defects that were mismatched by ventilation scan correlated highly (near 90%) with embolism demonstrated by angiogram, whereas a lesser (but not negligible) frequency of embolism was associated with all other scan patterns. A more extensive presentation of the PIOPED data was made at this meeting; and, as Dr. Saltzman indicated, the extensive data base generated can be better appreciated when the detailed reports are published.

The hemodynamic and gas exchange alterations imposed by pulmonary embolism were reviewed by Dr. David Dantzker. He noted that arterial hypoxemia commonly, but not invariably, follows embolism. There are several potential bases for the hypoxemia, including most prominently ventilation/perfusion disturbances and a widening of the arteriovenous difference (due to a reduction in cardiac output). Hyperventilation is also a characteristic response to acute embolism in animals and man; its physiologic basis is not clearly defined. He noted that the right ventricle is anatomically ill-equipped to overcome major increases in afterload; that is, in pulmonary arterial resistance and pressure. Therefore, with sudden increases in mean pulmonary artery pressure to 40 mm Hg or more, right ventricular failure is the usual consequence. Yet, in chronic pulmonary hypertensive states, compensatory mechanisms (e.g., hypertrophy) may allow higher afterloads to be tolerated without right ventricular failure.

Dr. Samuel Goldhaber reviewed prior data regarding the results with thrombolytic and anticoagulant therapy in acute pulmonary embolism, indicating that the value of thrombolytic therapy remains to be fully defined. He presented the preliminary results of a small trial in acute embolism in which urokinase alone and tissue plasminogen activator alone were given as initial therapy. With both agents, there was significant angiographic resolution of emboli during the first 24 hours. No long-term outcome data were provided. Dr. Goldhaber indicated his view that the efficacy and safety data favored tissue plasminogen activator (tPA) in this series. He noted plans to extend these studies of tPA to a larger, multicenter investigation in the future.

Dr. L. J. Greenfield presented his views of the current status of surgical approaches to the management of venous thromboembolism. He indicated that, over the years, the results with acute surgical embolectomy have been rather unsatisfactory, with a mortality approximating 50%. He reviewed his experience with the use of a transvenous device through which acute emboli can be removed using a distal suction system and suggested this as an alternative to surgical embolectomy in selected cases. He also presented the extensive experience with the use of a percutaneous filter of his design (generally referred to as the Greenfield filter) to prevent embolism from lower extremity venous thrombosis. He noted the low morbidity associated with placement, the high efficacy in prevention of embolic recurrence and the excellent long-term patency experience with the device, which has approximated 95%. Dr. Greenfield reviewed potential indications for filter placement, including the need for protection in patients with venous thrombosis in whom anticoagulant therapy cannot be applied. He further indicated that suprarenal placement had been carried out in more than 50 cases.

Dr. Moser related his group's growing experience with an uncommon entity: chronic, major vessel thromboembolic pulmonary hypertension. He noted that most patients with massive embolism who survive and are treated resolve quite well; but perhaps 0.1% fail to resolve, resulting in this entity. Recognition appears to be increasing because such patients are potentially curable with surgical thromboendarterectomy, a procedure his group has now performed in more than 100 patients. He indicated that the diagnosis is often overlooked for long periods among patients who present with unexplained dyspnea on exertion. The lung scan, demonstrating one or more segmental perfusion defects, often is the central clue to the diagnosis, particularly in differentiating this disorder from primary pulmonary hypertension. Surgical selection criteria, operative approach, postoperative complications and long-term outcome were also discussed. A surgical mortality of 13% was reported; because these mortalities occurred almost exclusively in Class IV NYHA patients, he suggested that earlier recognition should reduce surgical risk. He indicated that among the near-100 surgical survivors, long-term hemodynamic and functional outcomes were excellent, with the majority achieving NYHA Class I status.

In summary, the symposium presented a variety of data that emphasize both residual controversies and the present data base, which guide the current diagnosis and management of venous thromboembolism.

Current Issues in Occupational Lung Disease

Chair: James E. Lockey, Marc B. Schenker
Participants, David G. Howden, Marc J. A. Desmeules, Rodolfo Saracci, Nancy L. Sprince, Philip I. Harber

Respiratory Hazards of Welding: Occupational Exposure Characterization

Welding provides a powerful manufacturing tool for high quality joining of metallic components. Essentially, all metals and alloys can be welded; some with ease, others requiring special precautions.

The high current electric welding was first used for welding at the end of the 19th century. This rapidly became the most efficient method of locally melting the adjacent edges of components to be joined. The welding arc is a high energy density heat source with associated temperatures in the arc plasma on the order of 30,000° C (similar to the surface temperature of the sun). These temperatures, capable of melting all known materials, create ultraviolet, visible, and infrared electromagnetic radiation. In addition, the extreme temperatures lead to superheating of welding consumables and base metals, a situation that liberates vapors into the arc atmosphere.

There are a number of commonly used arc welding processes that are selected based on their suitability for the materials being joined, quality of weld required and process economics. These include gas tungsten arc welding (GTAW), gas metal arc weldings (GMAW), shielded metal arc welding (SMAW), and flux covered arc welding (FCAW). The American Welding Society, Miami, Florida, can provide further information concerning these welding techniques.

Fumes are generated in the arc welding process by evaporation of metals (including alloying elements) and fluxes primarily at the tip of the electrode. These metal vapors are generally oxidized on contact with the air and hence form small particulates of complex metal oxides. In certain flux mixtures, liberal quantities of calcium fluoride are used and encountered in the fume. The hot gases generated by welding are less dense than the surrounding air and rise carrying with them the fine particles of solid fume. This rising column of hot gas and fume is referred to as the "fume plume" and contains high concentrations of both particulates and toxic gases.

Different pure metals evaporate at different rates at a particular elevated temperature depending upon their vapor pressures. Metals that evaporate readily are zinc, magnesium, and cadmium. Others that do not evaporate easily are molybdenum, nickel, and titanium. Most engineering materials are alloys consisting of mixtures of metals as exemplified by steels that may contain manganese, silicon, chromium, molybdenum, nickel, and others. Stainless steels usually contain about 20% chromium and often 10%

nickel. The rates at which these alloying elements evaporate also depend upon their concentration in the steel.

Another source of fume is the coating that may have been applied to the base metals for such purposes as corrosion resistance, oxidation resistance, or decorative purposes. Often these coatings such as paint, electroplated or sprayed, and hot dip coatings may contain elements such as zinc, chromium, aluminum, and mercury. In the event that these coatings are not removed prior to welding, the arc has the capability of volatilizing these agents.

The rate at which fumes are generated by a welding arc is dependent on the process, current level, and the compositions of the wire/flux used as the electrode. Larger current levels give higher fume rates. The presence of a flux generally leads to higher fume rates for a given current.

For GTAW, fume rates are low and for this reason are seldom measured. GMAW produces fumes at about 0.5 g/min as do most of the SMAW electrodes. The GMAW welding of aluminum alloys using an aluminum-magnesium filler wire produces relatively high fume rates due to the relative ease with which magnesium vaporizes. FCAW tends to produce relatively high rates of fume generation which, depending upon welding conditions, may reach 4 g/min.

The significance of high fume generation rates is that, in the absence of good ventilation (preferably local exhaust ventilation close to the arc), general contamination of the environment can occur quickly, particularly with welding in a confined space.

Studies on welding fume have shown particles to be of respirable size with a mean diameter of 0.5 μm. For steel welding fume, particle size distribution does not change with different welding processes nor does the distribution vary appreciably according to chemical species. The chemical composition of steel welding fume depends on the welding process, type of flux, and type of filler metal.

Several toxic gases may be generated in small quantities by the common arc welding processes. Among these are oxides of nitrogen, ozone, carbon monoxide, and phosgene.

Measurements have indicated levels of nitrogen dioxide up to about 7 ppm outside the welding hood during the FCAW process. Levels inside the welding hood were lower (less than 2 ppm) illustrating that the welder's hood may offer some protection to the breathing zone by deflecting the fume plume.

Ozone may also be produced around a welding arc. Ozone, which is an allotrope of oxygen, is generated from oxygen by the photochemical effect of ultraviolet radiation in the arc when certain elements in the arc plasma are excited. Notably, the elements aluminum, silicon, and oxygen have prominent spectral lines in the operative wavelength. Many steels and some nonferrous alloys have small additives of aluminum and silicon and these may cause some generation of ozone. The welding of aluminum, particularly when using the popular aluminum-silicon welding wires for GMAW, is particularly conducive to ozone production.

Carbon monoxide is often encountered during the welding of steel with the SMAW process when electrode coatings contain lime ($CaCO_3$) or with the GMAW process when the shielding gas is carbon dioxide or argon/carbon dioxide mixtures. At the high temperatures in the arc and at the molten metal surface, carbon dioxide is reduced to the more chemically stable carbon monoxide.

Degreasing chemicals (chlorinated hydrocarbons) are often used to ensure cleanliness of the base metals prior to welding. Trichloroethylene is one of the more commonly used agents and has a high vapor pressure at ambient temperature. The airborne vapors around the arc are subject to oxidation in a process that is enhanced by ultraviolet radiation from the welding arc to produce phosgene.

Pulmonary Disease and Welding

Metal fume fever is an acute flu-like syndrome characterized by throat irritation, sweet taste in the mouth, chest tightness, dry cough associated with general malaise, myalgia, fever, and sweating. The symptoms usually appear 6 to 8 h after inhalation of zinc, copper, or magnesium fumes or less frequently with other metal fumes, and resolve spontaneously within 24 h. Whether metal fume fever determines transient changes of pulmonary function remains unclear. No long term sequelae have been documented.

Acute upper or lower respiratory tract infections are slightly increased in terms of severity, duration, and frequency among welders, and excess mortality from pneumonia has been reported. Chemical irritation of the airways epithelium is a suspected but unproven cause of the increased incidence of respiratory infections.

Oxides of nitrogen and ozone can reach toxic level in some welding processes, resulting in acute chemical bronchoalveolitis and pulmonary edema. Bronchiolitis obliterans can be a sequela resulting in progressive respiratory impairment.

Several investigators have examined the prevalence of chronic obstructive lung disease in welders with conflicting results. These surveys are difficult to compare because of differences in study populations, industrial settings, welding techniques, and duration of exposures. Symptoms of chronic bronchitis appear slightly more prevalent among welders compared to controls. In most surveys, where the $FEV_{1.0}$ was measured, no striking effect of welding on airways obstruction could be demonstrated and cigarette smoking remained the main determinant related to chronic airways obstruction. The effects of cigarette smoking appear additive to those of long-term welding.

Occupational asthma may develop as a consequence of certain types of welding. In stainless steel welders, high concentrations of chromium and nickel in the fumes are considered responsible for airway sensitization. Aminoethyl ethanolamine, used in aluminum welding, has been identified as a cause of occupational asthma. Recently, asthma was also reported after soldering galvanized metal. Within the electronics industry, workers may develop a specific respiratory hypersensitivity to colophony used as a soldering flux. The heating of polyurethane-coated wires can liberate toluene diisocyanate, a known cause of occupational asthma.

Much remains unknown about the prevalence of occupational asthma, the role of atopy, the influence of chemical airways irritation on airways reactivity, and the pathophysiologic mechanisms and long-term consequences of asthmatic reactions in welders.

Siderosis in welders was first described in 1936. Iron oxide particles accumulate in alveolar macrophages and lung interstitium as a result of long-term exposure to arc welding fumes in confined places. There is usually little or no fibrosis within the lung parenchyma. On the chest radiograph small, ill-defined rounded opacities predominate. In a series of 27 cases of welders' pneumoconiosis followed for a mean period of 7 years, pulmonary infiltrates regressed in 14, remained stable in 5, and increased in 8. None developed large opacities. Pulmonary function tests revealed mild obstructive abnormalities that did not change significantly and blood gases at rest and exercise remained normal. The majority of welders who develop a pneumoconiosis from welding have siderosis, a benign condition that does not cause any functional respiratory impairment.

There are anecdotal reports in the literature on welders' pneumoconiosis in which conglomerated lesions developed. It is likely that some of these cases represent a mixed-dust pneumoconiosis where silicotic nodules or interstitial fibrosis may be associated with siderosis.

The prevalence of asbestos-related disorders has been surveyed in welders of British naval dockyards. Pleural plaques were present in 10% of the population. Nine percent of welders with pleural changes developed interstitial fibrosis within 10 years. Increased rates of mesothelioma were observed in these welders but the conclusions were derived from a small number of cases and must be interpreted cautiously.

Risk ratios for lung cancer in welders were significantly increased over general population in 9 out of the 22 surveyed epidemiological studies. Inhalation of fumes with a high content of hexavalent chromium generated by stainless steel welding could be responsible for the slight excess risk.

Respirator Use in the Work Environment

Respirators (respiratory personal protective devices) continue to be vital part of the worker protection programs. Although respirators should never be used as a cheap substitute for proper engineering controls, there are certain work situations in which their use is like-

ly to continue to be important. These situations include special maintenance and repair operations, highly variable work environments (e.g., in the construction industry), and management of emergencies (for emergency escape or control of accidental hazardous leaks). Respirators fall into two general categories: air purifying, which filter or chemically adsorb some of the toxic material from the air breathed by the worker, and atmosphere supplying, which provide an independent air source. Atmosphere-supplying respirators may be self-contained (SCBA), may rely upon an external source (airline respirators), or represent a combination. Atmosphere-supplying respirators must be used in particularly toxic atmospheres or those in which the ambient oxygen concentration is low (immediately dangerous to life and health). SCBA devices are quite heavy, and the weight of the device itself imposes a physiologic load that may be greater than that of the respirator itself. The efficacy of respirators is commonly quantified as the protection factor (ratio of the toxic material outside to inside the facepiece). Unfortunately, protection factors measured during simulated exposures may overestimate the actual protection afforded in the worksite. Respirator protection is limited by air leaks into the facepiece as well as by the efficacy of the filtration/adsorption system itself. There is considerable debate in the scientific literature and among regulatory agencies about the proper means of assuring adequate respirator fit. In a qualitative fit test, an irritant smoke or odoriferous material is placed outside the mask of the respirator, and the worker is asked whether he/she can detect it. Quantitative fit testing is considerably more accurate and directly estimates the protection factor for the individual worker.

Several major practical and research questions remain concerning respirator use. First, what factors determine who can safely and effectively utilize respirators? Second, how can adequate protection for the individual worker be assured in view of differences among workers in actual protection afforded and differences among work situations? Third, what is the optimal worker evaluation program? Fourth, what factors determine actual compliance with proper respirator use? Fifth, which design options will maximize worker use of respirators, worker tolerance of respirators, and chemical protection afforded? Sixth, how can an appropriate occupational health surveillance program be established to detect respirator-related problems? The latter is a particularly vexing question since the outcome of adverse respirator-related problems is more difficult to ascertain than the occurrence of bronchogenic carcinoma or abnormal declines in spirometric results.

Several general research approaches have been employed for determining respirator effects. Empiric studies employ actual respirators under laboratory conditions. Many depend upon the use of non-viable mechanically ventilated mannequins, particularly for estimation of protection factors. Early studies have assessed the effect of respirator use on the maximal exertion attainable by young, healthy volunteers; nearly all such studies have shown that there is a decrement in peak attainable exercise. More recently, studies have empirically assessed existing respirators at moderate exertion levels. Such studies have in general shown demonstrable effects upon physiologic parameters, but on the whole have not suggested that mechanical limitation to airflow imposed by the devices should limit healthy and near-healthy individuals at moderate exercise. Studies of impaired individuals have been reported by Hodous and by Raven. Hodous and colleagues have carefully studied a small group of obstructive disease and a small group of restrictive disease patients. Their work suggests that if one considers only ability to perform the ventilatory work, "if a man can do his job without the respirator, he can do it with the respirator."

An additional research technique employed by our group has been the use of respirator surrogates, individually adding single components of respirator respiratory loads (e.g., inspiratory flow resistance, expiratory flow resistance, dead space) alone and in combination under controlled circumstances. While less directly applicable to individual respirator types than the empiric studies, they provide generalizable information about the nature of adaptation. A third category of research includes the empiric studies of respirators in actual worksites (e.g., firefighting). A fourth general approach is studying the combined effects of respirators and other loads. The combination of heat stress with respirator loading may produce particularly adverse physiologic effects. This combined load occurs in many situations in which impermeable clothing is worn in conjunction with respirators (e.g., during asbestos abatement work and in the hazardous materials industries). Fifth, theoretical considerations may be relevant to respirator research; much of the information obtained during experimental physiologic studies with higher level loads may be applicable as well. Sixth, compliance with proper use is the end product and appropriate outcome measure for assessing the effect of respirators. There has, however, been a remarkable dearth of studies using actual effective compliance as the outcome of interest.

Both empiric studies and studies using respirator surrogates have characterized the nature of physiologic effects. The respirator load itself does not increase heart rate except for the effect of the weight of the device. Similarly, the effect upon total oxygen consumption is relatively minimal, a finding that is not surprising because the loads themselves are relatively slight and oxygen consumption due to ventilatory musculature constitutes only a small fraction of the total oxygen consumption in normal workers at exercise. Virtually all direct and indirect measures of ventilatory work are increased by respirator loading, whether studied empirically or with surrogates. The magnitude of this effect is greater at higher than at lower exercise levels, but in itself may not be limiting at moderate exertion. Respirator surrogate studies have fairly uniformly demonstrated that the inspiratory resistive load of respirators leads to changes in the respiratory timing parameters. Inspiratory time is prolonged both in absolute terms and as a fraction of the total respiratory cycle time ("the duty cycle"). Furthermore, preliminary studies suggest that the magnitude of the effect is relatively independent of the level of exertion. Theoretical studies suggest that the respiratory timing parameters may be useful indicators of respiratory control adaptation: the mean inspiratory flow rate (tidal volume/inspiratory time) representing the intensity of respiratory effort and the duty cycle (Ti/Ttot) representing the on/off switch for the ventilatory pump. Respiratory timing parameters are also significantly affected by disease states. Furthermore, it appears that respiratory timing adaptation to respirator surrogate loads reflects an individual subject's psychophysical load sensitivity and may be related to subjective sensation of respiration. Hence, the potential for clinical use of these parameters in assessing individual users and research application to provide measures of respirator effect is great since they are easily measured, consistently found, relatively independent of exertion level, have a theoretical basis for significance, and are affected by pulmonary disease states as well as anxiety.

Subjective responses to respirator use may be related to their actual compliance with their use. Very clearly, subjective response is affected by more than respiratory/ventilatory work. For example, we found dissociation between responses on visual analog scales for "How long could you continue?" and "How uncomfortable is the sensation?". Empiric and surrogate studies have assessed the relationship between respirator loads and subjective response (Shimozaki).

We have also studied psychophysical load sensitivity to added resistive loads. Such sensitivity is a characteristic of the individual, and it differs significantly among otherwise "normal" individuals. Sensitivity to added loads may condition the physiologic response (e.g., respiratory timing) as well as the subjective response to added loads. Objective measurement of personal psychophysical sensitivity is a relatively complex technique and is unlikely to be of clinical use, but it does provide considerable insight into possible mechanisms underlying the disparate responses of many apparently normal workers to respirator-induced loads.

Respirators have been used since the Romans used pig bladders in their lead industry, and it is likely that respirators will continue to be a significant component of worker protection in many situations. It is clear that there are interrelationships among the factors determining proper respirator design and use in a safe and effective manner. These factors include ventilatory work, respiratory sensa-

tion, subjective comfort, worker attitude and knowledge, added physiologic stressors as well as the efficiency of the device itself as a filter/chemical adsorbent. Each of these factors must be considered both clinically and for future research if respirators will achieve their potential in worker protection. Furthermore, these studies may illuminate the relationship between disease, exertion, and physiology.

Respiratory Hazards of Man-made Mineral Fibers: Types, Uses, and Health Risks

Man-made mineral fibers (MMMF) is a label collectively covering a range of inorganic synthetic fibers including: (*1*) amorphous wool-type fibers for thermal and acoustic insulation; depending on the raw materials and the fiberization production process they are divided into rockwool, slagwool (these two being sometimes designated as "mineral wool" in a narrow sense) and glasswool; (*2*) amorphous continuous filaments for textiles and for reinforcing plastics; (*3*) semicrystalline ceramic fibers for high-temperature insulation and specialty products. The commercial importance of MMMF can be gauged by the size of the total tonnage produced worldwide, approaching five million tons per year. A minor but rapidly increasing proportion is represented by ceramic fibers. Attention was drawn to the possible pathogenicity of MMMF in humans by animal experiments, the first dating from the early 1970s, showing that several varieties of MMMF are capable of inducing malignancies, namely mesothelioma in the pleura and peritoneum, when directly deposited in these cavities, as well as fibrosis when administered intratracheally. Much less clear-cut have been the results of subsequent inhalation experiments. To the extent that experiments by direct intracavitary or intraluminal administration are correctly conducted they demonstrate that, under a defined set of conditions, MMMF are capable of eliciting specific pathological responses. A recent (June, 1987) Working Group convened by the International Agency for Research on Cancer (IARC) within its program on the Evaluation of Carcinogenic Risk to Humans has judged the available evidence of carcinogenicity in experimental animals as "sufficient" for glasswool and for ceramic fibers, "limited" for rockwool, and "inadequate" for slagwool and for continuous filament. Laboratory data have also become available on the durability and kinetic behavior of the different varieties of fibers *in vitro* and *in vivo* systems, throwing some light on possible mechanisms of biological actions. Most important, over the last decade a substantial amount of observations have been carried out directly on workers occupationally exposed to MMMF. The results of these studies can be considered in respect to three long-term pathological endpoints: chronic pulmonary disease, respiratory (lung) cancer, and mesothelioma.

The issue of chronic respiratory disease has been addressed from different prospectives and at different levels of detail. Mortality studies include, besides one very small investigation on autopsied workers, data from seven historical cohort investigations, providing death figures for a disease category usually labeled as "nonmalignant respiratory disease." This reflects a heterogeneous mix of pathological and clinical conditions and therefore lacks both sensitivity in detecting and specificity in attributing an excess risk. Morbidity studies consist of 15 cross-sectional investigations, which have employed questionnaires eliciting symptoms, chest radiography, and lung function tests, or a combination of these methods. All have been conducted on workers still employed ("survivors" in the production industry), with a majority of subjects exposed for not more than 20 years. The best designed of these studies (involving 1,028 male workers at seven U.S. production plants) found an association between small opacities in the chest X-rays and duration of employment in the industry (in smokers).

Evidence on respiratory (essentially lung) cancer is derived from seven historical cohort studies investigating mortality (one study addressed cancer incidence as well) in workers of the MMMF production industry. The two largest and most informative were carried out in Western Europe and in the United States. Both included industrial hygiene surveys documenting that, under present-day conditions, concentrations of airborne respirable fibers are low, mostly in the range 0.01 to 0.1 f/ml. Only a small minority of environmental measurements reached values of 1 f/ml and above. Reconstruction of past exposure, essential to investigate the relationship, if any, with lung cancer risk, required indirect approaches, as virtually no measurements of airborne fibers were available from the past. In the European study, coordinated by IARC, an *ad hoc* historical environmental investigation was carried out, questioning key informants in a structured way on past plant conditions. The most recent analysis of this study includes 21,967 workers in 13 plants (seven rockwool/slagwool, four glasswool, two continuous filament) in seven European countries (Denmark, Federal Republic of Germany, Finland, Italy, Norway, Sweden, United Kingdom). For no cause of death, except lung cancer, was a consistent excess (within plants or across plants) found in respect to the expectation based on the mortality experience of the general population. For lung cancer, however, the standardized mortality ratio was elevated overall (189 observed deaths, 151.2 expected, SMR 125) and showed an increase with time since first exposure but not with duration of employment. When the results of the historical environmental investigation were taken into account, the excess lung cancer was found mostly concentrated in the small subcohort of workers (331 subjects) first employed in an early technological phase of the rockwool/slagwool production process, when no dust suppressing agents (oil, binders) were used and/or there was use of the manual batch manufacturing process. This phase was ranked as the one with the highest level of airborne fibers (observed lung cancer deaths 10, expected 3.9, SMR 257, $p < 0.05$). The excess declined with the introduction of dust-suppressing agents. No similar excess could be demonstrated in the glasswool production process, which was ranked as likely to involve lower levels of airborne fibers than the rockwool/slagwool production process. These results are consistent with those from the study in the United States in which 16,661 workers were followed up at 17 plants (six rockwool/slagwool, 11 glasswool and continuous filament). An excess of lung cancer was found 20 years or more after first exposure, greater for rockwool/slagwool workers (45 observed, 34.4 expected, SMR = 130.8), for glasswool workers (52 observed, 46.9 expected, SMR = 110.8). In addition, in a case-control study within the cohort, taking smoking into account, a weak (statistically significant) relationship was found with time-weighted cumulative exposure in the rock/slagwool workers but not in the glasswool and continuous filament workers. As to mesothelioma, there was no findings of an increased risk in either study.

On the basis of these results what can we state as being known about MMMF and respiratory disease? First, the epidemiological evidence indicates that fibers, as present in the environmental conditions of the early slagwool/rockwool production processes, are likely to have played an etiological role in the production of lung cancer. This, taken together with the evidence from experiments with animals, led the June 1987 IARC Working Group to classify rockwool/slagwool as "possibly carcinogenic" for humans. Because of "sufficient" evidence in animals, glasswool and ceramic fibers were also classified as "possibly carcinogenic" for humans, notwithstanding the inadequate epidemiological evidence for the first and the absence thereof for the second. Continuous filament simply could not be classified because of the inadequacy of both epidemiological and animal data. Second, no clear conclusion can be put forward as to chronic respiratory disease, with only one adequate cross-sectional study indicating a probable causal link, between exposure to fibers and chest X-ray anomalies (small opacities) in smokers. While current information delineates the potential for adverse long-term health effects of MMMF, most segments of the MMMF production industry, particularly the modern ones, have not been associated with detectable adverse health effects. Additional research is needed concerning a number of issues: (*1*) the carcinogenicity of rockwool in animals; (*2*) the risk of lung cancer in glasswool production workers; (*3*) the exposure-response relationship of MMMF in animals and in humans; (*4*) the relationship between MMMF and fibrosis in animals and chronic respiratory disease in humans, the latter through longitudinal observations; (*5*) the long-term health effects in MMMF end users. Studies currently in progress will help answer some of these questions.

Highlights: ATS Symposia Summaries and Topics

Dyspnea: Mechanisms, Evaluation and Treatment

Chair: N. K. Burki
Co-Chair: M. J. Tobin
Participants: A. Guz, J. T. Sharp, R. B. Banzett, D. A. Mahler

Dyspnea, one of the most common symptoms of lung disease, remains poorly understood, but recent studies have begun to shed some light on the mechanisms of the genesis of this common symptom. Newer techniques for more objective evaluation have been described and various treatment modalities have been attempted.

The relationship among breathlessness (dyspnea), ventilation, and the chemical control of breathing has been examined in recent studies in normal subjects. Various techniques for quantifying breathlessness have been examined; the technique of linear visual analogue scaling and the technique of ratio magnitude estimation have been shown to be valid and applicable in naive individuals. A series of studies using these techniques has shown that there is a wide variability of sensory scaling of breathlessness between individuals; however, each individual behaves "characteristically," irrespective of the type of stimulus, i.e., hypercapnia, hypoxia, or physcial exercise. Studies of airway anesthesia suggest that stretch receptors in the airways may be involved in the genesis of breathlessness induced by exercise or CO_2 inhalation. Of great significance are studies that have shown that the sensation of breathlessness at a given level of ventilation is markedly diminished if the subject achieves that ventilation voluntarily as compared to reflex stimulation, e.g., during hypercapnia or exercise. These data suggest that the intensity of breathlessness depends on the level of reflex stimulation of the respiratory-related neurons in the medulla, and cannot be explained solely in terms of perception of afferent neural information arising from peripheral receptors. The fundamental importance of cerebral cortical mechanisms may have been underestimated in terms of its role in dyspnea. There are no studies of "mapping" of the cerebral cortex in terms of respiratory sensations, as has been described for other motor and sensory modalities by Penfield. Studies in a patient with Ondine's curse suggest that motor output from the medullary respiratory centers is essential for the genesis of dyspnea. It is likely that major advances in understanding dyspnea and the role of cortical influences will come from investigations in patients with well defined central neurologic lesions that affect specific pathways and spare other neuronal areas.

Studies of respiratory sensation indicate that the sensation of respiratory muscle force can be distinguished from the sensation of respiratory effort. This has focused attention on the respiratory muscles in the genesis of dyspnea. It has been suggested that the sensation of inspiratory effort, which is closely related to the outgoing central motor command to the inspiratory muscles, is similar to the sensation of dyspnea. Thus, in conditions where there is an increased demand for ventilation, increased mechanical impedances to breathing, or inspiratory muscle weakness due to disease, dyspnea might occur. In patients with severe hyperinflation due to chronic airways obstruction, the flattening of the diaphragm and the associated shortening of its fibers, results in a diaphragmatic mechanical disadvantage; in these patients, the relationship of these respiratory muscle factors to dyspnea has been well illustrated. Respiratory muscle fatigue and its relationship to dyspnea have also been examined recently. These studies found a very poor relationship between the sensation of inspiratory effort and the presence or absence of respiratory muscle fatigue. Investigations of the respiratory muscles during exercise have led research workers to suggest that there may be chemoreceptors in the thoracic musculature that respond to some metabolites produced by the exercising skeletal muscle. Investigators have postulated that the sensory input to the central nervous system from these chemoreceptors may be involved in the sensation of dyspnea. However, many studies have shown that the intensity of the sensation of breathlessness is not simply a reflection of the increased rate of work of breathing performed by the respiratory muscles.

The relationship of various respiratory sensations to dyspnea is unclear. It is well known that sensory signals from the upper airways can be perceived; thus, airflow in the upper airways, as well as pressure, can be detected by the individual. It is also suggested that afferent information from muscle and joint receptors in the chest wall and diaphragm may be involved in the perception of ventilation and lung volume and in the sensation of added respiratory loads. Recent studies indicate that changes in lung volume can be perceived via vagal pathways. A study of quadriplegics with complete spinal cord lesions at C1-C2 found that these subjects were able to detect changes in tidal volume. Since these patients lacked sensory information from the chest wall, and because they were tracheostomized and lacked upper airway information, the only source for the sensory signal would be from receptors in the lungs and/or airways, and the pathway would be via the vagus nerves. In one subject, this perception of tidal volume was abolished by aerosolized, inhaled 20% lidocaine. Recent studies also suggest that individuals can detect a rise in arterial P_{CO_2} quite separately from the CO_2-induced increase in ventilation. Other data suggest that hypoxemia has a dyspnogenic effect, again, separate from its ventilatory stimulant effect.

Techniques for quantifying dyspnea have recently received much attention, especially for clinical application. Starting with the original dyspnea scale described by the Medical Research Council of Great Britain, many other techniques have been devised. Perhaps the two most commonly used scales are the visual analogue scale and the category scale devised by Borg. These scales can be used to provide quantitative information about dyspnea for assessing acute or immediate effects of therapy. On the other hand, for a more detailed and multidimensional analysis quantifying dyspnea, the recently described "baseline and transition dyspnea indices" and the "chronic respiratory questionnaire" provide additional information that includes data about functional status and the magnitude of effort that provokes a given level of breathlessness. These multidimensional tools may provide enhanced sensitivity for assessing changes in breathlessness in response to therapeutic interventions.

A large number of investigations have been published on the sensation of added respiratory loads; although these studies have generated much valuable information regarding respiratory sensation, the relationship of the "load sensation" to dyspnea is unclear. Studies on the perception of the magnitude of an added respiratory load have provided valuable insights into the sensation of muscle effort and of central motor command in relationship to respiratory sensation. A recent study in patients with restrictive lung disease and in patients with airways obstruction found that detection of an added load is likely to occur when the muscular effort or pressure generated by the respiratory muscles increases by 10 to 20% above the value in the control, unloaded state.

Current information suggests that dyspnea is related to: (*1*) the intensity of the central motor command output; (*2*) *reflex* (as opposed to *volitional*) stimulation of respiration; (*3*) respiratory muscle activity appears to be necessary for the genesis of dyspnea; (*4*) a rise in P_{CO_2} and hypoxia appear to be dyspnogenic stimuli, independent of their effects on ventilation; (*5*) the major role of central neural processing mechanisms in modulating inputs from the peripheral sensors (receptors in the lungs, chest wall, and diaphragm, and chemoreceptors) very likely accounts for the large individual differences in the sensation of dyspnea that have been described.