>Metal fume fever</td>
</tr>
<tr>
<td>Iron (Fe)</td>
<td>Pneumoconiosis (Siderosis)</td>
</tr>
<tr>
<td>Lead (Pb)</td>
<td>Lung cancer?</td>
</tr>
<tr>
<td>Lithium (Li)</td>
<td>Pulmonary oedema (LiH)</td>
</tr>
<tr>
<td>Manganese (Mn)</td>
<td>Metal fume fever, Acute pneumonitis</td>
</tr>
<tr>
<td>Mercury (Hg)</td>
<td>Acute pneumonitis</td>
</tr>
<tr>
<td>Nickel (Ni)</td>
<td>Asthma, Eosinophilic pneumonia, Lung cancer</td>
</tr>
<tr>
<td>Platinum (Pt)</td>
<td>Acute pneumonitis [Ni₂(CO₃)₄]</td>
</tr>
<tr>
<td>Rare earth metal</td>
<td>Pneumoconiosis</td>
</tr>
<tr>
<td>Rhodium (Rh)</td>
<td>Asthma</td>
</tr>
<tr>
<td>Titanium (Ti)</td>
<td>Chronic bronchitis, Granulomatous lung disease</td>
</tr>
<tr>
<td>Uranium (U)</td>
<td>Acute pneumonitis</td>
</tr>
<tr>
<td>Vanadium (V)</td>
<td>Tracheobronchitis</td>
</tr>
<tr>
<td>Zinc (Zn)</td>
<td>Respiratory disease syndrome (ZnCl₂), Metal fume fever, Asthma, Hypersensitivity pneumonitis</td>
</tr>
<tr>
<td>Zirconium (Zr)</td>
<td>Acute pneumonitis</td>
</tr>
</tbody>
</table>
related to metals, such as granulomatous lung disease, if elemental or metal analysis of the lung samples is available. Giant cell interstitial pneumonitis is pathognomonic for hard metal lung or cobalt lung. Allergoimmunological tests such as lymphocyte transformation test with metal antigens and specific antibodies are of high specificity, but of less sensitivity, although these test are generally still to be regarded “as adjuncts to clinical diagnosis, and not as independent proof of causation or of diagnosis”\(^255\). When hypersensitivity is suspected, bronchial challenge testing may be justified\(^257\). Bronchoalveolar lavage can contain more lymphocytes responding to metal antigens than peripheral lymphocytes. Bronchoalveolar lavage (BAL) is increasingly used, mainly in the assessment of interstitial lung disease\(^258\). Begin\(^259\) has recently advocated the use of this technique for pneumoconiosis 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. The latter were found in BAL from subjects with cobalt-related fibrosing alveolitis\(^155\). Analysis of mediators of inflammation and fibrosis\(^260\), cellular subtypes and responsiveness of lymphocytes to \textit{in vitro} challenge\(^260\) 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, urine, or hair taken for biological monitoring\(^261\), although failure to detect the relevant metal in biological samples is not necessarily a denial of relevance. For instance, cobalt is excreted very rapidly in the urine after being absorbed through inhalation\(^262\).

In addition, elemental analysis may be carried out on BAL, on biopsy tissue or on autopsy material. Both macro-analytical (or bulk) and microanalytical techniques may be applied\(^263–265\). One of the disadvantages of this technique in the field of pulmonary metal-toxicity is that it does not allow the detection of beryllium. This latter metal can, however, be detected by electron energy loss spectrometry (EELS)\(^266\) and laser microprobe mass analysis (LAMMA)\(^267\). A potential danger in the indiscriminate use of these techniques is that the finding of metallic elements in certain disease states may be unduly associated with a causative role for these elements\(^268\). 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.

Treatment of metal-related lung diseases is not specific, but a combination of infusion of steroid hormone with oxygen inhalation is sometimes crucial for acute chemical pneumonitis due to cadmium, beryllium and so on\(^269\). Treatment of chronic beryllium disease with corticosteroid hormone has been shown to be effective\(^270\). Chelating agents such as sodium diethylthiocarbamate for nickel carbonyl pneumonitis are recommended\(^271\). Desensitization with platinum failed in a platinum asthma case\(^272\).

Prevention of metal-related lung diseases can be attained as for other occupational lung diseases. Metals hazardous to the respiratory system should be notified to employers and employees through the MSDS sheet. Exposure to these metals, and to what extent, should be notified at workplaces. The regulations contribute to enforcing these actions by employers and industries. Exposure standards developed on the basis of epidemiological studies, if present, are appropriate indicators for comparison to keep working environments safe. If exposure exceeds certain levels, technological intervention and personal protection are necessary. Health examinations associated with biological monitoring for individuals are obligatory for some metals in Japan. Educating employees about the health effects of toxic metals, for effective preventive measures, are crucial.

Epidemiological studies and case studies adopting basic scientific techniques have revealed some factors relevant to the onset of metal-related pulmonary diseases: atopy, genetic background, smoking, malnutrition, and so on. Knowledge of these issues should be considered when recruiting workers to aid in risk assessment.

Another recent concept, which has emerged consistently from follow-up studies of occupational asthma from various causes, is the need for rapid and total removal of symptomatic people from exposure in order to prevent permanent asthma\(^273, 274\). 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.

It is necessary to develop diagnostic methods specific to each metal. Experimental studies can generate evidence for chemical forms of metals exerting toxicity which can make a contribution to monitoring and diagnosis. Experimental research also helps in developing pharmaceutical agents. Protective agents and physiology can also be clarified by means of such experiments. Further epidemiological studies are needed to determine occupational exposure limits for many of the toxic metals which are still lacking or poorly understood.

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