2.3 Chemical-Induced Lung Injury and Its Long-Term Sequelae

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CONTENTS

2.3.1 Introduction and Scope

Although many respiratory diseases are caused by chemicals, they will not all be discussed here. Thus, lung disorders caused by tobacco smoking will not be addressed, even though tobacco smoke contains hundreds of irritant, toxic and carcinogenic chemicals and even though smoking is the most common cause of toxic damage to the airways and the lung parenchyma. Similarly, although mineral dusts and fibers are also "chemicals", the pneumoconioses and other long-term disorders that result from chronic occupational exposures to these agents will not be covered. The effects of exposure to urban air pollutants resulting from traffic, industrial activities and domestic heating will not be addressed either.

The focus of this chapter will be on the acute or subacute respiratory health effects – and their possible long-term sequelae – of exposures to high amounts of chemicals and pollutants. Such exposures are generally accidental, and they occur mainly in the workplace, but they may also occur at home or in the community, for instance, as a result of fires and explosions, volcanic eruptions, industrial disasters (e.g. Bhopal in 1984) and accidents involving trains or trucks transporting chemicals, as well as warfare or terrorism.

A great variety of substances can cause inhalation injury. The toxic compounds may be in a gaseous state, or they may consist of aerosols of liquid or solid particles. Chemicals causing lung injury may be simple gases (oxygen, ozone, carbon monoxide, sulphur dioxide, etc.), inorganic compounds in liquid or vapour form (sulphuric acid, nitric acid, etc.), simple or complex minerals (silica, cement, asbestos, man-made vitreous fibers, etc.), metallic agents (mercury, zinc, iron, steel, alloys) or composite materials (hard metal, ceramics), simple organic agents of natural or synthetic origin (acetic acid, acrolein, benzene, toluene diisocyanate, plastic monomers, pesticides, therapeutic drugs, etc.), complex synthetic materials (plastics), mixtures of organic chemicals such as fuels or their combustion products (aliphatic hydrocarbons, polycyclic aromatic hydrocarbons, etc.) and complex biological agents (vegetable, animal or microbial products, such as cellulose, enzymes, lipopolysaccharides, etc.). Most often, exposures are to mixtures of many diverse chemicals, which may be present as gases and particles, thus forming aerosols, as is the case with burning wood, plastics or other materials.

This contribution is a shortened and updated version of a book chapter (Nemery 2002), in which specific references can be found.

2.3.2 Deposition of Inhaled Chemicals in the Respiratory Tract

The site and severity of the respiratory damage caused by inhaled compounds depend mainly on the nature of the agent and the amount inhaled (Schwartz

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1987). As a general rule, gaseous irritants that have a high solubility in water mainly affect the upper respiratory tract, causing rhinitis, pharyngitis, laryngitis, tracheitis or bronchitis. Such water-soluble irritants are easily trapped in the aqueous surfaces of the upper respiratory tract and the eyes, where they cause rapid irritation, thus, leading the subject to avoid further exposure. In contrast, poorly water-soluble gases are not so well scrubbed by the upper respiratory tract, and they can more easily reach the deep lung, where they may lead to pulmonary oedema, usually after a latency of several hours. Moreover, as they cause much less sensory irritation, significant exposure to such gases may be tolerated without much trouble and may even go relatively unnoticed. Consequently, such insoluble gases are more hazardous. Gases of intermediate solubilities mainly affect the upper respiratory tract and large bronchi, but high or prolonged exposures to these agents may also injure the lung and cause chemical pneumonitis. The latter may, in fact, also occur when massive quantities of highly water-soluble gases are inhaled.

With aerosols, the degree of penetration into the respiratory tract depends mainly on the size of the particles, with the smallest particles (<5 µm aerodynamic diameter) having the greatest probability of reaching the distal airways and alveoli. Such small particles are often produced by combustion processes or by condensation of vapours. The particles may be toxic by themselves (e.g. cadmium oxide, CdO), or they may carry irritants, such as sulphates or aldehydes adsorbed onto soot particles.

Chemical-induced lung injury may also be caused by routes other than inhalation. Thus, the lungs may be damaged by the aspiration of ingested liquids, such as solvents or fuels. Some chemicals, most notably agrichemicals such as paraquat or cholinesterase inhibitors, may cause lung injury following ingestion or dermal absorption. Toxic pneumonitis may also result from inhaling or injecting illegal drugs (Wesselius 1997) or as a side effect from various drugs, but this will not be covered here.

Toxic lung injury may have various clinical presentations, which, for convenience, are separated here into three main categories. A first category concerns relatively mild, febrile reactions, collectively known as inhalation fevers. The second category is that of acute chemical pneumonitis with non-cardiogenic pulmonary oedema, which follows a single or brief exposure to a toxic agent. The third category covers subacute or chronic pulmonary inflammation, resulting from a more or less prolonged exposure to pneumotoxic agents.

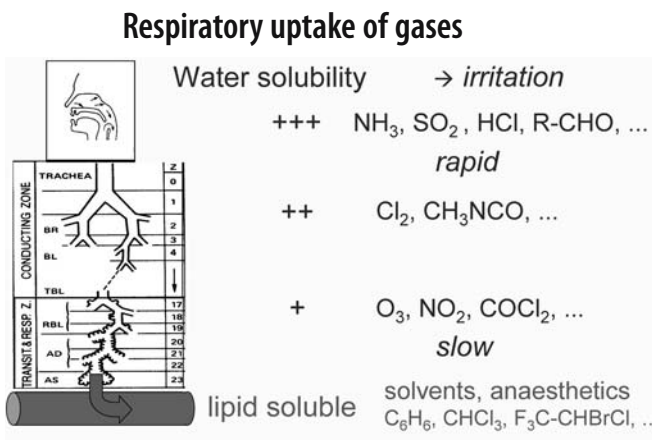

Fig. 2.3.1. The site of uptake of gases depends on their water solubility (+++ high; ++ intermediate; + low). Water soluble gases usually cause rapide sensory irritation; poorly water soluble gases cause little sensory irritation but may lead to delayed pulmonary edema.

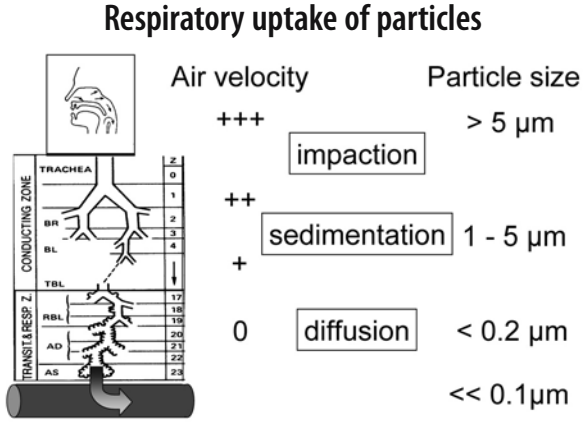

Fig. 2.3.2. The site of deposition of particles depends on air velocity (0 to +++) and particle size. Larger particles are deposited mainly in the upper respiratory tract; smaller particles may reach the bronchioli and alveoli.

2.3.3 Inhalation Fever

Inhalation fever is the name given to cover a group of flu-like clinical syndromes, such as metal fume fever, polymer fume fever and the organic dust toxic syndrome (ODTS) (Rask-Andersen 1992). The term "inhalation fever" is of relatively recent creation, and for a while it competed with the term "toxic alveolitis". There are arguments in favour of both terms, because the former emphasizes the clinical presentation and relatively benign nature of the condition, whereas the latter indicates the (presumed) main site

of the toxic (i.e. non-allergic) inflammatory reaction. It seems, however, that the more clinical term has been preferred by most authors, probably because toxic alveolitis suggests a much more dramatic condition than is usually the case.

Metal fume fever is an old syndrome that is quite well known, not so much by doctors, but by those who are especially at risk of suffering from it, such as welders or other workers in metal trades (Blanc 1993). The most frequent and best documented cause of metal fume fever is that caused by heating zinc. Zinc fumes, which oxidize to fine particles of zinc oxide (ZnO), are produced, for instance, when zinc is smelted to make alloys, when zinc-containing scrap metal is molten, when metal surfaces are sprayed with zinc or when galvanized steel is welded or cut. Metal fume fever occurs when the fumes are not properly exhausted, which is often the case when these jobs are done in enclosed spaces. Both freshly formed zinc fumes and fine zinc oxide dust have the ability to cause metal "fume" fever.

The fumes of many other metals are said to cause metal fume fever too, but this seems not to have been satisfactorily documented, except for magnesium and copper.

ODTS is caused by the inhalation of large quantities of agricultural and other dusts of biological origin (Rask-Andersen 1996). Such bio-aerosols are often heavily contaminated with microorganisms that produce toxins (e.g. bacterial endotoxin, mycotoxins), which are believed to contribute to the pathogenesis of the syndrome. The syndrome is also known by various other names, such as mycotoxicosis.

Polymer fume fever is a less common cause of inhalation fever (Shusterman 1993). It occurs after exposure to the fumes that are produced when fluorine-containing polymers, such as polytetrafluoroethylene (PTFE), also known as Teflon, are heated above 300°C. This may occur when such polymers are extruded or machined or when welding metals that are covered with a PTFE layer. PTFE may also be used as a tape and also be sprayed, e.g. as a mould-release agent, and pyrolysis of this PTFE may occur in a burning cigarette, which explains why polymer fume fever occurs mainly in workers who smoke at work. Although polymer fume fever has only been well described after exposure to the fumes of fluorine-containing polymers, it may possibly occur after exposure to fumes evolving from heating other plastics.

The clinical features of the inhalation fevers are best described as those of a beginning influenza. The actual exposure may or may not have been experienced as irritant or troublesome to the eyes and respiratory tract. Then 4–8 h after the exposure, the subject begins to feel unwell, with fever, chills, headaches, malaise, nausea and muscle aches. In the case of metal fume fever, there may be a metallic taste in the mouth. Respiratory symptoms are usually mild and consist mainly of cough and/or sore throat, but occasionally subjects may have more severe responses with dyspnoea. The body temperature may rise as high as 39–40°C, but there are also less full-blown inhalation "fevers", even without fever, but with malaise, headache or systemic symptoms.

In general, chest auscultation and chest X-ray are normal, but in the more severe cases, which are more likely to seek medical attention, crackles may be heard, and there may be transient infiltrates on chest X-ray. (In the latter circumstances, one would be justified to challenge the diagnosis of inhalation fever and consider that there is a real chemical pneumonitis). Although pulmonary function is often within normal limits, reductions in vital capacity and FEV_1 are perhaps more common than generally accepted; in severe cases there may be a decrease in transfer factor and arterial hypoxaemia. Increased peripheral blood leukocytosis, with a rise in neutrophils, is a consistent finding until 24 h after the exposure; other blood tests should be normal, except, probably, for indices of an inflammatory response. Bronchoalveolar lavage studies have shown very pronounced and dose-dependent increases in polymorphonuclear leukocytes on the day after exposure to zinc fumes or organic dust.

The pathogenesis of metal fume fever and ODTS is considered to be based on a non-specific, i.e. non-allergic, activation of macrophages or pulmonary epithelial cells with local and systemic release of pyrogenic and chemotactic mediators. The mechanism of polymer fume fever is unknown, and the exact components of the fume that cause the toxicity are also unknown. It has been shown that the heating rate of PTFE influences the type and quantity of thermal decomposition products, some of which appear to be extremely toxic.

In principle, inhalation fever is a self-limited syndrome, and recovery normally takes place after a night's rest. Tolerance exists against re-exposures occurring shortly after a bout of metal fume fever or ODTS, but it seems that this feature is less typical of polymer fume fever.

The most important thing to say with regard to the diagnosis of inhalation fevers is that physicians must know the existence of such reactions and the circumstances in which they occur. The diagnosis rests essentially on the exposure history and the

clinical condition, and when these clearly point to inhalation fever, no sophisticated investigations are required. However, it is important not to confuse inhalation fever with other more serious conditions, including chemical pneumonitis, which in its early phases could be mistaken for inhalation fever. One should also be aware that fumes of heated polymers, including fluorinated polymers, may be extremely hazardous and lead to severe pulmonary injury. Obviously, a differential diagnosis must also be made with various types of infectious pneumonias or with acute extrinsic allergic alveolitis (EAA), in which fever, malaise and systemic symptoms occur. This is particularly relevant in the case of exposure to bioaerosols, which is a common cause of acute EAA.

2.3.4 Acute Chemical Pneumonitis

The response to acute chemical injury in the respiratory tract is rarely compound specific. Following exposure to water-soluble irritants, there may be pronounced signs of upper airway irritation, with severe cough, hoarseness, stridor or wheezing, retrosternal pain, discharge of bronchial mucus, possibly with blood, mucosal tissue and soot. Death may occur as a result of laryngeal oedema. If the lung parenchyma is also involved, non-cardiogenic pulmonary oedema may develop over the course of several hours. It is important to realize that victims of serious inhalation accidents may feel perfectly well and walk into the infirmary or an emergency room, or even go home following the inhalation, and then experience progressive dyspnoea, shallow breathing, cyanosis, frothy pink sputum and eventually ventilatory failure. A clinical picture of adult respiratory distress syndrome (ARDS) may, thus, develop gradually over 4–72 h, even after a period of clinical improvement. In the days that follow, severe acute inhalation injury, pulmonary infectious complications may also occur.

Depending on the circumstances of the accident, there may be thermal or chemical facial burns, as well as signs of mucosal irritation and oedema, and even haemorrhage and ulcerations in the air passages. Auscultation of the chest may or may not be abnormal, with wheezing, rhonchi or crepitations. Pulmonary function can be used to monitor ambulatory subjects who have been exposed. Arterial blood gases show varying degrees of hypoxaemia and respiratory acidosis, depending on the severity of the injury. The chest radiograph is usually normal if only the conducting airways are involved, but there may be signs of peribronchial cuffing. After exposure to deep lung irritants, the chest radiograph is unremarkable in the first hours after presentation, but signs of interstitial and alveolar oedema may become visible, and, with time, patchy infiltrates, areas of atelectasis and even "white lungs" may develop. These changes may be due to tissue damage and organization, or they may reflect superimposed infectious (broncho)pneumonia.

As indicated above, a large number of inhaled agents can cause inhalation injury (Table 2.3.1). In the following paragraphs, specific categories of chemicals are briefly highlighted.

Table 2.3.1. Possible causes of toxic pneumonitis

Irritant gases:
High water-solubility: NH_3, SO_2, HCl, etc.
Moderate water-solubility: Cl_2, H_2S, etc.
Low water-solubility: O_3, NO_2, $COCl_2$, etc.
Organic chemicals:
Organic acids: acetic acid, etc.
Aldehydes: formaldehyde, acrolein, etc.
Isocyanates: methylisocyanate (MIC), toluene diisocyanate (TDI)
Amines: hydrazine, chloramines, etc.
Tear gas (CS) and mustard gas
Organic solvents, including some leather treatment sprays
Some agrichemicals (paraquat, cholinesterase inhibitors)
Metallic compounds:
Mercury vapours
Metallic oxides: CdO, V_2O_5, MnO, Os_3O_4, etc.
Halides: $ZnCl_2$, $TiCl_4$, $SbCl_5$, UF_6, etc.
$Ni(CO)_4$
Hydrides: B_2H_5, LiH, AsH_3, SbH_3
Complex mixtures:
Fire smoke
Pyrolysis products from plastics
Solvent mixtures
Spores and toxins from microorganisms

2.3.4.1 Irritant Gases and Organic Chemicals

In general, gases with high water solubility, such as ammonia (NH_3), sulphur dioxide (SO_2), hydrochloric acid (HCl), formaldehyde (HCHO), acetic acid (CH_3COOH), which also have good warning properties, only cause mild upper airway irritation, unless the exposure concentration (or duration) has been considerable. Massive inhalation accidents include explosions or accidents in mines or chemical instal-

lations causing the release of, for instance, SO_2 or NH_3 (from refrigeration installations).

The same considerations apply to chlorine (Cl_2), hydrogen sulphide (H_2S) or methyl isocyanate (CH_3CNO), which have intermediate water solubilities. Accidental release of chlorine is probably one of the most frequent causes of inhalation injury, not only in industry but also in the community as a result of transportation accidents or the use of chlorine for the disinfection of swimming pools (Das 1993). An important cause of inhalation in the domestic setting is that which results from the mixing of bleach (NaClO) with acids, thus leading to the release of gaseous chlorine, or with ammonia, thus leading to the release of volatile chloramines (including trichloramine, NCl_3) (Olson 1993). Interesting case histories of severe pneumonias, which were not immediately recognized as being of toxic origin, have been reported in (elderly) ladies who had done their cleaning in a too enthusiastic fashion (Reisz 1986). Hydrogen sulphide (H_2S), which is formed by the putrefaction of organic material in sewage drains, manure pits or ship holds and is also a frequent contaminant in the petrochemical industry, has special properties as an irritant gas because not only does it cause mucosal irritation, but it also leads to chemical asphyxia by mechanisms that are somewhat similar to those of cyanide. Victims who survive massive inhalation of H_2S may exhibit (haemorrhagic) pulmonary oedema, as well as pneumonia in the days following the event (Reiffenstein 1992). Methyl isocyanate (CH_3CNO, MIC) has gained notoriety as the chemical that caused the highest number of casualties in a single accident, when it was released from a tank in a pesticide factory in Bhopal, India, in December 1994 (Dhara 1995). MIC caused intense eye and upper airway irritation, but it may also lead to pulmonary oedema.

As indicated above, the poorly water-soluble gases are the most hazardous because they are hardly noticed, and they can penetrate down to the distal airways and cause delayed non-cardiogenic pulmonary oedema. The best-known examples of such gases are nitrogen dioxide (NO_2), ozone (O_3) and phosgene ($COCl_2$). NO_2 is a reddish-brown gas, heavier than air, and is often incorrectly referred to as "nitrous fumes". It may be encountered in a wide variety of occupational settings. A well-known risk in agriculture is that of "silo filler's disease" (Douglas 1989) (not to be confused with "silo unloader's syndrome", which is a form of the organic toxic dust syndrome). Silo filler's disease occurs because NO_2 is produced within a few days of fermentation of the silage, thus posing a risk of fatal inhalation injury for anyone entering the silo. Fatally high quantities of NO_2 may also be produced when special jet fuels explode, when tanks of nitric acid (HNO_3) explode, when materials containing high quantities of nitrogen are burned in fires or when nitric acid reacts with metals, wood or other cellulose materials. Outbreaks of acute respiratory illness in players and spectators attending ice hockey matches have been attributed to NO_2 as a result of malfunctioning ice resurfacing machines. Phosgene (carbonyl chloride) is a well-known cause of pulmonary oedema, since it was used in chemical warfare during the first world war. This chemical is used in chemical syntheses, notably in the manufacture of isocyanates, and it may be produced by thermal or ultraviolet decomposition of chlorine-containing chemicals, such as methylene chloride or trichloroethylene.

Some chemicals are made intentionally to cause respiratory irritation. The most common lacrimating agents, known as tear gases (although they are in fact aerosol-dispersed chemicals), used in riot control operations or as personal anti-harassment weapons, are *ortho*-chlorobenzylidene malononitrile (CS) and 2-chloroacetophenone (CN). The action of these agents is usually short-lived and limited to the mucous membranes of the eyes and upper respiratory tract, but their use in confined spaces (e.g. prison cells) may lead to more serious lung damage. Lung-damaging chemical warfare agents include the choking agents (chlorine, phosgene, diphosgene, and chloropicrin) and the vesicants (or blister agents). Mustard gas (sulphur mustard) caused severe bronchopulmonary damage in soldiers during the Iran–Iraq war (Willems 1989).

Exposure to organic solvents is only rarely a cause of toxic pneumonitis. However, acute exposure to very high concentrations of solvent vapours in confined spaces (e.g. in chemical tanks) may be a cause of chemical pneumonitis and pulmonary oedema, often in victims who have been unconscious. Pneumonia and respiratory distress syndrome caused by loss of alveolar surfactant may also result from the aspiration of intentionally (e.g. by "fire eaters") or unintentionally (e.g. from siphoning petrol) ingested solvents or fuels.

A special mention should also be given to cases of severe acute respiratory illness caused, generally in the domestic environment, by acute exposure in confined spaces to fluorocarbon-containing water-proofing sprays and leather conditioners (Burkhart 1996).

Some agrichemicals may cause toxic pneumonitis after non-inhalatory exposure. The best known of these agents is the herbicide paraquat, which exerts a selective toxicity for the pulmonary epithelium

and causes either multi-organ failure or a delayed pulmonary fibrosis, depending on the dose, after ingestion or, more rarely, after dermal exposure (Bismuth 1995). Poisoning by cholinesterase inhibitors, such as the organophosphate or carbamate insecticides, is also associated with significant respiratory symptoms such as bronchospasm, bronchorrhea, respiratory depression and sometimes also (delayed) pulmonary oedema (Tsao 1990).

2.3.4.2 Metallic Compounds

In general, the principles governing the site and type of damage caused by inhaled agents also apply to metallic compounds, many of which may cause lung injury (Nemery 1990). Metallic compounds may be inhaled as fumes (i.e. generally as oxides), very fine particles or as salts. It is important to realize that many metals also exert their toxicity in non-pulmonary organs.

Cadmium-pneumonitis is perhaps the best-documented example of metal-induced acute pneumonitis, and accidental cases still occur. Cadmium is a by-product of the zinc and lead industry. It is used in metal plating and in special alloys, as well as in the production of batteries, pigments and plastic stabilizers. From a practical point of view, it is important to be aware that cadmium may be liberated, often unknowingly to the worker, from the welding or burning of cadmium-containing alloys and cadmium-plated metal, from the use of hard solders or from the smelting of zinc or lead (or scrap metal), which often contain significant levels of contaminating cadmium. As with other pneumotoxic agents, exposure to toxic levels of cadmium fumes does not necessarily lead to immediate respiratory symptoms, but symptoms of pneumonitis may start many hours after the exposure. Severe chemical pneumonitis may also result from exposure to high levels of mercury vapours. Several fatalities or severe pulmonary involvement have been reported as a result of the refining of gold or silver (using amalgams) in confined spaces.

The embolization of droplets of metallic mercury in the pulmonary circulation following the deliberate injection or accidental inoculation of mercury leads to a peculiar pattern of small very radiodense dots on the chest radiograph. This condition does not appear to be associated with either pulmonary or systemic manifestations of disease.

Vanadium pentoxide (V_2O_5) may be present in significant quantities in slags from the steel industry (ferrovanadium) and, because some fuel oils contain high quantities of vanadium, in furnace residues from oil refineries or in soot from oil-fired boilers. Dust containing V_2O_5 may cause upper and lower airway irritation: rhinitis with sneezing and nosebleeds, pharyngitis, acute tracheobronchitis with cough, wheeze and (possibly) airway hyperreactivity ("boilermakers' bronchitis"), as well as possibly bronchopneumonia.

The older literature also indicates that exposure to high levels of oxides of beryllium, cobalt, manganese and osmium may cause airway irritation and even bronchopneumonia. However, new technologies, such as those involving the thermal spraying of metals, may also prove to be particularly hazardous.

Cases of ARDS, some with a protracted course, have been reported in military or civilian personnel accidentally exposed to smoke bombs that liberate zinc chloride ($ZnC1_2$).

Accidental exposure, e.g. as a result of explosions, burst pipes or leaks in chemical plants, to antimony trichloride ($SbCl_3$) and pentachloride ($SbCl_5$), zirconium tetrachloride ($ZrCl_4$), titanium tetrachloride ($TiCl_4$) and uranium hexafluoride (UF_6), may also lead to severe and even fatal inhalation injury. Nickel carbonyl [$Ni(CO)_4$] is a volatile liquid of very high toxicity for the lungs and brain. Lithium hydride (LiH), phosphine (hydrogen phosphide, PH_3, used as a doping agent for the manufacture of silicon crystals, or released from aluminium phosphide grain fumigants or zinc phosphide rodenticides), hydrogen selenide (SeH_3) and diborane (B_2H_5, used as high energy fuel) have also been reported to cause acute inhalation injury with, possibly, pulmonary oedema (Cordasco 1973).

2.3.4.3 Complex Mixtures

Probably one of the commonest causes of toxic pneumonitis is smoke inhalation caused by domestic, industrial or other fires. Respiratory morbidity is often the major complication in burn victims. It may be caused by direct thermal injury (particularly if hot vapours have been inhaled), but more generally the lesions are caused by chemical injury (Loke 2000). The composition of smoke is highly complex and variable, depending on the materials that are involved and the stages of the fire. The toxic components of smoke are numerous and involve gaseous asphyxiants (CO, HCN) and irritants, as well as particulates. Of particular concern are conditions

that involve the burning or pyrolysis (e.g. caused by overheating) of plastics, such as polyurethanes, polyacrylates and other polymers that are known to give off numerous, generally poorly characterized but potentially highly toxic chemicals.

2.3.5 Pathology of Toxic Pneumonitis and the Issue of "Organizing Pneumonia"

The pathology of acute toxic pneumonitis is that of diffuse alveolar damage with epithelial disruption, interstitial and alveolar oedema, haemorrhage and formation of hyaline membranes and, depending on the stage of the lesions, varying degrees of infiltration by polymorphonuclear leukocytes, hyperplasia of the alveolar and bronchiolar epithelium and interstitial or intra-alveolar fibrosis. Understandably, only few human pathology reports of acute toxic pneumonitis are available, except from autopsies of the most fulminant cases.

One of the difficult issues is that of chemical-induced organizing pneumonia (OP) or (BO)OP (bronchiolitis obliterans organizing pneumonia), as it is called by some. This entity, which has fairly distinct clinical, functional and radiological features (Cordier 2000) essentially consists pathologically of the presence of (polyps of) granulation tissue in the bronchiolar and alveolar lumen. It is often stated that OP may result as a late or delayed consequence of the inhalation of toxic substances. However, the body of evidence linking toxic exposures to the development of (BO)OP is not very large. Irritant-induced (BO)OP only constitute a minority of the originally described cases of BOOP (Douglas 1994). Almost all published instances of (alleged) irritant-induced (BO)OP have been attributed to single, generally poorly characterized inhalatory exposures. The inhalation of NO_2 is the best-documented cause of bronchiolitis obliterans. Following resolution of the acute pulmonary oedema caused by massive exposure to NO_2, a relapse in the clinical condition may occur after 2–6 weeks with dyspnoea, cough, fine crackles, a radiographic picture of miliary nodular infiltrates, arterial hypoxaemia and a restrictive or mixed impairment, with low diffusion capacity. The site of cellular damage caused by NO_2 is the centriacinar region, and the relapse phase has been attributed to bronchiolar scarring with peribronchiolar and obliterating fibrosis of the bronchioli. It is not clear whether these instances of (BO)OP result from the "normal" repair of a particularly severe form of epithelial injury (i.e. with disruption of the basement membrane) or whether they result from an abnormal pattern of cellular proliferation in this critical region of the lung. Besides NO_2, other agents reported to cause bronchiolitis obliterans in humans have included SO_2 and poorly defined fumes of plastic fires, cleansing agents and trichloroethylene degradation products (phosgene?), as well as cocaine smoking and even mycotoxins. In several of these anecdotal reports, the diagnosis of BO has been inferred mainly from clinical and functional criteria, without the distinct radiological appearance of (BO)OP, let alone its pathological features, and it is not always certain that these are all instances of toxic (BO)OP. In some instances, most notably after inhalation of water-soluble agents (SO_2 and NH_3), the disease appears to consist of a constrictive bronchiolitis obliterans, rather than the "classical" organizing BO.

It could be argued that any severe chemical injury to the epithelium of the bronchiolo-alveolar region has the potential to be followed by organizing pneumonia with obliterating bronchiolitis, which may or may not be so labelled. It follows that in clinical cases of "cryptogenic" organizing pneumonia, one should always evaluate seriously the possibility of an underlying toxic cause for the condition. This is particularly true in view of the occurrence of outbreaks of organizing pneumonia such as the "Ardystil syndrome" (see below).

2.3.6 Possible Sequelae of Acute Inhalation Injury

Following acute inhalation injury, there is often complete recovery. However, this is certainly not always the case. The experience with ARDS caused by aetiologies other than acute inhalation injury suggests that a substantial proportion of patients recover with more or less severe dyspnoea and functional impairment, often a reduced diffusing capacity. However, it is still not well known whether and how frequently pulmonary fibrosis occurs after diffuse lung injury of toxic origin. The possible occurrence of residual lesions in the airways is better documented, even though the evidence is also often based on single instances only. Thus, various chronic sequelae, such as constrictive bronchiolitis, bronchiectases, and other bronchial lesions, such as strictures or

polyps, have been reported to result from acute inhalation injury, depending on the severity of the initial damage and perhaps also depending on treatment modalities, although very little hard data, let alone controlled studies, are available regarding the latter issue.

Moreover, even in the absence of structural sequelae, which may be identified by imaging studies or through bronchoscopy, or in the absence of significant defects in basal spirometry, a state of permanent non-specific bronchial hyperreactivity may be observed. This condition of adult-onset, non-allergic asthma has been named "reactive airways dysfunction syndrome" (RADS) (Brooks 1985, Nemery 1996) and occurs in a number of survivors of (severe) airway injury. The incidence and mechanisms giving rise to post-inhalation asthma and irritant-induced asthma still remain to be elucidated. Recent observations in fire fighters and other personnel involved in rescue operations during and following the collapse of the World Trade Center on 11 September 2001 suggest that RADS may occur in a high proportion of exposed subjects even without the occurrence of clinically serious injury (Banauch 2003, Nemery 2004).

An important, but in practice often neglected, aspect concerns the documentation of the lesions and their severity in victims of inhalation injury. This then leads to difficult medicolegal problems when victims seek compensation, sometimes many months or years after the event. It is, therefore, important that physicians treating victims in the early days after the incident document accurately the clinical condition and all relevant data in these patients. Documentation of the damage by bronchoscopy and high resolution computed tomography may be justified. Repeated measurements of ventilatory function and arterial blood gases must be carried out, and victims of acute inhalation injury should never be discharged without a comprehensive assessment of their pulmonary function.

2.3.7 Subacute Toxic Pneumonitis

The concept of "subacute toxic pneumonitis" is not standard. The term "subacute" is used here to indicate both the pattern of exposure (as is done in toxicology) and the clinical presentation of the disease. Thus, subacute toxic pneumonitis refers to conditions of toxic lung injury in which the onset of the disease is not so sudden as that caused by an accidental exposure, and where the exposure itself consists of repeated peaks or a more prolonged exposure over weeks to months. There are not many published examples of such situations.

The alveolar proteinosis caused by heavy exposure to silica ("acute silico-proteinosis") and possibly by other agents (Blanc 1992) would qualify for this entity. Similarly, some instances of exogenous lipoid pneumonitis seem to correspond well to the concept of subacute toxic pneumonitis. The pulmonary haemorrhagic syndrome associated with exposure to trimellitic anhydride and, possibly, to methylene diphenyl diisocyanate is also a potential form of toxic response; but, in this instance, the role of specific immunological mechanisms is likely.

The Ardystil syndrome represents, hitherto, the most convincing example of occupationally induced organizing pneumonia. This outbreak of severe respiratory disease occurred in 1992 in Spain and involved several workers from factories where textiles were air-sprayed with dyes. Most of the affected workers had worked in a factory named Ardystil, hence the name given to the disease. Six subjects died from the disease over the course of a few months (Moya 1994). A similar, though smaller, outbreak was also reported from Algeria (Ould Kadi 1994). The clinical features of the disease included cough, epistaxis, dyspnoea and chest pain, as well as crackles on auscultation. Radiology showed patchy infiltrates in two-thirds of patients and a micronodular pattern in one-third of the studied patients (Romero 1998). There was a restrictive functional impairment and rapid progression to irreversible respiratory failure, despite corticosteroid treatment, in several patients. The Ardystil syndrome seems to differ from cryptogenic organizing pneumonia with respect to its severity, with a rapidly fatal outcome in several patients and an evolution towards chronic pulmonary fibrosis in others.

Another recently described form of subacute toxic lung injury is "popcorn worker's lung" (Kreiss 2002, Akpinar-Elci 2004). This severe lung disease, characterized as bronchiolitis obliterans, occurred in subjects occupationally exposed to vapours of butter flavouring (containing diacetyl) in factories making microwave popcorn.

These outbreaks of bronchiolar disease make it conceivable that sporadic cases of organizing pneumonia or bronchiolitis obliterans are sometimes also caused by occupational or environmental exposures. It is, therefore, important to remain vigilant when such conditions are diagnosed and always think of the possibility of a toxic aetiology.

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