Alveolar Proteinosis and the Overfed Macrophage

In a now classic article, Rosen and associates\textsuperscript{1} described an alveolar filling disease which they named pulmonary alveolar proteinosis. This disorder is of unknown origin and usually occurs as a primary process, although it may also be seen in association with hematologic neoplasms.\textsuperscript{2} In alveolar proteinosis the distal air spaces become filled with a lipoproteinaceous material that has chemical properties similar to surfactant, although the material does not usually have surface-tension-lowering properties. This lipid-rich material does not elicit a cellular inflammatory response nor often lead to fibrosis. The major effect of alveolar proteinosis is interference with the exchange of gases and an impaired pulmonary defense against microorganisms.

There have been many theories on the pathogenesis of this disorder. Although the data are inconclusive, it is probable that overproduction of surfactant by the type-2 cell (granular pneumocyte) is the primary pathogenetic event.\textsuperscript{3,4} Others have believed that the underlying cause is defective clearance of surfactant by alveolar macrophages.\textsuperscript{5} Indeed, there is evidence that the alveolar macrophages are abnormal in this disorder; however, it seems that the defect is secondary to the overingestion of the surfactant-like material.

There are few documented acquired disorders of human macrophages. In this issue (see page 156), Harris provides compelling evidence for abnormal function of the pulmonary macrophages in alveolar proteinosis. Golde et al\textsuperscript{6} have previously reported that pulmonary macrophages from three patients with alveolar proteinosis manifested decreased adherence, chemotaxis, and candidacidal activity in vitro. Harris has now demonstrated a defect in bacterial phagocytosis and killing. These defects in the function of alveolar macrophages may be correlated with the high incidence of exotic infections seen in patients with alveolar proteinosis; for example, nocardiosis is a rare disease that is seen with high frequency in patients with alveolar proteinosis.\textsuperscript{7} Infections with Aspergillus and Cryptococcus are also unusually common. It is tempting to speculate that the reduced host defenses of the lung in alveolar proteinosis are at least in part due to the impaired function of the macrophages observed in vitro.

The question may be raised whether the dysfunction of the pulmonary macrophages is a secondary feature of the disease or whether the impaired function is primary to the pathogenesis of the syndrome. Several lines of evidence imply that the defect in the function of the macrophages is secondary to the overingestion of the surfactant-like material. The fact that the disease is acquired suggests that a stimulus to overproduction of surfactant is more likely than a postulated metabolic defect of the macrophage. Also, the monocytes in the peripheral blood of these patients appear to function normally, and normal alveolar macrophages exposed to the lipoproteinaceous material in vitro develop the striking morphologic structure of macrophages lavaged directly from patients with alveolar proteinosis.\textsuperscript{8} Pulmonary macrophages from patients with the disease contain abundant cytoplasmic lamellar bodies morphologically identical to those seen in type-2 pneumocyttes. It seems that the macrophages gallantly scamper about, ingestion (and attempting to clear) the lipoproteinaceous material, until they become bloated. The phagocytic load leads to the formation of giant phagolysosomes and depletion of lysosomal enzymes. At this point, the macrophages are no longer able to function effectively as the primary cell involved in the defense of the host against microorganisms.

A parallel to this situation may be seen in patients with chronic myelogenous leukemia and related myeloproliferative disorders. In some of these individuals, macrophages with the morphologic characteristics of Gaucher's cells may be seen in the bone marrow and spleen. In this circumstance the macrophages do not have the enzymatic deficiency of Gaucher's disease, but rather they are overburdened by the need to phagocytose and sequester the large amount of cellular material resulting from the overproduction and destruction of mature hematopoietic cells in the bone marrow and spleen.
The disease of pulmonary alveolar proteinosis provides an important and unique example of an acquired defect of tissue macrophages in man. There are many unanswered questions regarding the pathogenesis of this disorder; however, it seems clear that the overfed pulmonary macrophage is lethargic and functionally impaired.

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"Routine"
A Practice to be Abjured

Early in our medical training, we are taught the value of a systematic approach to solving problems. Often this takes the form of algorithms or logic trees, the climbing of which should lead to the correct diagnosis. One unfortunate aspect of this process is the formulation of standard operating procedures or routines, which come to supplant active thoughtful evaluation of each case on its own merits.

In this issue (see page 140), Kvale and colleagues report the low productivity and substantial costs entailed in the routine culturing for mycobacteria on nearly all bronchoscopic specimens in their institution. They suitably emphasize the point that topically administered anesthetic agents suppress mycobacterial growth and thereby reduce the probability of recovering the organisms at bronchoscopic examination. In this regard, it should be noted that as much as 96 percent of the bronchoscopic aspirate consists of topical anesthetic. Despite this microbial inhibition, the cases of Kvale et al, as well as the experience of others, demonstrate that it is possible to recover Mycobacterium tuberculosis from bronchial washings at bronchoscopic examination. In certain patients, from whom it is difficult to obtain the secretions from the lower respiratory tract that are appropriate for mycobacterial studies, this technique may be the only way to recover the microbe. Thus, if tuberculosis is a reasonably probable (admittedly a vague term, related to the notion of clinical judgment) element in the differential diagnosis and if other less invasive procedures have not yielded a diagnosis, bronchoscopic examination might be performed and cultures obtained, heeding the caveat of Kvale et al to minimize the concentration of anesthetic in the aspirate.

In general, the practice of performing a bronchoscopic procedure to establish the diagnosis of suspected tuberculosis should be discouraged. Certainly in the great majority of patients, evidence adequate to support the diagnosis may be acquired using less invasive, less hazardous, and less expensive methods such as induction of sputum, gastric aspiration, or transtracheal aspiration.

Although the prevalence of tuberculosis in the United States is declining, there were nearly 30,000 new cases reported to the Center for Disease Control in 1978. Tuberculosis still merits a prominent role in the differential diagnosis of unknown pulmonary disease; however, rather than "routinely" culturing "all bronchoscopic washings," a systematic approach to solving this problem should take the form of a checklist. If, on a review of the checklist before endoscopic examination, there is a reasonable likelihood of tuberculosis, obtain the cultures. If not, routine culturing should not be done; it is part of our professional responsibility to exercise this judgment as one small element in restricting the soaring costs of health care.

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