model with other experimental animal models of acute lung fibrosis, such as that induced by intra-tracheal bleomycin, should also prove interesting. Especially fascinating would be carefully documented comparisons of structure and function of fibrotic lungs containing deposits of collagen in different anatomical areas. We believe that the O₃ model of lung fibrosis will be especially helpful in this regard.

References

Discussion
Dr. Renzetti: Have there been physiologic studies to suggest an obstructive lesion, as one would predict from the localization?

Dr. Cross: There are physiologic studies in animals and in people who show airway effects. The problem is that things are happening in two parts of the lung at the same time, the parenchyma and the peripheral airways, and the physiologic changes haven't been put together as carefully as they could be.

Occupational Lung Diseases
State of the Art

Hans Weill, M.D., F.C.C.P.*

The papers presented in this session illustrate the scope of investigations which are being carried out on the breadth of workplace inhalants and their health effects. A number of these depend upon availability of occupational populations for study. Gaining access to such occupational groups requires convincing both management (and their lawyers), as well as workers (and their unions) that even in this somewhat polarized, regulated and litigious society, it is in their self-interest to participate in such investigations. In this overview, I would like to summarize several examples of how studies of populations exposed to mineral and organic dusts, or chemical gases and vapors, have contributed to our knowledge of both dose-related and non-dose-related determinants of these conditions, and raise some of the questions which remain.

Mineral Dusts

The oldest of the recognized pneumoconioses is silicosis which has for centuries been associated with the dust exposures encountered in hard rock and metal mining, and subsequently in such diverse occupations as foundry and pottery work, tunneling, abrasive soap making, and sandblasting. Recently, there has been a resurgence of interest as the result of the recognition of accelerated silicosis in silica flour mills where finely ground silica produces a high proportion of respirable particles. In addition, a silicosis risk was among the earliest fears following the eruption of Mt. St. Helens; the potential biologic effects of volcano ash are considered elsewhere in this special issue.

Our findings in studies of silicotic sandblasters are concordant with the general view that the primary determinant of silicosis is the dose of free crystalline silica capable of penetrating to the alveolar component. The form of the disease is importantly influenced by airborne concentration and length of exposure, the components of dose. Slowly progressive silicosis can result from a working lifetime of exposure in mining and other occupations where silica dust levels are moderate. Accelerated and acute silicosis have been recognized since the 1930's as the result of abrasive soap making, tunneling and sandblasting where airborne concentrations of fine silica particles are extremely high.

The mechanism of silicosis is probably related to the toxic effect of silica on the macrophage which impairs function and may result in cell death with subsequent release of cellular enzymes. The relationship between enzyme release and stimulation of fibroblasts remains unclear. It has been noted that both autoimmune antibodies and clinical manifestations of such collagen vascular disease as systemic lupus, scleroderma...
and rheumatoid arthritis may be associated (perhaps in as many as 5 percent) in the more aggressive forms of silicosis, such as in the silicotic sandblasters whom we have been following. The significance of such evidence of autoimmunity remains to be elucidated. Finally, it has been our conclusion that abrasive blasting should be performed only with non-silica-containing substitutes such as the coal slag which is now more widely used, particularly in shipbuilding and repair. Work by Heppleston and Morris\(^a\) 15 years ago, however, suggests that hematite (ferric oxide) may, in the animal model, enhance the silicotic effect associated with previous silica exposure. Since the substitutes contain approximately 50 percent ferric oxide, it remains to be shown that such enhancement of previous silica effects does not occur in human exposures, since many of these blasters previously used sand. Additionally, there is some evidence, with further work required, that the substitute itself may be weakly fibrogenic.

The fibrotic and carcinogenic consequences of exposure to asbestos dust are well recognized. The risk is associated with exposure in mining and milling, manufacture of asbestos-containing products, and in the use of these products. Scarring occurs in the lungs and on the pleural surfaces. Malignant effects are primarily respiratory and pleural (mesothelioma) with inconstant findings regarding an excess risk for the development of gastrointestinal neoplasms in exposed populations. Fortunately, it has been demonstrated that both fibrotic and malignant effects of asbestos exposure are dose-related,\(^a\)\(^b\) and indeed more recently that progression of asbestosis (pulmonary fibrosis) is related to both estimates of cumulative dose, as well as average concentrations of airborne asbestos dust.\(^a\) Conversely, the progression of pleural thickening and calcification is related primarily to length of time since first exposure and does not appear to be significantly related to dose, although it seems probable that a critical minimum exposure dose is necessary for the pleural effects to occur. Having said that asbestos and asbestos-related tumors are dose-related, it must be conceded that at present, there is no convincing evidence that this relationship is not linear and the dose of exposure which is free of such effects during the lifetime of a worker is not known.

What are some of the important questions which remain to be answered by scientific inquiry regarding asbestos-related health effects? First, as indicated above, more information concerning the level of risk associated with the low airborne concentrations currently experienced in most segments of this industry must be further examined and because of the latency period of these consequences continuing surveillance of exposed populations is necessary. Low dose effects are discussed in this conference by Devenport. Second, it is likely that different types of asbestos fiber exposure are associated with differing levels of risk. Most investigators believe that the amphiboles (eg, crocidolite and amosite) are more hazardous than chrysotile. Such differing levels of biologic potency seem to be present for both fibrotic and malignant effects\(^a\)\(^b\) and may be related to differing deposition and clearance patterns. The paper by Arnold Brody is of interest in this regard. It has not been fully demonstrated that the asbestos exposure dose required to produce excess risk for a malignant effect also is likely to produce fibrosis, but such may very well be the case.\(^a\) Further work on the relationship between the fibrogenic and carcinogenic effects is needed.

**Organic Dusts**

The paper by de Pico provides an update of information concerning the risk of occupational airways disease in grain workers. There has been an appropriate increase of interest in recent years in the respiratory health consequences of cotton dust exposure, particularly in the textile industry. In the past, attention has been directed to "byssinosis" which is defined by the acute bronchoconstrictor response detected by a characteristic pattern of responses on the questionnaire or by pre- and post-shift ventilatory function testing. Determinants of byssinosis defined in this way include the job in the textile industry (earlier or preparation jobs carrying increased risk), cotton dust dose, and smoking. However, we have demonstrated that residual variability is accounted for by unknown "mill factors" which could include grade of cotton used, level of past dust exposure in the mill, and contamination with microorganisms such as gram-negative bacilli which produce endotoxins.\(^a\) Host factors might increase risk of byssinosis with some evidence that atopy or bronchial hyperresponsiveness may be such determinants.\(^a\)

Of greater importance in regard to public health, which appropriately must focus on conditions likely to produce disabling functional impairment or reduced longevity, are the questions concerning the presence and extent of the risk for development of chronic airways obstruction as a result of cotton dust exposure. Such an effect may very well exist in spite of negative mortality studies, a relatively insensitive way to study chronic airways disease risk. If such an effect occurs, is it dose-related, and what is the dose-response relationship? Of considerable importance is whether the acute bronchoconstrictor response (byssinosis) is a predictor of a chronic effect. These questions will best be answered by a careful longitudinal study which can quantify environmental exposures, the risk of the acute effect and average annual decline in lung function (an excess suggesting a chronic effect), and take into account other possible non-dose-related determinants. Such an investigation will soon be started. Finally, additional work regarding the pathogenesis and etiology of byssinosis and its mechanism is ongoing and undoubtedly will continue for some time. In regard to etiology, endotoxins produced by contaminating microorganisms may be important and are receiving considerable attention. As to mechanism, some investigators feel that an immunologic basis for bronchoconstriction in cotton dust exposures has by no means been excluded. Ultimately, there remains the question of...
whether the acute symptoms collectively called “byssinosis” and perhaps the chronic effect constitute one disease. Certainly, the latter will be importantly influenced by smoking, a confounder which must be taken into account in any longitudinal studies undertaken. (NOTE: For a comprehensive review, see the Chest supplement of the International Conference on Byssinosis (1981; 79:1S-138S).

IRRITANT VAPORS AND GASES

Colin Soutar provides the results of an interesting study of workers exposed to polyvinyl chloride (PVC) dust. Our five-year longitudinal study of workers exposed to toluene diisocyanate (TDI) in its manufacture has recently been concluded. In collaboration with John Salvaggio, we have followed previously non-exposed workers during the first five years of operation in a new manufacturing facility. Comprehensive personal exposure information was obtained through the use of continuous personal TDI monitors and a modest dose-related excess annual decline in expiratory flows was detected in non-smokers. In addition, approximately 5 percent of the exposed population became “reactive” to TDI exposure, manifested by the clinical picture of occupational asthma. Bronchoprovocation confirmed the familiar immediate and late bronchoconstrictor effects of a single exposure in reactive individuals. We found that TDI at certain concentrations acts as a partial agonist on lymphocytes to stimulate cyclic adenosine monophosphate (cAMP) levels. At low concentrations it can block cyclic AMP stimulation by isoproterenol and prostaglandin E₂. Lymphocytes of TDI-sensitive individuals have decreased ability to respond to cyclic AMP stimuli, such as beta agonists. Stuart Brooks at this conference provides further information concerning malfunction of beta receptors in TDI reactivity. We have found that specific IgE measurement (RAST) using p-tolyl isocyanate conjugated to human serum albumin is relatively insensitive in detecting reactors. Finally, some individuals who have become intolerant of TDI exposure apparently continue to have airways functional impairment, even after leaving the exposure. This is consistent with the findings of Moira Chan-Yeung in Vancouver in studies of her Western red cedar-sensitized workers.

However, questions remain concerning the occupational asthma associated with exposure to simple chemicals, first in regard to precise mechanism. Are there differences in TDI effects in manufacturing and urethane foaming? The influence of peak exposures vis-a-vis time-weighted average concentrations requires elucidation, and finally, as with cotton, the relationship, if any, between acute and chronic responses of the airways must be established.

High level single exposures to irritant gases such as chlorine have well recognized devastating acute consequences which include severe damage of the airway mucosa, pulmonary edema, and often death. Survivors of the acute exposure may have bacterial complications which ensue in the post-exposure week or two, and in those who apparently “recover” after such a single high-level exposure there remains the question of whether a longterm effect on respiratory health may result. While in recent years a number of reports have suggested that complete recovery occurs in the survivors, an ongoing longitudinal study of a community population heavily exposed to chlorine gas as the result of a train derailment suggests that after two years, excess annual decline in lung function is occurring, particularly in the smokers. Additional follow-up will determine whether late recovery will occur or chronic airways obstruction is a risk of such exposure. Irritant gas exposure is discussed in the paper of Zamel.

In conclusion, as biomedical investigators working in this field, we have as our primary responsibility the generation of a scientific data base which will lead to the prevention of environmentally-induced disease in the workplace and the general population. To do this, we must also prevent revisionism, by which I mean manipulation, alteration and obscuration of data or misleading analysis and interpretation, often for reasons other than the maintenance of public health. I am indeed hopeful that greater reliance on scientific inquiry to prevent occupational lung disease will prevail in the coming years.

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Pulmonary Reaction to Grain Dust and Its Constituents

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The adverse effects of grain dust on the health of grain handlers has been recognized for centuries. In recent years, epidemiologic studies have demonstrated a high prevalence of respiratory abnormalities among grain handlers and the effects of grain dust appeared to be at least equal and perhaps synergistic with smoking.1-3

Grain dust contains a wide variety of organic components: grain, fungi, bacteria, and endotoxin. The components responsible for the pulmonary reaction and their mechanism of action have not been elucidated. The latter could range from nonspecific irritation to type I or type III allergic reactions.3

In this presentation, we report the results of our cross-sectional epidemiologic study to determine the relative importance of the effects of cigarette smoking and grain handling on symptom prevalence and lung function, and of a study undertaken to identify the constituent of grain dust responsible for grain handlers’ respiratory symptoms and the potential pathogenic role of mediator release and complement activation.

METHODS

We compared respiratory parameters between 310 year-around grain handlers and 239 outside city workers of comparable age, sex, height, weight, and smoking habits who resided and worked in the same geographic area of the United States. The information was obtained by a standard, self-administered questionnaire, by medical examination, and by standard pulmonary function tests performed and measured by recommended methods.4

We performed bronchial provocation challenges using standard procedures,5 with saline extracts of durum wheat, airborne durum wheat dust from grain elevators, grain insects or grain mites, Aspergillus fumigatus and methacholine in 11 grain handlers with symptoms of occupational asthma.

Total serum C3 complement levels were done by the Mancini immunodiffusion technique.6 Activation of C3 by the classic or the alternate pathway was ascertained by immunoelectrophoresis using anti C3 (β1A/β1C) and anti C4 proactivator generously donated by Dr. Goetz, La Jolla, CA.7 Detection of factor Bb fragment (C4 activator) and intact C4 proactivator (C4PA) indicated activator by the alternate pathway. Detection of C8d fragment would indicate activation of C9 by the classic pathway.

RESULTS

Epidemiologic Study

The prevalence of most respiratory symptoms was

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