



RESPIRATORY ALLERGY: CLINICAL ASPECTS

I. L. BERNSTEIN

Division of Immunology, Department of Medicine, University of Cincinnati Medical Center,
231 Bethesda Avenue, M.L. no. 563, Cincinnati, OH 45267, USA

Summary—Human expression of pulmonary disease after exposure to chemicals is highly dependent on the locale and circumstances of the exposure. Most of the information about environmental hazards that is currently available has been obtained from epidemiological investigations. Chemical agents in the workplace have received considerable attention because the workplace is an ideal mini-epidemiological model of air pollution. Many instances of pulmonary immunotoxicology are engendered by adverse reactions to drugs but of necessity these can only be studied on a case-by-case basis. Although the overall expression of pathological processes in the anatomical structures of the respiratory system is limited, many of the clinicopathological features induced by chemicals present with features that are characteristic enough to suggest that several stimulus-response paradigms may be applicable. In this review the immunotoxicological impact of chemicals on the major anatomical components of the lung (the conducting airways, the alveolar, interstitial and capillary compartments, the pleura and the pulmonary vasculature) is considered. The two major classes of hypersensitivity induced in humans by chemicals are those involving IgE humoral and cell-mediated immune responses. Although other isotypic antibodies (IgM, IgG, IgA), as well as complement activation, have been demonstrated after specific types of exposure, the role of these immune components in the pathogenesis of disease does not appear to be of major importance. Chemicals with a special propensity for IgE sensitization and effects on the airways include polyisocyanates, acid anhydrides and platinum salts. Conditions that involve the lung parenchyma are exemplified by hypersensitivity pneumonitis, drug-induced pneumonia and berylliosis.

Introduction

Pulmonary immunotoxicological responses are mediated by toxins, chemicals, drugs, large molecular weight proteins, or infectious agents. There have been reports of a wide spectrum of respiratory disorders after systemic or inhaled exposure to chemical xenobiotics. Among the major clinical disorders that have been recognized are asthma, hypersensitivity pneumonitis, pulmonary infiltrates with eosinophilia, pulmonary oedema and pulmonary fibrosis (Bernstein *et al.*, 1988). Although the overall expression of pathological processes in the respiratory system is limited, many of the clinical pathological features induced by chemicals present with features that are characteristic enough to suggest that several stimulus-response paradigms may be applicable. On the basis of this assumption, this review will consider how the immunotoxicological consequences of chemicals affect the major anatomical components of the lung: (1) the conducting airways; (2) the alveolar, interstitial and capillary compartments; (3) pleura; (4) the pulmonary vasculature.

Pulmonary expression of disease after exposure to chemicals is highly dependent on the locale and

circumstances of the exposure. General exposure to immunotoxicants in both indoor and outdoor environments is of obvious concern (Bates *et al.*, 1990). Some air pollutants may also function as enhancers or immune adjuvants (Molfino *et al.*, 1991; Muranaka *et al.*, 1986). Although it is possible to study the effects of some pollutants in affected patients under controlled laboratory conditions, most of the medical information about environmental hazardous agents has been obtained from long-term epidemiological investigations. Since World War II the immunotoxicological effects of chemical agents in the workplace have received considerable attention (Bernstein, 1992). The work environment is in some respects an ideal mini-epidemiological model of air pollutants. In many situations, the agent and source can be identified, the immune responses can be measured and associations between clinical symptoms can be made during the course of the exposure and after the exposure has concluded. It is not surprising, therefore, that much of our knowledge about human pulmonary immunotoxicology derives from occupational xenobiotics. Finally, many immunotoxicologically induced syndromes occur in relation to medical procedures or treatments. These involve adverse responses to drugs and chemical diagnostic reagents (Bernstein, 1982). The determination of the natural history of and mechanistic approaches to these problems are difficult because these reports are usually anecdotal and the diagnostic evaluations are not characterized in a uniform

Abbreviations: HP = hypersensitivity pneumonitis; LRSS = late respiratory systemic syndrome; MDI = methylene-diphenyl diisocyanate; RADS = reactive airways dysfunction syndrome; TePA = tetrachlorophthalic anhydride; TDI = toluene diisocyanate; TMA = trimellitic anhydride.

manner. Moreover, with few exceptions, very rarely do medical centres manage to accumulate enough cases for prospective approaches to pathogenetic determinants.

There has been significant progress in diagnostic approaches to respiratory allergic diseases (Bernstein, 1993). In the case of airway diseases, serial studies of non-specific bronchial hyperreactivity and peak expiratory flow rate determinations often provide useful information about clinical changes in relationship to exposures. For many chemicals it is possible to perform specific bronchial challenge tests that will define the role of suspected agents. New radiographic techniques, such as lung CAT scans and MRI, have improved the assessment of parenchymal lesions. Bronchoalveolar lavage combined with bronchial biopsies now permit assessment of cell subpopulations which can be classified according to lymphocyte phenotypes and degree of activation (Fabbri *et al.*, 1993). Analysis of these fluids for various cytokines and mediators is now being actively pursued in many research centres. Finally, in addition to routine histochemical techniques, the *in situ* hybridization technique for specific mRNA cytokine immunostaining is a novel adjunct for helping to identify the appropriate cellular components of pulmonary inflammation. Improved humoral and cell-mediated immunoassays are also available to ascertain correlations between antibody responses and clinical manifestations. Finally, applications of sensitive molecular genetic techniques are beginning to emerge. It is anticipated that this methodology will help to define genetic risk factors for developing immunotoxicological diseases of the lung.

Although both short- and long-term toxic effects of chemicals on respiratory tissues are often indistinguishable from the pathological sequelae of hypersensitivity, this discussion will focus primarily on chemicals that induce immunological injury. Nevertheless, it should be appreciated that whether toxic or allergic pathogenetic effects predominate depends directly on the concentration/exposure conditions for many chemicals, and in those cases where there is a narrow dose difference between toxic and allergic responses, clear-cut distinctions between the two cannot always be assured (e.g., pulmonary fibrosis induced by beryllium).

Many chemicals have been associated with respiratory disorders in the workplace (Bernstein, 1992). A relatively small proportion of these have been documented to cause hypersensitivity reactions. Low molecular weight chemicals are also referred to as haptens because they do not confer immunogenicity unless they are conjugated with human endogenous protein carriers to form hapten-protein conjugates. Once this occurs, immunological specificity(ies) may be demonstrated against the hapten, the neoantigen (a new epitope domain in the protein carrier formed after combination with the hapten) or the carrier protein itself. Immunologically induced

pulmonary disease is mediated either by humoral antibody or cellular immunity. The majority of pulmonary hypersensitivity disorders associated with humoral antibody involve specific IgE antibodies although there are special situations where cytotoxic antibodies or immune complexes may play a role.

The conducting airways

Clinical hypersensitivity in these structures is almost always mediated by specific IgE antibodies. The clinical spectrum of symptoms and signs in these organs occurs as a direct result of mediator/cytokines released by interaction of appropriate allergenic epitopes with mast cell-bound specific IgE antibodies.

Upper airways

Investigation of the nose and nasopharynx as major shock organs for chemically induced hypersensitivity responses has not received major attention, despite the fact that allergic rhinitis is a well documented precursor of asthma in several well studied occupational syndromes caused by high molecular weight proteins, including allergy to laboratory animals and bakers' asthma (Bernstein and Malo, 1993). However, careful perusal of the literature reveals that allergic rhinoconjunctivitis is a regular occurrence among acid anhydride and platinum refinery workers with or without asthma (Bernstein and Malo, 1993; Zeiss and Patterson, 1993). In most of these workers, evidence of IgE sensitization can be obtained by either positive prick or *in vitro* tests. Preceding atopy is not necessarily a risk factor for developing this type of hypersensitivity reaction. Recently, in a prospective study of polyisocyanate workers, a very high incidence of nasal symptoms was noted in workers irrespective of the concurrent or subsequent occurrence of asthma. Whether rhinitis is induced by immunological or irritative stimuli remains to be established in this group of workers (D. I. Bernstein, *et al.*, 1993). Clearly, there should be more emphasis on the epidemiology of rhinitis in the workplace, especially in the context of whether it can predict the subsequent occurrence of lower airways disease in sensitized workers.

Lower airways

According to a recent expert consensus, occupational asthma is defined as a disease characterized by variable airflow limitation and/or airways hyperresponsiveness due to causes and conditions attributable to a particular occupational environment and not to stimuli encountered outside the workplace (I. L. Bernstein *et al.*, 1993). Two types of occupational asthma are distinguished by whether they occur after latency periods. The first, with a latency period, encompasses all instances of immunological asthma for which an immunological mechanism has been identified, and includes most high molecular weight agents and some low molecular

weight agents. For some agents causing this type of occupational asthma, evidence for an immunological mechanism is still lacking or may not exist. The second type, without a latency period, is best illustrated by irritant-induced asthma or the reactive airways dysfunction syndrome (RADS) (Brooks *et al.*, 1985). Under certain exposure conditions, immunological and non-immunological asthma may co-exist.

Occupational asthma is the most commonly diagnosed respiratory hypersensitivity disorder. Several current surveys of the incidence of occupational asthma suggest that chemicals account for the majority of new cases.

The classic case of occupationally induced asthma occurs after a variable period of exposure or 'sensitization' to the offending agent during which time the worker is asymptomatic. When clinical sensitization occurs, the worker may first experience immediate symptoms shortly after re-exposure to the chemical. This is most apparent on Mondays after a weekend away from the workplace. In some cases, asthmatic symptoms become noticeable or more severe as exposure becomes more intense during the work week. As symptoms worsen, late-phase asthmatic responses begin to appear. The late-phase response may occur anywhere from 2 to 12 hr after the acute asthmatic response subsides. It is not unusual for some workers with occupational asthma to complain of persistent symptoms at night, and in some cases even after 1 or 2 work-free days. There are also instances of patients without an immediate phase reaction but with a much more severe late clinical response pattern. The terminology for these varied responses recognizes three categories: (a) immediate responders, (b) late responders, and (c) dual responders. Recently, it has been recognized that asthma may persist for long periods of time after removal from exposure (Chan-Yeung *et al.*, 1987). In some cases this may be as long as 4 yr and under these circumstances it is easy to appreciate how easy it might be to overlook the contribution of the earlier occupational exposure.

Polyisocyanates and their prepolymers are responsible for more cases of occupationally related lung disease than any other class of low molecular weight chemical. It is estimated that 5–10% of these workers develop occupational asthma (D. I. Bernstein, 1992). Because of this selectivity in occurrence, it has been assumed generally that allergic sensitization is the underlying pathogenetic mechanism. This is not always the case but when it does occur, there is considerable variation among individual polyisocyanate compounds. Only about 10–15% of toluene diisocyanate (TDI) workers show evidence of IgE sensitization by *in vitro* tests. On the other hand, a majority of symptomatic TDI workers have evidence of cell-mediated immunity, as manifested by TDI-specific lymphocyte proliferation and cytokine assays (Gallagher *et al.*, 1981). Recently, broncho-

alveolar lavage studies in symptomatic TDI workers have revealed the presence of TDI specific CD8⁺ cells (Bentley *et al.*, 1992). The significance of these findings remains to be elucidated but the preliminary interpretation is that local or systemic T cell-derived regulatory factors may ultimately determine whether IgE sensitization develops in certain workers. This variability in the generation of immune responses is also observed in workers exposed to other diisocyanate compounds. In our experience, workers with hexamethylene diisocyanate-induced asthma tend to show positive specific IgE *in vitro* tests more often than TDI-induced asthmatics. On the other hand, methylenediphenyl diisocyanate (MDI) asymptomatic workers often show high levels of specific IgG antibodies (Lushniak *et al.*, 1990). These have been interpreted as biomarkers of exposure but the possibility of protective functions cannot be ruled out completely. Asthma in the latter group of workers appears to occur more often in relation to unforeseen spills and in some situations after skin contact with MDI, even though respirable levels of MDI are well below acceptable threshold limits (D. I. Bernstein *et al.*, 1993). The latter observation in our centre suggests that respiratory sensitization may occur by way of the skin route of exposure. Because of the wide array of immunological findings and disparate experiences among investigators, it is apparent that the immunopathogenesis of polyisocyanate-induced asthma will require long-term longitudinal studies in both asymptomatic and symptomatic workers exposed to the compounds. It should also be emphasized that polyisocyanates may induce non-immunological asthma such as RADS. In rare cases after large spills, bronchiolitis obliterans has been reported.

A significant number of workers exposed to acid anhydrides [i.e. phthalic anhydride, trimellitic anhydride (TMA), himic anhydride, hexahydrophthalic anhydride and tetrachlorophthalic anhydride (TCPA)] develop asthma (Zeiss and Patterson, 1993). Specific IgE antibodies have been demonstrated in a majority of these workers. These IgE-mediated reactions have been demonstrated against both the hapten and the newly formed antigen determinants (neoantigens) (D. I. Bernstein *et al.*, 1984). Increased IgG levels have also been reported in some cases and in one study, elevated IgG₄ levels were thought to be involved in the immunopathogenesis of occupational asthma (Nielsen *et al.*, 1988). Some workers exposed to TMA may develop atypical syndromes. One of these has been termed the late respiratory systemic syndrome (LRSS). Chest discomfort begins 4–12 hr after exposure and is associated with productive cough, fever, chills and arthralgias/myalgias. Four workers exposed to extremely high concentrations of TMA developed dyspnoea and haemoptysis which were associated with pulmonary infiltrates and anaemia. IgG and IgA antibodies were demonstrated in the LRSS syndrome while total antibody levels

were elevated in the pulmonary disease-anaemia syndrome. A prospective study of T CPA-specific IgE antibodies in workers with T CPA-induced asthma suggested that IgE sensitization and asthma were more likely to occur in atopic patients.

Airway diseases induced by platinum salts have been investigated intensively with general agreement that IgE-mediated mechanisms are paramount (Bernstein and Brooks, 1993). Prick test reactivity to chlorinated platinum salts can be detected directly with a platinum salt solution alone without conjugation to a protein carrier. Reactivity has been observed at concentrations as low as 10^{-9} g/ml. The specificity of skin-test reactivity has been corroborated by *in vitro* tests. The risk of sensitization in platinum workers is increased 1.3 times per $1 \mu\text{g}/\text{m}^3$ increment in the ambient concentration of platinum dust. There was a significant correlation between positive prick tests and upper/lower airways symptoms. Previous atopic status was not a risk factor but cigarette smoking was strongly associated with positive skin tests and clinical symptoms. Almost all human respiratory allergic responses to platinum occur only after exposure to chlorinated platinum salts which are the major end-products of the refining process. Since workers are exposed to higher concentrations of chlorine gas during the manufacturing process, it is postulated that the chlorine gas could enhance the sensitization response. Analogous interactions between ozone and platinum salts have been demonstrated in subhuman primates (Biagini *et al.*, 1986).

Several other notable examples of IgE sensitization and subsequent airway involvement induced by chemicals have been documented (Malo and Bernstein, 1993). Sulfonechloramide, an antibacterial used in the brewing industry, induces IgE-mediated asthma. Skin reactivity to this agent may be detected by testing with the agent alone without conjugation to protein. About 30% of workers with asthma induced by exposure to Western red cedar demonstrate specific IgE antibodies to plicatic acid. IgE-mediated respiratory hypersensitivity of the conducting airways has been reported and confirmed in workers exposed to antibiotics, azoreactive dyes and several transitional metallic salts.

Airways responses to IgE systemic reactions

The life-threatening sequelae of anaphylactic reactions occurring after ingestion or injection of drugs may involve any or all of the airway conducting pathways. The most dreaded complication is laryngeal oedema which is responsible for the majority of deaths (I. L. Bernstein, 1982). Symptoms of rhinitis frequently precede laryngeal oedema and often wheezing supervenes. The major causes of drug-induced anaphylaxis of the airways are penicillin and its analogues. Fortunately, reliable skin tests are available for detection and prevention of these

reactions. Skin tests are not available for the vast majority of drugs that induce anaphylaxis.

Alveolar, interstitial and capillary compartments

Alveolitis

Extrinsic allergic alveolitis or hypersensitivity pneumonitis (HP) was first described in farmers after exposure to thermophilic actinomycetes (Pepys, 1969). The majority of cases occur after exposure to organic dust but specific chemicals and drugs may also induce the characteristic pathological lesions, which are diffuse inflammation and pneumonitis of the interstitium, alveoli and terminal bronchioles. Although types of HP induced by organic dust may exist in chronic form, the lesions induced by chemicals and drugs are either acute or subacute. Chest X-rays may be normal, or show fine nodular densities or large peripheral lung infiltrates. Bronchoalveolar lavage is an important diagnostic adjunct. The cell count consists predominantly of activated lymphocytes, the chief phenotype of which is a CD8⁺ suppressor type cell. This syndrome has been reported after exposure and sensitization to TDI, MDI and a quaternary amine (Bernstein *et al.*, 1993; Blake *et al.*, 1965; Malo and Zeiss, 1982). Precipitating antibodies have been detected in cases of HP due to MDI (Zeiss *et al.*, 1980). Many drugs (e.g. gold, non-steroidal anti-inflammatory drugs, penicillamine, trimethoprim, sulfasalazine and amiodarone) have been reported to cause HP. In the case of drugs, alveolar infiltrates often are composed exclusively of eosinophiles and this may also be associated with eosinophilia.

Alveolar haemorrhage

Pulmonary haemorrhage in association with haemolytic anaemia has been reported in four men who were exposed to very high doses of trimellitic anhydride (Zeiss and Patterson, 1993). The immunological basis of this syndrome was established by the presence of increased total antibody. It is postulated that cytotoxic anti-lung antibodies produced the brisk alveolar haemorrhage. A rat model of this disease demonstrated a significant linear relationship between the antibody concentration and the degree of pulmonary haemorrhage. A pulmonary syndrome similar to Goodpasture's syndrome has been observed in a few patients on penicillamine drug therapy (Sternlieb *et al.*, 1975). These patients developed severe haemoptysis, haematuria and uraemia.

Alveolar oedema

Many commonly used drugs have been reported to cause non-cardiogenic pulmonary oedema (Cooper *et al.*, 1986). Among these are aspirin, lidocaine, nitrofurantoin, hydrochlorothiazide, terbutaline and several of the opiates. Although the cause of this condition is unknown, one theory is that capillary

leakage is secondary to endothelial damage caused by complement activation. For example, heroin addicts with pulmonary oedema have been shown to have a significant reduction in serum IgM (Smith *et al.*, 1975). This immunoglobulin and complement can be detected in the lungs of some of these patients. Lung sequestration of polymorphonuclear leucocytes may also play a role.

Granulomatosis and fibrosis

The chief chemical exposure that exemplifies these manifestations of lung pathology is berylliosis (Kriebel *et al.*, 1988). Acute berylliosis occurs after unusually heavy exposure and may lead to chemical pneumonitis. However, once the exposure subsides, these lung lesions disappear and there are few permanent residual effects. However, chronic exposure to beryllium leading to lung disease is associated with an immune pathogenesis. Symptomatic workers show delayed hypersensitivity reactions on skin tests and also evidence of specific lymphocyte sensitization as indexed by lymphocyte proliferation. In addition, bronchoalveolar lavage studies reveal large increases in activated MHC class II restricted CD4⁺ cells. The characteristic lung changes in chronic berylliosis reveal a diffuse interstitial infiltration of mononuclear cells with or without non-caseating granulomata. Lung nodularity is observed in many cases. As the disease progresses, interstitial fibrosis supervenes and diffusing capacity is markedly reduced. Recently, it has been shown that the occurrence of the chronic disease is disproportionately higher in workers with a characteristic HLA profile [i.e. HLA-DPb₁, GLU 69 (Richeldi *et al.*, 1993)].

The pleura

Effusion

Effusions may be observed in patients who develop non-cardiogenic pulmonary oedema (Cooper *et al.*, 1986). Those drugs that are prone to induce a lupus syndrome may also have the potential to involve the lung and pleura. Chief drugs among this group are hydralazine, procainamide, penicillin, sulfa analogues, hydantoin and isoniazid. The incidence of pleural involvement may be much higher in cases of drug-induced than idiopathic lupus.

Fibrosis

Cytotoxic drugs may also cause both pleural and lung fibrosis by several toxic pathways. Non-cytotoxic drugs such as methysergide and hexamethonium are rare causes of pleural fibrosis (I. L. Bernstein, 1982). In these instances it is not known whether immunological factors are involved. Drugs such as methotrexate, nitrofurantoin and procabazine may cause both interstitial lung and pleural fibrosis on a hypersensitivity basis.

The lung vasculature

This involves both systemic and pulmonary circuits. Anaphylactic reactions may release cardiogenic mediators (e.g. LTC₄) with direct toxicity to the myocardium, resulting in arrhythmias, cardiac failure and pulmonary hypertension. The shock associated with anaphylaxis also leads to a decrease in perfusion of both the pulmonary and bronchial circulatory systems. Chemicals or drugs that affect endothelial integrity will also have a profound effect on the pulmonary vasculature. Some drugs are thought to cause non-cardiogenic oedema by lowering the intravascular colloid osmotic pressure, the consequence of which would be systemic and pulmonary capillary leakage. Vasculitis of pulmonary vessels has been attributed to nitrofurantoin, hydralazine, sulfa derivatives and penicillin (Cooper *et al.*, 1986).

Treatment and prevention

Long-term surveillance of ambient exposure levels in the work place and the monitoring of the health of workers by periodic examinations are the best approaches for preventing the occurrence of pulmonary diseases in workers. Modification of the general environment to prevent exposure is much more difficult, but the success of recent efforts to limit cigarette smoking as a passive indoor exposure agent in the United States indicates that the future good health of our citizens mandates such government intervention. In the United States, curtailment of ozone pollution should also be an attainable goal in the near future. Iatrogenic diseases induced by drugs that physicians prescribe are much more difficult to control but education and the availability of new diagnostic reagents should help to prevent many of the untoward pulmonary complications of drug hypersensitivity.

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