Clinical Pathology Workshop Summary

Nylon Flock–Associated Interstitial Lung Disease

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A work-related interstitial lung disease has been diagnosed in workers at five nylon flock facilities in three different states and a Canadian province. The National Institute for Occupational Safety and Health hosted a workshop at which consulting pulmonary pathologists reviewed lung tissue samples from all the cases for which lung biopsy material was available (15 of 20 cases known in January 1998). After independent review and scoring of these lung tissue specimens, the pathologists reached consensus that the histopathological findings revealed a characteristic lesion—a lymphocytic bronchiolitis and peribronchiolitis with lymphoid hyperplasia represented by lymphoid aggregates. The pathologists noted that the pathological findings were distinctive when compared with known lung conditions. The clinical presentation for the cases generally included cough, dyspnea, restrictive ventilatory defect with reduction in diffusing capacity, and interstitial markings on chest radiographs or high-resolution computed tomography (HRCT) scans. Six of the cases improved after removal from workplace exposure without medical treatment. Six others, who had recovered with medical treatment and removal from the workplace, had relapses in both symptoms and objective findings after attempting to return to nylon flock work. With this and other evidence supporting the existence of chronic interstitial pneumonitis associated with nylon flock processing, workshop participants recommended surveillance for early identification of affected workers and their removal from further workplace exposure. Eschenbacher WL, Kreiss K, Lougheed MD, Pransky GS, Day B, Castellan RM. Nylon flock–associated interstitial lung disease. AM J RESPIR CRIT CARE MED 1999;159:2003–2008.

INTRODUCTION

Flock is cut or pulverized fiber (synthetic or natural) of small diameter that produces a velvet-like coating when applied to adhesive-coated fabric or other material. Flocked fabric is increasingly popular, especially as upholstery covering and as blankets. Synthetic materials used to make flock include nylon, rayon, and polyester. Two separate outbreaks of occupational interstitial pneumonitis among workers at nylon flock processing plants in Ontario and Rhode Island had been reported in the literature (1–5) whereas two other cases attributed to nylon flock work at plants in Massachusetts had been reported directly to the National Institute for Occupational Safety and Health (NIOSH). It was uncertain whether the disease process and lung tissue injury were similar in the workers at the different sites. To better characterize the pulmonary pathological lesions associated with occupational exposure in nylon flock plants, NIOSH invited clinicians and hospital pathologists who had recognized cases to a workshop in Morgantown, West Virginia. At this workshop, consulting pulmonary pathologists reviewed lung histopathology from clinically identified cases, and clinical aspects of these cases were presented and discussed. The following case description is used as an illustrative example chosen from the cases presented at the workshop.

CASE DESCRIPTION

In December 1996, a 29-yr-old never-smoker presented to a pulmonologist for evaluation of persistent cough and shortness of breath of about 24 mo duration. He had been diagnosed with asthma at 12 yr of age and had experienced occasional attacks of wheezing and chest tightness triggered by certain foods and pollens. These asthmatic attacks, which were not accompanied by significant cough, had always been easily reversible with inhaled medications.

In February 1992, the patient began work at a facility where nylon flock is applied to adhesive-coated fabric. His initial job was as a material handler in charge of warehouse storage of bagged flock and other materials and deliveries and

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pickup within the plant, excluding the flocking rooms where the flock application occurs. In March 1995, he transferred to a quality control job in which he was responsible for checking flock with a variety of tests. In this assignment, he worked with loose flock and in many different production areas throughout the plant, including the flocking rooms. The patient reported that his exposure to loose flock and flock-associated dust was substantially higher in his quality control job than in his previous materials handling job.

During the early summer of 1995, within 3 mo of transferring to the quality control job, he developed gradually increasing shortness of breath on exertion and paroxysmal cough, without wheezing. The cough, productive upon waking, was disruptive of sleep at night and often interrupted conversation during the day. His respiratory symptoms were unresponsive to inhaled bronchodilators and corticosteroids. Approximately 1 yr later, he developed constant achiness and fatigue without fever or chills and noted a 20-lb weight loss. Working a 6-d, 66-h week, he noted no work-related pattern of symptoms, nor did he perceive symptomatic improvement during a 2-wk plant shutdown in mid-summer 1996.

On presentation in December 1996, he had rare inspiratory crackles on physical examination, an FEV_1 of 3.44 L (76% predicted) and an FVC of 3.77 L (64% predicted). A standard chest radiograph at that time was reported as within normal limits. In January 1997, during subsequent testing, he was noted to have a severe coughing episode with shortness of breath and had oxygen desaturation to 93% with exercise. He was started on two successive tapering schedules of prednisone, each beginning with 50 mg/d. He underwent antireflux surgery in April 1997. On return to his pulmonologist several weeks later, he reported some improvement in his cough, but his dyspnea and generalized achiness continued to gradually progress. A repeat chest radiograph in May 1997 was normal, but peripheral ground glass opacities were evident in the anterior portion of both lungs on high-resolution computed tomography (HRCT) scan in June 1997. He had lost a total of 45 lb during his course of illness before thoracoscopic lung biopsy (Figure 1) in June 1997.

With a postsurgical work absence, along with oral steroids tapered over 5 wk, pulmonary functions improved (FEV_1 4.0 L; FVC of 4.4 L; 97% oxygen saturation with exercise). An occupational medicine consultant recommended an extended absence from work. After 8 wk off work, he noted continued clear improvement in his symptoms. With 10 wk work absence, he felt back to normal and had begun to gain weight.

He returned to work in September 1997 in an office job that involved walking through the plant several times a day. One month later, he noted mild symptomatic recurrence and had worsening of lung function test results. He again showed objective signs of improvement only after being out of all processing areas of the plant for an extended period of time. A follow-up HRCT in November 1997 revealed no evidence of ground glass opacities. He is now off all medications, has remained out of all processing areas of the plant, and is doing well.

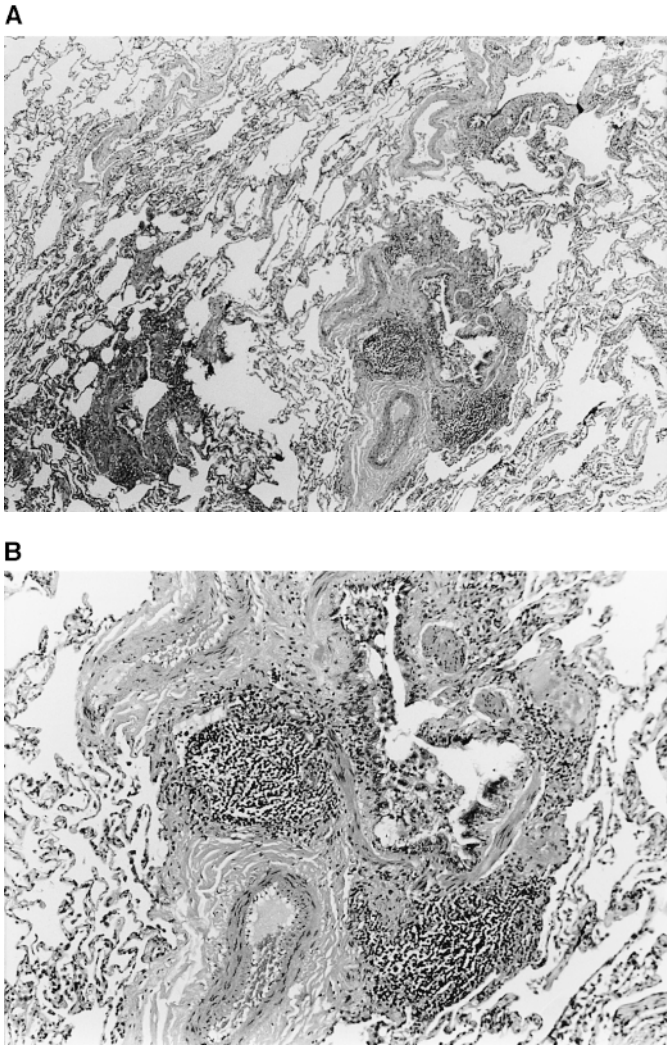

Figure 1. Photomicrographs of thoracoscopic lung biopsy specimen from nylon flock plant worker. Histology reveals lymphocyte-predominant infiltrate surrounding bronchiole in center of lobule. Original magnification of photomicrograph: (*A*) ×100; (*B*) ×250.

OUTBREAK UPDATES

During 1990 and 1991, five workers from a nylon flock processing plant in Ontario presented with cough and dyspnea (1). Three of these workers were quite ill; one required mechanical ventilatory support for 4 wk. These three individuals had undergone lung biopsy with the findings of a diffuse interstitial pneumonitis characterized by a lymphocyte-predominant infiltrate and desquamation into alveolar spaces. Lougheed and coworkers (1) conjectured that the lung disease process in these workers represented a response to a toxic inhalational injury. Subsequent to publication of this report, four more cases, two of whom underwent lung biopsy, were evaluated among workers at this same plant which employed approximately 90 individuals.

In 1995 and 1996, two workers from a similar nylon flock processing plant in Rhode Island presented separately to the same physician with cough and dyspnea. The initial working diagnosis for the lung disease in these two workers was work-related hypersensitivity pneumonitis. With additional case finding investigation at the Rhode Island location, a total of eight cases among the approximately 150 workers at the plant were identified by January 1998 based upon a screening questionnaire (symptoms of cough and dyspnea), pulmonary function abnormalities (restrictive pattern with reduced diffusing capacity), radiographic findings (interstitial markings on routine chest radiographs or ground glass opacities on HRCT scans), and/or histological findings on tissue obtained by open lung or transbronchial lung biopsy (2, 3, 5). One of these cases had been evaluated as interstitial lung disease in 1985 while

TABLE 1

NUMBER OF CASES HAVING SELECTED HISTOPATHOLOGICAL DESCRIPTORS BY MEDIAN SCORE AND TYPE OF LUNG BIOPSY

	Wedge Biopsies ($n = 8$)					Transbronchial Biopsies ($n = 7$)				
Finding	Specimen Inadequate	Absent	Mild/ Rare	Moderate/ Some	Severe/ Many	Specimen Inadequate	Absent	Mild/ Rare	Moderate/ Some	Severe/ Many
Overall cellularity	0	0	1	4	3	0	0	3	4	0
Overall fibrosis	0	2	4	2	0	1	2	4	0	0
Giant cells	0	7	1	0	0	2	5	0	0	0
Granulomas	0	7	1	0	0	2	5	0	0	0
Desquamation	0	0	3	5	0	4	0	3	0	0
Lymphoid aggregates	0	1	0	6	1	5	1	1	0	0

the patient was employed at the plant. Based upon the aggregate histopathological results from biopsied cases, the disease process was not thought to be hypersensitivity pneumonitis.

In 1996, two workers from two other nylon flock processing plants presented with interstitial lung disease. These plants, located in Massachusetts, have a combined employment of approximately 240 workers. Clinical findings for these two workers were similar to the previously reported cases.

As of January 1998, interstitial lung disease had been diagnosed in a total of 20 workers exposed to nylon flock and flock processing at four different plants employing less than 500 workers in two different states (Rhode Island and Massachusetts) and in Canada (Ontario). Lung tissue specimens (8 wedge biopsies and 7 transbronchial biopsies) were available from 15 of these cases; five patients had not undergone biopsy.

WORKSHOP REVIEW PROCESS

At NIOSH, slides of the tissue specimens from the 15 cases were coded and randomized to obscure the original hospital and worker identities. Using a modification of a standardized scoring sheet for aspects of idiopathic pulmonary fibrosis (6), the three consulting pathologists (Drs. Colby, Roggli, and Travis) independently assessed the adequacy of the specimens and, for those deemed adequate, scored specific findings on a 4-point qualitative scale reflecting absent (score = 0), mild/rare (score = 1), moderate/some (score = 2), and severe/many (score = 3). After all scoring was complete, clinicians presented history, physical findings, radiographic findings, pulmonary function test results, management, treatment, and course of illness, followed by the pathologist's presentation of the biopsy findings for each case. Workshop participants discussed each case individually and all cases in aggregate through the course of the workshop.

RESULTS

Histopathology

We categorized cases by median scores for selected descriptors of the pathological findings (Table 1). Despite some intercase variability in severity and extent of tissue involvement, the consulting pathologists together with the clinical pathologists who had initially examined the case material at their respective hospitals, reached consensus regarding the characteristic pathological lesion common to this set of interstitial lung disease cases. The underlying lesion was described as a lymphocytic bronchiolitis and peribronchiolitis with lymphoid hyperplasia represented by the presence of lymphoid aggregates (Figure 1). One of the consulting pathologists noted that, except for the lack of giant cells, the injury distribution was similar to hard metal pneumoconiosis or giant-cell interstitial pneumonia resulting from cobalt exposure (7). Other secondary histological features that were variably present included acute alveolar injury (showing patterns of diffuse alveolar damage [DAD] or bronchiolitis obliterans with organizing pneumonia [BOOP]) and increased macrophages with some foci reminiscent of desquamative interstitial pneumonitis (DIP). Significantly, granulomas and giant cells were absent from the pathological findings in all but one of the 15 cases, in which their presence was rare. In addition, fibrosis was not a predominant feature.

For the eight cases with wedge biopsies, the pathologists agreed that seven cases met their consensus criteria for the typical lesion of this interstitial lung disease. The biopsy from the eighth case revealed a mild respiratory bronchiolitis consistent with that patient's smoking history. For the seven cases with transbronchial biopsies, the pathologists noted abnormalities including lymphocytic inflammation in all samples. However, the characteristic findings that were used to identify the typical lesion seen in the wedge biopsies could not be assessed in the transbronchial biopsies because tissue quantities were inadequate to describe changes in bronchiolar and lobular architecture.

Clinical Findings

The 20 cases from the three geographic locations (including the five patients who did not have lung biopsy) shared symptoms of dyspnea and cough, with and without sputum production. These symptoms were present for months to years before

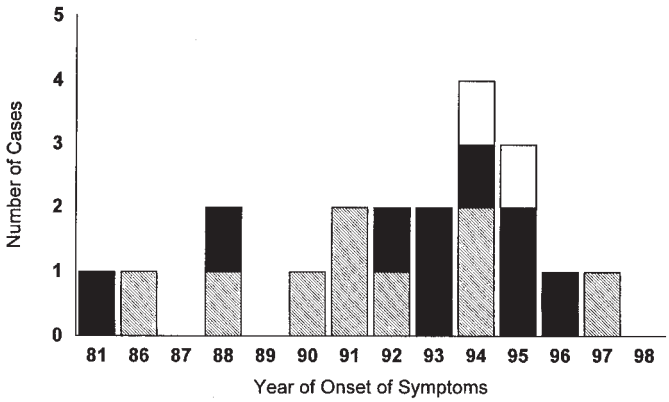

Figure 2. Year of symptom onset for 20 cases from three geographic locations: Rhode Island, *closed bars*; Ontario, *hatched bars*; Massachusetts, *open bars*.

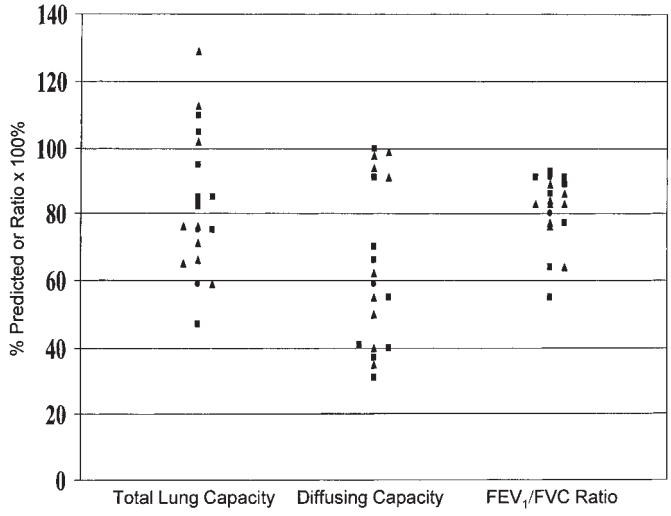

Figure 3. Pulmonary function test results (total lung capacity, diffusing capacity, and FEV_1/FVC ratio) at the time of presentation for the 20 cases from three geographic locations: Rhode Island, *triangles*; Ontario, *squares*; Massachusetts, *circles*.

clinical presentation, which, for some cases, seemed precipitated by an acute exacerbation in the preceding few days. Symptom onsets for the 20 patients occurred over a 15-yr period, with no apparent concentration of onsets for any plant location (Figure 2). Few nonrespiratory symptoms were noted. Weight loss was noted in two patients (including the example case described previously) and two workers had arthralgias or myalgias. Eight of the 20 patients were noted to have asthma, increased bronchial responsiveness to methacholine, or increased bronchodilator responsiveness. Three of the 20 patients were current smokers at the time of presentation; 10 were ex-smokers (including several who had quit smoking shortly after the onset of their symptoms).

Pulmonary function test results (Figure 3) revealed a restrictive pattern (total lung capacity [or forced vital capacity in the absence of lung volumes] $<$ 80% predicted) in 10 of the 20 cases; in several other patients, these indices were in the low normal range. Thirteen of the 19 patients tested were found to have reduced diffusing capacity ($<$ 75% predicted). In three cases, including the patient with the histopathological findings consistent with respiratory bronchiolitis, the FEV_1/FVC ratio was reduced to $<$ 65%, suggesting an obstructive lung defect. No correlation existed between the lung function findings (TLC, FVC, FEV_1, diffusing capacity of the lungs for carbon monoxide [D_{LCO}], etc.) and the pathological scores, probably because the number of cases was small and the scoring results had a narrow range.

Chest radiograph and computed tomographic (CT) scan results for one of the cases are shown in Figure 4. In several of the cases, the initial chest radiograph was read as normal but the CT scan (most often a HRCT scan) revealed abnormalities such as ground glass opacities with a peripheral predominance in some. No mediastinal, hilar, or pleural abnormalities existed in any of the radiographic studies.

The medical management for most of the affected workers included removing them from further exposure at the nylon

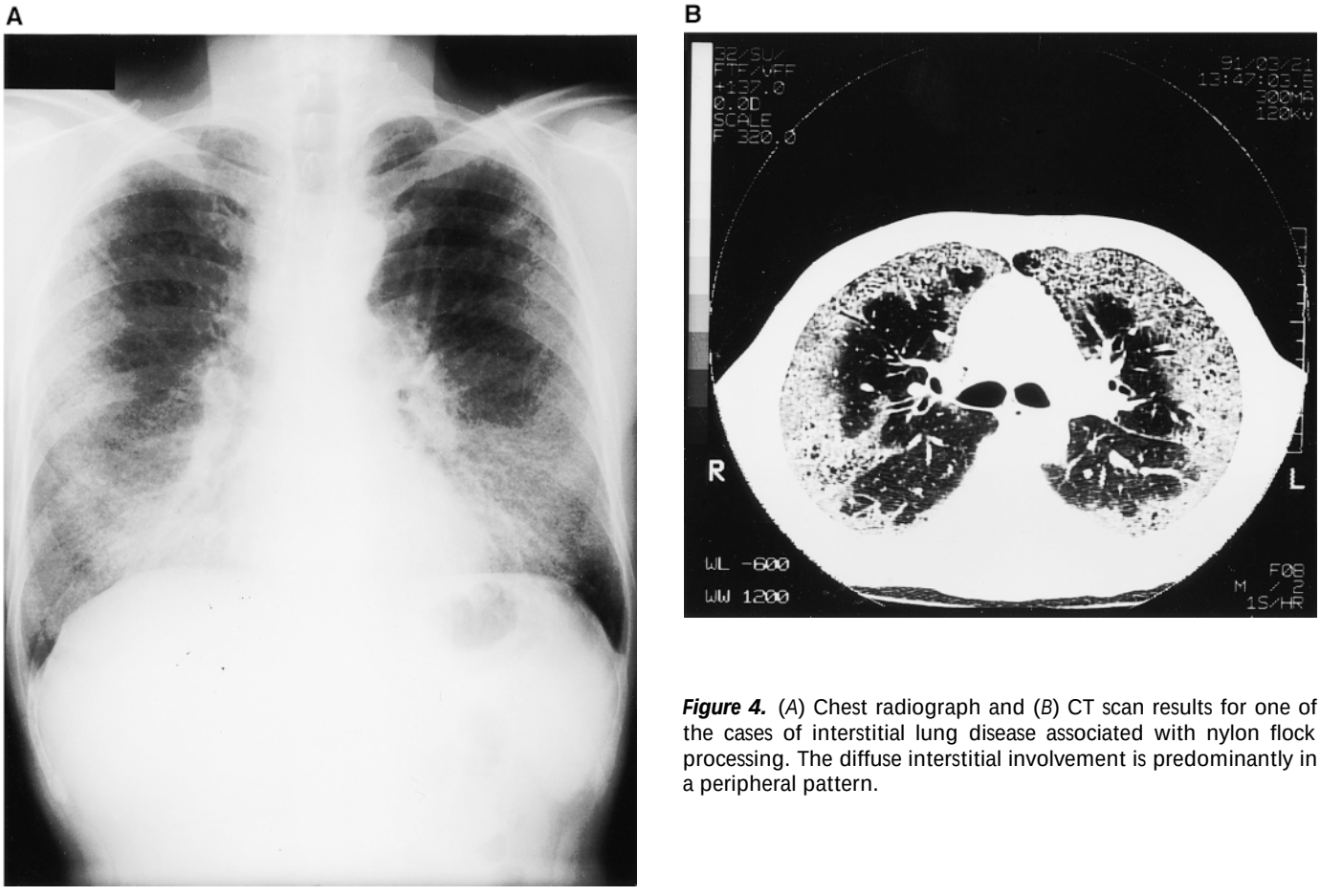

Figure 4. (*A*) Chest radiograph and (*B*) CT scan results for one of the cases of interstitial lung disease associated with nylon flock processing. The diffuse interstitial involvement is predominantly in a peripheral pattern.

flock plants. Seventeen of the 20 patients left work after medical evaluation. Eight of the 20 workers were initially treated with high-dose oral or intravenous corticosteroids, six were treated with inhaled steroids, and six received no medical treatment. The six workers who did not receive any form of medication improved in terms of symptoms and objective pulmonary function and radiographic abnormalities with removal from further exposure at the nylon flock plant. Of the three workers who did not leave the workplace, two continued to have problems requiring increasing dosages of medication including oral corticosteroids; the third had no improvement despite job relocation to outside the processing areas of the plant. Of the 17 workers who left the workplace, six tried to return but all six had relapses in symptoms and objective findings. In general, recovery occurred over months to years and has not always been complete for all patients, with some having persistent dyspnea, exercise limitation, or requirements for chronic supplemental oxygen.

DISCUSSION

The interstitial pneumonitis we have studied among nylon flock processing workers has a histopathological pattern—bronchiolar and peribronchiolar lymphocytic inflammation and lymphoid hyperplasia—which suggests an inflammatory and possibly immunologic response to a respirable toxic agent. The similarity of symptoms, predominant restrictive pattern of lung function test results, and histopathology among cases occurring in these different geographic locations and occurring over a several year period of time suggest an endemic risk associated with nylon flock work.

Several key points provide evidence for work-relatedness of this condition. First, some affected workers improved in symptoms and objective abnormalities after leaving workplace exposure, even without the use of any medical treatment; and workers who had improved after leaving the workplace experienced worsening in symptoms and objective findings following return to work at the flock plants. In addition, for a few cases, increased symptoms and onset of recognized disease occurred with increased occupational exposure to flock-associated dust. Second, the occurrence of 20 cases among an estimated 500 workers in the combined cross-sectional workforces of four plants constitutes an impressive epidemic of a rare disease; the estimated standardized incidence ratio for interstitial lung disease at the Rhode Island flock processing plant suggests an incidence rate approximately 50 times that of the general population (2). Third, apart from recognized clinical cases of this disease, respiratory symptoms and reports of respiratory conditions including pneumonia were significantly increased in production workers compared with office workers in the Rhode Island location (4), suggesting possible misdiagnosis in coworkers. Fourth, respirable particulate material collected from the air in the Rhode Island plant caused an intense acute inflammatory pulmonary response following intratracheal instillation in rats, as did laboratory-generated respirable fragments of nylon (8).

The case review and workshop discussion of cases offers important observations for clinicians. Patients usually did not report a work-related pattern of symptoms, because improvement required weeks to months of removal from the workplace. Misclassification of diagnosis may be common, examples being asthma and recurrent pneumonia among cases presented for discussion. Indeed, asthma or the presence of bronchial hyperresponsiveness may be part of the spectrum of disease associated with exposures in this industry, and further investigation is needed to establish the full extent of respiratory illness in the industry, now that a severe lung disease hazard has been established. Several cases had normal chest radiographs, and HRCT scans offered greater sensitivity in detecting abnormalities including ground glass opacities. Transbronchial biopsy may prove helpful in the consideration of alternate diagnoses, but wedge biopsy by thoracotomy or thoracoscopy is necessary to adequately examine the characteristic lesion of this interstitial lung disease in relation to the pulmonary lobular architecture. Workshop participants recommended that workers with this interstitial lung disease be medically restricted from further workplace exposure.

Since the January 31, 1998, workshop, three additional flock workers with interstitial lung disease have been identified in plants in North Carolina and Rhode Island. An additional case with characteristic pathology but with yet to be established exposure was identified by one of the workshop consulting pathologists. With these cases, a total of 24 cases from five plants in three states and in Canada implicate a widely disseminated common etiologic exposure in the industry.

Preliminary toxicologic studies suggest that ultrafine respirable fragments of nylon (many fibrous in morphology [9]) cause an acute inflammatory lung injury in rats after a single intratracheal instillation (8). However, flock finishing agents or other components of the particulate matter present in the air of flock processing plants cannot yet be ruled out as contributing to the etiology of this disease in affected workers. In the face of uncertainty about the definitive etiologic agents, limiting worker exposure to respirable particulate material in nylon flock processing facilities is warranted to prevent this disease. Means for reducing worker exposures include local ventilation to exhaust particulates out of the workplace from the processes where they are generated, general workplace dilutional ventilation, personal respiratory protection, and shorter work schedules, as well as improved work practices and process changes. Respirable dust levels should be controlled to well below the permissible exposure limit for nonregulated airborne particles. Further investigations, now ongoing, may lead to more specific guidance regarding protective exposure limits. Medical surveillance of all workers in this industry would be prudent to identify those individuals with early or mild symptoms before progression to more severe involvement can occur, as well as to establish process-related risk factors with implications for etiologic agent, exposure control, and prevention of interstitial lung disease associated with nylon flock processing.

Workshop Participants

Invited Participants: Alexander H. Boag, M.D., Kingston, Ontario; Thomas V. Colby, M.D., Scottsdale, Arizona; Armando E. Fraire, M.D., Worcester, Massachusetts; Charles Kuhn, M.D., Pawtucket, Rhode Island; Gary M. Liss, M.D., Toronto, Ontario; M. Diane Lougheed, M.D., Kingston, Ontario; Glenn S. Pransky, M.D., Worcester, Massachusetts; Victor L. Roggli, M.D., Durham, North Carolina; William D. Travis, M.D., Washington, DC.

NIOSH Participants: Robert M. Castellan, M.D., M. P. H., Vincent Castranova, Ph.D., Debra Cumro, DVM, Feroza Daroowalla, M.D., M. P. H., William Eschenbacher, M.D., Ann Hubbs, DVM, Ph.D., William Jones, Ph.D., Kathleen Kreiss, M.D., John E. Parker, M.D., Edward L. Petsonk, M.D., Dale W. Porter, Ph.D., Val Vallyathan, Ph.D., Gregory R. Wagner, M.D., David Weissman, M.D.

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