The Integration of Epidemiology and Fundamental Biology in Occupational Lung Disease*

Thomas A. Neff Lecture

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It is both an honor and a source of sadness that I present this first Thomas A. Neff Lecture. Tom had the primary attributes of the academic chest physician—he was a fine and dedicated teacher, and a caring, highly competent practitioner of his specialty. I also have it from someone who should know that he was a favorite of the fellows. At a time when specialty medicine needs more Tom Neffs, these skills and personal attributes may become in short supply. Pulmonary medicine will miss Tom!

It is my intent to address three fundamental issues regarding environmental and occupational lung diseases, and for illustration, provide a summary of the evidence obtained from several of our studies of exposed populations. I shall suggest some approaches and hypotheses which can, perhaps, be profitably explored by the fundamental biologist in his/her quest toward a fuller understanding of the mechanisms of disease, and all the potential health benefits which stem from such better understanding.

The issues that I will address include the following: (1) the linkage between lung fibrosis and lung cancer risk—asbestos, possibly other mineral dusts; (2) the relationships and determinants of acute inhalant-induced bronchoconstriction and chronic progressive airways obstruction—occupational asthma and byssinosis; and (3) acute severe deep lung injury and the determinants of long-term respiratory consequences—chlorine and other irritant gases and chemical vapors.

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LUNG FIBROSIS AND LUNG CANCER

Is asbestos a lung carcinogen because of its fibrogenicity? If so, excess lung cancer risk in an exposed population should be restricted to those with asbestosis. In a prospective mortality study of asbestos-cement manufacturing workers, lung cancer risk 20+ years after hire was determined in relation to x-ray category.1 Those with radiographically detectable small opacities (1/0 or greater by the International Labor Organization classification) were assumed to have asbestosis, and were found to have more than a fourfold excess risk of lung cancer (Fig 1). Those with marginal evidence of small opacities (0/1) had a nonsignificant elevation of risk. Former workers with pleural changes only and those without parenchymal or pleural abnormalities, even if they had long duration exposure to asbestos, had no elevation of risk. We concluded that asbestos-attributable lung cancer risk was limited to those with radiographic evidence of asbestosis.

A biologically plausible hypothesis (not necessarily the correct one) linking asbestos-induced fibrosis and lung cancer is provided in Figure 2. Other authors have also pointed to a linkage between these processes. In a published review,2 they stated that “Asbestosis is an inflammatory and fibrotic process of the alveolar structures mediated, at least in part, by cytokines released by ‘activated’ alveolar macrophages—cancer and asbestos is more vexing. The processes of inflammation, fibrosis, and carcinogenesis appear to be closely intertwined. For example, proto-oncogenes such as c-sis [PDGF B-chain] are upregulated in activated alveolar macrophages from fibrotic lungs; these and possibly others may play an important role in asbestos carcinogenesis.” It is clear that further human population data will strengthen the...
hypothesis that asbestos-attributable lung cancer occurs only in the presence of asbestosis (or, more likely, the biological process that leads to lung inflammation and fibrosis), and our cell and molecular biologist colleagues will ultimately provide the "why" of this posited relationship.

**Linkage Between Acute and Chronic Airways Obstruction**

Cotton dust and diisocyanate vapor are both known to cause recurring bronchoconstriction (byssinosis and occupational asthma). In worker populations exposed to these inhalants, my colleagues and I have investigated the potential determining effects of the acute constrictor response and exposure variables on chronic airways obstruction. In a longitudinal study of cotton textile workers, we found byssinosis (airways obstruction exhibiting work week periodicity) and long-term decline in lung function to be dependent on the following: airborne cotton dust concentration, segment of textile manufacturing (yarn production vs later processes), mill (probably related to variation in biological potency of the dust—e.g., grade of cotton or endotoxin contamination), and smoking. In addition, we found that the short and long-term effects of cotton dust exposure are related, and that both exposure and postshift decline in lung function were significant predictors of excess annual decline in lung function (Fig 3). In an earlier study of workers in cottonseed crushing mills, an interaction between cotton dust exposure and atopy occurred in the bronchoconstrictor response.

Toluene diisocyanate (TDI) is the most widely used of the diisocyanates. It is a low molecular weight chemical used to make polyurethane foam, coatings, and other products. It is the most common cause of occupational asthma worldwide, and in an occupationally exposed population, 5 to 10% of exposed workers can be expected to become sensitive, as assessed by work-related symptoms and, when available, a specific inhalation challenge test. Immediate and/or late asthmatic responses are characteristically produced by inhalation challenge testing in reactive individuals. To our knowledge, there is no reliable antibody test for TDI sensitivity, and there is no demonstrated relationship to atopy.

In a 5-year longitudinal study of TDI manufacturing workers, nonsmokers had a dose-dependent excess annual decline in FEV1, even after removing "sensitized" workers who had asthmatic symptoms. The effect of TDI exposure on average annual decline in FEV1 during a 5-year follow-up is shown by smoking category in Figure 4. A dose-dependent excess decline in FEV1 is demonstrated, particularly in nonsmokers, in whom the average annual decrement related to the higher exposure to TDI is comparable in magnitude to the effect of smoking. In another population-based study of polyurethane foam producers (exposed to TDI), longitudinal analysis of lung function showed an exposure-related effect on initial level, but not on annual change in lung function.

In summarizing the relationship between acute and chronic airways obstruction in cotton dust and TDI vapor exposures, both may produce exposure-related short-term bronchoconstriction (byssinosis, asthma), as well as chronic airways obstruction, as indicated by longitudinal annual decline in baseline lung function. There are probably other examples. It is not understood what fundamental mechanism(s) link these temporal patterns of airways narrowing. Nor is it clear whether recurrent variable airways obstruction

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**Figure 3.** Effect of dose, smoking, and acute constrictor response on FEV1 annual decline in yarn manufacturing workers.

**Figure 4.** Effect of TDI exposure on average annual decline in FEV1 (by smoking category; 5-year follow-up).
inevitably leads to fixed, progressive airways disease. More grist for the fundamental biologist’s mill!

**IRRITANT GAS AND CHEMICAL VAPOR EXPOSURES**

Accidental, high-concentration short-term exposures to irritant gases and chemical vapors are usually the result of transportation mishaps or manufacturing malfunctions. The most widely known of the latter cause is the 1984 disaster in Bhopal, India, with a massive discharge of methyl isocyanate from a pesticide plant.⁹ The acute clinical consequences are well recognized, ranging from irritative symptoms of the upper respiratory tract to lethal deep lung injury manifested by pulmonary edema and widespread inflammatory effects of the airways. Despite the devastating consequences that may occur as the result of high-level exposures to such gases as chlorine, ammonia, and phosgene, recovery of respiratory health is the rule rather than the exception. When long-term adverse effects on respiratory health do occur, the mechanisms and determinants of a long-term effect are unclear. Figure 5 illustrates several models of the lung function course that may follow acute inhalation injury. Acute loss of function is detectable by reduction in level of the measured parameter. During a recovery period, this loss of function may be completely regained, or not. The long-term course is then revealed by the slope of the annual change (decline during most adult years) in lung function, which may reflect the expected decline as the consequence of aging, or may be accelerated (excess decline), predicting potential impairment as the result of chronic airways obstruction.

My colleagues and I had the opportunity to study the health consequences of survivors of high-level chlorine exposure consequent to a train derailment and rupture of a tank car containing chlorine. There were eight deaths and the scores of persons who sustained deep lung injury. This single, high-level exposure did not result in long-term adverse respiratory effects, as measured primarily by annual lung function testing (more frequent intervals in the first year) in survivors of the short-term exposure. Surprisingly, proximity to the leak source (the ruptured tank car) or severity of the acute injury did not predict lung function course over the 6-year follow-up. We concluded that, in the survivors of this massive chlorine exposure, long-term adverse consequences to respiratory health did not occur.

Our research group is presently following more than 10,000 chemical workers to assess their lung function after short-term irritant gas exposure episodes. These workers have potential short-term exposures to CI₂ or ClO₂ in ten plants. They are being followed up longitudinally with questionnaires, pulmonary function tests, and exposure information. As of the time of the most recent analyses, 43 had short-term gas exposure episodes with sufficient preexposure and postexposure lung function follow-up for longitudinal analysis (a subset of the 422 workers who had such incidents—see below). After an average of 3.2 years of follow-up, excess annual decline of FEV₁ (in relation to nongassed workers) was found to be 10.2 mL/yr for every 100 mL across-incident (acute) decline. With 4.6 years of follow-up, the excess annual decline per 100 mL acute drop declined to only 4.4 mL/yr, no longer statistically significant and reverting toward normal.¹⁰

We have also investigated the incidence of first-time asthma following short-term irritant gas exposure in this population by questionnaire. From among the more than 10,000 chemical workers who had potential short-term irritant gas exposure episodes, a total of 422 with questionnaire data had such incidents. Only two workers reported new onset of asthma during the 4 years of follow-up after the exposure episode (one after 2 years, the other with reported wheezing and dyspnea prior to the exposure). This extremely low asthma incidence was too small to enable us to assess relative risk in comparison with a nonexposed group, but thus far, our data provide little support for the notion that single irritant exposure episodes lead to the onset of asthma in previously nonasthmatic individuals.¹¹

There has been considerable recent interest in reactive airways dysfunction syndrome (RADS) and irritant-induced asthma. The primary support for the use of these diagnostic terms, which includes the causal inference of exposure to a nonspecific irritant inhalant, comes from case series. The “original” definition of RADS was based on ten cases and included the presence of asthma (nonspecific) following a single short-term high-level exposure to an irritant gas, vapor, or smoke. Initial symptoms developed within minutes or hours of exposure (ie, no latent period) with continuing symptoms and bronchial hyperresponsiveness noted to be present for more than 1 year. Finally, the absence of preexisting respiratory complaints was a requirement of this diagnosis.

The concept of RADS was recently expanded and is now labeled “irritant-induced asthma.”¹³ The bronchial hyperresponsiveness could now be causally associated with multiple exposures that were not necessarily high level. The proposed pathogenesis was that epithelial injury leads to inflammation, which in turn results in nerve injury. There is no invariable relationship with work exposures, and diurnal variation is said to be usually present. The methacholine test is positive. One may reasonably ask: How does this differ from other types of asthma? An alternative view regarding this subject seems appropriate. Asthma and nonspecific bronchial hyperresponsiveness are very common in the general population.¹⁴ When present, intolerance to irritants is a common symptom. There are known specific chemical inducers of asthma—eg, TDI, acid anhydrides. Nonspecific irritants may exacerbate asthmatic symptoms, but there is no credible evidence that they induce the first-time onset of asthma, the condition of recurrent, long-term bronchoconstriction, or variable airways obstruction. To establish this nexus requires prospective assessment of a potentially irritant-exposed population.
that is followed up for development of asthma, not a retrospective collection of cases (or claimants), with its inevitable selection bias.

The observations on humans following short-term irritant inhalation injury leave fundamental questions unanswered, the most important being what determines whether the airways undergo complete recovery, reverting to normal structure and function, or if chronic, either variable (asthma) or progressive (bronchiolitis obliterans), airways obstruction results from the injury. Figure 6 illustrates some possible pathways of the postinjury biological processes.

The development of new knowledge in occupational lung diseases depends on the contribution of multiple disciplines—biologists, epidemiologists, statisticians, and industrial hygienists, to name only a few. Either those in fundamental research or in the investigation of exposure-response relationships in working populations can generate hypotheses that can be tested by the other. My emphasis has been on describing observed relationships in human populations exposed to workplace inhalants, and suggesting approaches by the basic scientist that may confirm and explain some of these relationships. The ultimate public health objective is to prevent or successfully intervene in occupationally related lung disease.

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Beryllium Stimulates Release of T Helper 1 Cytokines Interleukin-2 and Interferon Gamma From BAL Cells in Chronic Beryllium Disease*

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Chronic beryllium disease (CBD) is an occupationally acquired lung disease that begins as a sensitizing cell-mediated immune response to beryllium antigen that, over

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