dependent cobalt-induced mast cell degranulation, although this does not provide definite proof for the involvement of these antibodies in the pathogenesis of this asthma.

Cobalt has also been shown to be a skin sensitizer, and lymphocyte sensitization had been demonstrated in patients with cobalt dermatitis by means of patch tests and in vitro lymphocyte stimulation tests. This provides a potential immunologic basis for cobalt-induced fibrosing alveolitis, a hypothesis which is also supported by the occasional occurrence of cobalt eczema and positive patch tests in such patients. However, several pathologic features argue against an underlying delayed-type hypersensitivity: epithelioid cell granulomas and lymphocytic infiltration, which are found in hypersensitivity pneumonitis, have not been seen in most biopsies, while very unusual multinucleated giant cells are characteristically present.

Alternatively, a model of a nonimmunologic mechanism can be proposed in which a high susceptibility of macrophages to cobalt activation or a high reactivity of the target cells to macrophage-derived mediators such as chemotactic factors, interleukin-1, fibronectin, leukotrienes, prostaglandin-F₂α, and platelet-activating factor play a key role. Release of such substances might explain both early and late asthmatic responses, development of airway hyperresponsiveness, neutrophil infiltration after challenge, and fibrosis on chronic exposure.

From all this it is apparent that the pathogenesis of cobalt-induced asthma and fibrosing alveolitis is not yet completely unravelled. However, the report by Shirakawa et al evidences the possible involvement of an IgE-mediated mechanism, and it warrants further work in search of an immunologic basis of cobalt-induced pulmonary diseases.

Maurits Demedts, M.D., F.C.C.P.; and Jan L. Ceuppens, M.D.
Leuven, Belgium

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Bronchoalveolar Lavage Lipids in Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) (synonym: cryptogenic fibrosing alveolitis) is a disorder characterized by progressive dyspnea, infiltrates noted on chest radiograph, restrictive pulmonary dysfunction, and gas exchange abnormalities. The pathogenesis remains unclear, though events such as lung cell injury due to direct insult, oxygen radicals, inflammatory cell enzyme release and alterations in the immune system, have been implicated. A particular problem has been the identification of markers useful as prognostic and therapeutic guides. Bronchoalveolar lavage (BAL) lavage cell and fluid analyses have received widespread attention in this regard. Changes in the amounts and patterns of BAL immune cells and fluid constituents have been described.

Alveolar epithelial cell injury with associated type 2 cell hyperplasia and alveolar re-epithelialization is a central feature of IPF. Similar observations have been made in a number of animal models of interstitial fibrosis and suggest the importance of rapid alveolar repair if interstitial fibrosis is to be prevented. Analyses of BAL serum proteins, urea or other tracers introduced into the lung or circulation can be useful in assessing the permeability of the alveolar epithelium. An additional key function of alveolar type II cells is to produce pulmonary surfactant, a complex group of lipids and glycoproteins that is responsible for maintaining low surface tension at the air-epithelial

Department of Pathophysiology, Catholic University of Leuven.
Reprint requests: Dr. Demedts, Universiteit Ziekenhuis, Kareldeerplein 1, 3000 Leuven, Belgium 83001
cell interface. Changes in component phospholipids such as disaturated phosphatidylcholine (DSPC), phosphatidylglycerol (PG) and phosphatidylinositol (PI) in BAL fluids have been described in a number of animal models of rapidly developing pulmonary fibrosis, as well as in patients with ARDS. Decreases in the proportions of PG (percentage of phospholipid) and the PG/PI ratio often are observed. Such changes likely reflect altered alveolar type 2 cell function in terms of injury and/or the re-epithelialization process.

The article by Hughes and Haslam in this issue (see page 82), as well as the recent studies of Robinson et al, are promising with regard to the usefulness of analyses of surfactant lipids to understanding IPF. Hughes and Haslam report that the percentage of PG in BAL fluids recovered from many IPF patients was low compared to control subjects, with no changes in phospholipid recovery or percentage of PI. Pretherapy percentage of PG did not predict response to prednisolone, but followup studies indicated that an early and maintained increase in the percentage of PG following therapy was associated with clinical improvement, defined by improvement in FVC, UC/1LO radiographic perfusion score and breathlessness grade (MRC four-point scale). Robinson et al report decreased BAL phospholipid in IPF patients. They also found a fall in the percentage of PG, a rise in percentage of PI and hence a fall in the PG/PI ratio. More normal initial phospholipid recovery was associated with alveolar septal inflammation; while the initial PG/PI ratio was lowest in patients with histologically advanced fibrosis with relatively lesser cellularity, it correlated negatively with the degree of radiographic abnormality. Corticosteroids, known to increase surfactant production, increased phospholipid recovery, though this did not always lead to clinical improvement, defined by a composite clinical-radiographic-physiologic (CRP) scoring system. Clinical improvement correlated positively with pretreatment phospholipid recovery, but not with PG/PI. Thus, more normal lavage phospholipid recoveries were associated with positive outcome.

Further studies are required to interpret differences between the studies in phospholipid profiles, their uniqueness of changes to IPF, and their clinical significance. The resemblance of results to those from studies of animal models of fibrosis, ARDS and also fetal development provides an important framework for interpretation. Determining how such alterations affect surface activity and hence lung function will be an important undertaking, as will be studies to determine if there are changes in other surfactant components. As well, the immunosuppressive activities of surfactant phospholipids must be factored into our understanding of the role of altered immune function in IPF, in the context of alterations in the phospholipid profile.

In any case, the findings of altered BAL phospholipids in IPF identify an important new approach that doubtless will improve our understanding of alveolar epithelial cell function in the disease, and provide important guidance for prognosis, as well as the investigation and application of proper management.

Robert B. Low, Ph.D.
Burlington, Vermont

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