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SHORT COMMUNICATION

Popcorn lung and bronchiolitis obliterans: a critical appraisal

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Abstract
Purpose To perform a critical review of a series of journal articles and Health Hazard Evaluation Reports (HHER) by the National Institute for Occupational Safety and Health (NIOSH), where they have described the incidence of fixed obstructive pulmonary disease in a population of workers exposed to butter flavorings.
Methods The clinical presentations, diagnostic modalities frequently employed and a review of the pertinent clinical literature are discussed for constrictive bronchiolitis and bronchiolitis obliterans with intraluminal polyps; two distinct forms of bronchiolitis obliterans (BO). An analysis of the NIOSH reports and scientific articles is provided, followed by suggestions for evaluating this public and occupational health concern moving forward.
Findings Cases of lung disease in the food flavorings industry discussed in the literature have not been sufficiently documented to allow the conclusion that BO has been caused by diacetyl or butter flavoring. Further research is required to establish the causative agent(s).
Conclusion The diagnosis of bronchiolitis obliterans should be reserved for those individuals who have diagnostic lung biopsy findings, obtained and interpreted by clinicians who are experienced with this complex disorder.

Keywords Bronchiolitis obliterans · Butter flavoring · Diacetyl · Lung biopsy · Popcorn lung

Abbreviations

ATS	American Thoracic Society
BO	Bronchiolitis obliterans
BOOP	Bronchiolitis obliterans organizing pneumonia
BOS	Bronchiolitis obliterans syndrome
CB	Constrictive bronchiolitis
CDC	Centers for Disease Control and Prevention
CDHS	California Department of Health Services
COP	Cryptogenic organizing pneumonia
COPD	Chronic obstructive pulmonary disease
ERS	European Respiratory Society
FEV1	Forced expiratory volume in one-second
FVC	Forced vital capacity
HHER	Health hazard evaluation report
HRCT	High resolution computed tomography
ISHLT	International Society for Heart and Lung Transplant
NHANES	National Health and Nutrition Examination Survey
NIOSH	National Institute of Occupational Safety and Health
PFT	Pulmonary function testing
RADS	Reactive airways dysfunction syndrome
VATS	Video-assisted thoracoscopic surgery

Drs. Galbraith and Weill are consultants in litigation for companies that have produced butter flavorings and for companies that have been users of butter flavorings in their manufacturing processes where workers may have been exposed to flavorings. The research performed and opinions expressed are those of the authors.

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Introduction

In the spring of 2000, several former employees of a processing and packaging plant for microwave popcorn were found to have signs and symptoms of fixed respiratory obstructive disease (Parmet and Von Essen 2002). After a request from the Missouri Department of Health, the National Institute of Occupational Safety and Health (NIOSH) evaluated several microwave popcorn production facilities between 2000 and 2006. Their work has been reported in NIOSH Health Hazard Evaluations (NIOSH, NIOSH, NIOSH, NIOSH, NIOSH, NIOSH), as well as several journal publications (Akpinar-Elci et al. 2004; Fedan et al. 2006; Hubbs et al. 2002; Kanwal et al. 2006; Kreiss et al. 2002; Boylstein et al. 2006) where it has been suggested that butter flavoring may be associated with a variety of respiratory diseases, most notably bronchiolitis obliterans (BO).

Overall, NIOSH concluded that mixers of butter flavoring at five of six plants had medical findings "consistent with bronchiolitis obliterans," and that mixers with more than 12 months of job experience were at highest risk for developing obstructive pulmonary disease (Kanwal et al. 2006). These and other accounts of respiratory disease in popcorn plant workers have been reported to be the result of exposure to butter flavoring or its components (usually diacetyl), used to make microwave popcorn (Parmet and Von Essen 2002; Kanwal et al. 2006; Kreiss et al. 2002; Boylstein et al. 2006; Akpinar-Elci et al. 2006, 2005). We believe the conclusions reached by NIOSH regarding butter flavoring exposure and BO in popcorn workers require more substance than has been presented. In reaching this view, we examine the disease bronchiolitis obliterans, summarize pertinent medical literature, review key facility evaluations and critically examine published NIOSH papers.

Bronchiolitis obliterans

Constrictive bronchiolitis and bronchiolitis obliterans with intraluminal polyps have both been referred to as "bronchiolitis obliterans" (Colby 2000; Laohaburanakit et al. 2003; Kraft et al. 1993; Epler and Colby 1983; Colby 1998). Non-invasive measures for making the clinical diagnosis of BO were historically suggested by the measurement of a forced expiratory volume in one-second (FEV1) less than 60% of predicted, as well as the absence of a number of exclusion criteria (Turton et al. 1981). A certain diagnosis of BO, however, still requires lung biopsy (Laohaburanakit et al. 2003; Chan and Allen 2004; Verleden et al. 2005).

Bronchiolitis obliterans—organizing pneumonia (BOOP) was described by Epler (Epler et al. 1985). It has also been referred to as "cryptogenic organizing pneumonia" (Colby 1998; Chan and Allen 2004; Sharma et al. 2002) and "classic bronchiolitis obliterans" (Wright et al. 1992). The origins of BOOP date back to 1901 when "polyps of connective tissue" within the bronchioles of two patients were noted (Lange 1901). BOOP has been associated with many disease processes (Wright et al. 1992; Epler 1995; Cordier 2002). The histopathologic injury pattern of BOOP represents a common reaction to a wide variety of agents causing lung injury. Granulation tissue is noted to obstruct the distal airways in a patchy distribution, and interstitial inflammation is also characteristic. BOOP has frequently been used by lung pathologists to describe a nonspecific tissue reaction (e.g., "BOOP"—like pattern).

Constrictive bronchiolitis (CB), on the other hand, represents a condition where bronchioles become progressively more obstructed over a period of months or years as a result of the proliferation of fibrous tissue, often to the point of complete obliteration (Colby and Myers 1992; Garg et al. 1994; Colby 1998). It has also been called "cryptogenic obliterative bronchiolitis" and "idiopathic constrictive bronchiolitis." CB was coined in an attempt to distinguish it from BOOP, since CB is not associated with granulation polyps (Gosink et al. 1973). It likewise has been related to many disorders (Wright et al. 1992; Hansell 2001; Janigan et al. 1997; Roggli and Chiang 1996).

An important distinction between BOOP and constrictive bronchiolitis is that the architecture of the lung is largely kept intact in BOOP and can return to a completely normal histologic appearance (Epler and Colby 1983; Epler et al. 1985; Epler 1995, 2001). In contrast, CB creates irreversible destruction of lung structures and permanent loss of function. It is a peribronchiolar process of fibrosis, that "surrounds rather than fills the lumen," resulting in "extrinsic compression and obliteration of the airway" (Ryu et al. 2003). Even though the two types of BO share many associations, "one rarely can document the former evolving into the latter, re-emphasizing the fact that they represent separate and distinct clinicopathologic groups as they present to the surgical pathologist" (Colby 1998).

"Temporal heterogeneity" reflects different anatomic areas of the lung being at different stages of disease evolution in CB (Chan and Allen 2004). This is in contrast with the usual histological appearances of other lung processes such as resolving bacterial pneumonia, BOOP or recovery from an acute toxic exposure. With these conditions, the affected portions of the lung will generally present a more consistent appearance that relates to the timing of the original infection or inhalation (Epler et al. 1985).

It is worth noting that toxic inhalations have been associated with both BO and BOOP. Diacetyl does have some acute and sub-chronic toxicity (Hubbs et al. 2002; Research Institute for Fragrance Materials Flavor or fragrance ingredient data sheet: diacetyl 2006; Hubbs et al. 2004; Wright

1993), making it logical to think that exposures to butter flavoring could initiate significant lung injury. However, the patterns of exposures and symptoms identified by NIOSH in their HHEs of popcorn facilities were not substantial inhalations leading to abrupt respiratory failure, as might be expected following acute toxic exposures. Instead, in the Missouri plant where the most cases were seen, "The affected former workers of the Gilster-Mary Lee microwave popcorn plant became ill over several years from 1993 through 2000" (NIOSH). This insidious and gradual deterioration of pulmonary function suggests an entirely different mechanism from that of exposure to an acute irritant leading to reactive airways dysfunction syndrome (RADS). These irritants have typically been either highly corrosive themselves (nitric acid, hydrochloric acid) or form highly noxious agents in an aqueous environment (chlorine, phosgene, nitrogen oxides, ammonia) (Wright 1993). Diacetyl is neither a strong acid nor base, is extremely soluble in water, and is not known to form caustic intermediates in aqueous solution.

Clinical presentation

Bronchiolitis obliterans organizing pneumonia seems to affect men and women in equal proportion. There does not appear to be any relationship to tobacco smoking. Wheezing is rarely observed, but coughing is common (Epler 1995). As many as one-half of patients have had a precursor flu-like illness with fever and upper respiratory symptoms. Pulmonary function testing (PFT) generally shows a restrictive pattern, with reductions in both FVC and FEV1. Chest X-ray shows diffuse patchy infiltrates, and hyperinflation of the lung fields is rarely seen. CT findings confirm peripheral patchy infiltrates and are otherwise not distinctive. The diseases associated with BOOP are interstitial processes, and tend to respond to steroid therapy. Bronchoalveolar lavage may also be quite helpful in establishing the diagnosis (Epler 1995). A complete recovery can be expected in 65–80% of patients (Epler 2001). Interestingly, the only case of BO in the flavorings industry prior to those reported in popcorn workers occurred in a spice worker (Alleman and Darcey 2002). His physical exam demonstrated no wheezing, PFTs showed moderate restriction, and an open lung biopsy confirmed the presence of BOOP.

CB, on the other hand, is a very rare condition in the general population. It is frequently associated with connective tissue diseases, such as rheumatoid arthritis (Chan and Allen 2004). In individuals who have undergone a lung transplant, however, various studies have reported an incidence of 34–65%, reaching levels as high as 60–80% at 5–10 years following transplant (Hachem and Trulock 2004; Paradis 1998; Valentine et al. 1996). Dyspnea is the most common reported symptom. Wheezing, as in BOOP, is rarely observed on lung exam and chest X-rays are often normal, or may show signs of hyperinflation (Laohaburanakit et al. 2003; Kraft et al. 1993; Turton et al. 1981). PFTs demonstrate airflow obstruction, or may show signs of mixed obstruction and restriction (Waitches and Stern 2002). CT scanning often shows segmental areas of decreased lung density (mosaic pattern) and air trapping, which appear worse on expiration (Sharma et al. 2002; Lynch 1993; Hansell et al. 1997; Worthy et al. 1997; Stern et al. 1995). Air trapping on high resolution computed tomography scanning (HRCT) is often seen, but is also seen in other disease processes, including asthma and extrinsic allergic alveolitis, as well as in healthy individuals (Verschakelen et al. 1998). Mild bronchial wall thickening and bronchiectasis can also be seen. Typical lung biopsy findings in CB include mostly normal-appearing lung parenchyma, accompanied by severe narrowing of distal bronchioles, generally with little to no signs of active inflammation. Treatment with steroids is usually not helpful (Laohaburanakit et al. 2003).

Diagnosis

In the absence of a lung biopsy showing dense fibrous scar tissue affecting the small airways, a certain diagnosis of constrictive bronchiolitis is difficult. One must make the distinction between (1) an active inflammatory process affecting the small airways and (2) a progressive eccentric or concentric fibrotic scarring process, arising after resolution of lung injury. The latter finding is strong evidence for constrictive bronchiolitis (Colby 1998; Chan and Allen 2004).

The histologic appearance of BOOP is that of an organizing pneumonia. The presence of extensive fibrosis or a "honeycomb" appearance rules out the diagnosis of BOOP (Colby and Myers 1992), and the appearance of frequent granulomas is more suggestive of hypersensitivity pneumonitis (Hayakawa et al. 2002) or sarcoidosis.

After performing a careful clinical evaluation, determining that patients have BO (either CB or BOOP) can be quite challenging. Significant overlap has been noted with several other disease processes where the clinical picture can mimic that of BO (Laohaburanakit et al. 2003). In severe asthma, for example, obstruction of peripheral airways with mucus plugging can produce the same patient complaints. Advanced asthma "can also present as a chronic, incapacitating process, eventually leading to irreversible obstructive pulmonary disease" (Sharma et al. 2002). Bronchial wall thickening and expiratory air trapping are also common to asthma and BO. Centrilobular emphysema may generate a very similar HRCT appearance, but tends to involve the upper lobes of the lung; spreading gradually to the lower

portions of the lung with advancing disease (Lynch 1993; Hansell 2001).

Some feel that BO in post—lung transplant patients might be diagnosed by physical exam and through the use of noninvasive testing, such as HRCT and PFTs (Estenne et al. 2002; Verleden et al. 2005). These methods, however, are less able to distinguish BO from other forms of lung disease. For example, Jensen et al. (Jensen et al. 2002) searched for reliable discriminating features between severe asthma and BO that might be detected by HRCT studies. Unfortunately, "With the exception of mosaic pattern, there was no significant difference in the presence of the HRCT findings… between severe asthma (SA) and BO". Moreover, mosaic pattern was present in only 50% of BO patients in their series. The gold standard for making the diagnosis of BO remains lung biopsy (Laohaburanakit et al. 2003; Chan and Allen 2004; Muller and Miller 1995).

There is great importance in making an accurate clinical diagnosis when suspecting BO:

- Treatments for progressive CB have significant associated risks.
- Other more treatable causes for diminished pulmonary function may be overlooked.
- Long term prognosis and possible need for lung transplant will be very different depending on the underlying disease process.

A brief summary of findings in BOOP, CB, severe asthma and hypersensitivity pneumonitis appears in Table 1.

Review of literature and reports

Studies of workers at the Gilster-Mary Lee popcorn Plant

Eight cases of serious lung disease were originally reported in May of 2000 at the Gilster-Mary Lee plant. Four of these individuals had worked as mixers; the other four as packagers. Soon thereafter, NIOSH conducted voluntary medical testing of 117 workers at the plant (87% of the entire working population), a process that included questionnaires, spirometry testing, and chest X-rays (Kreiss et al. 2002).

Partial results of the NIOSH studies were made publicly available several years later where it was concluded that the facility workers (all job categories combined) experienced chronic cough, shortness of breath upon exertion, wheezing, and signs of respiratory obstruction at rates typically three- to fourfold those reported in the National Health and Nutrition Examination Survey (NHANES) database (NIOSH). It was also concluded that the findings indicated a facility-wide, work-related increase in respiratory disorders.

As a result of the excessive rates of lung disease, PFT abnormalities, and what they felt was a clear relationship between degree of exposure and pulmonary disease risk, NIOSH concluded that the eight workers described "probably had occupational bronchiolitis obliterans caused by the inhalation of volatile butter-flavoring ingredients" (NIOSH 2006).

Some shortcomings of popcorn plant studies

National Institute for Occupational Safety and Health claims of increased disease relied heavily on subjective data from worker questionnaires. It is interesting that a history of wheezing, one of the key subjective questions asked of workers, has historically been an *exclusion criterion* for BO (Turton et al. 1981). Other more common airway diseases, such as asthma and COPD, are traditionally characterized by wheezing on physical examination. Furthermore, both asthma and COPD commonly present with signs of fixed obstruction (Bergeron and Boulet 2006; Gaga 2004). Despite heavy doses of inhaled and systemic corticosteroids, a significant fraction of patients with COPD and asthma will experience little symptomatic relief. In the absence of more definitive testing, refractory asthma may provide a much more common alternative diagnosis for workers with signs of fixed obstructive disease.

In comparing worker spirometry to NHANES data, NIOSH failed to provide any tests for statistical significance at the Gilster location. In NIOSH investigations of workers at several other popcorn plants, analyses were conducted and the differences in respiratory symptoms were not found to be statistically significant.

At the Agrilink plant in Illinois (NIOSH), the researchers included spirometry studies in their analysis that they acknowledged were sub-par in quality, and not performed by NIOSH scientists. Only by including what they described as "B" and "C" grade studies were they able to achieve statistical significance for showing an increased incidence of obstructive findings.[1]

Aggregated spirometry data across all microwave popcorn manufacturing plants evaluated by NIOSH were reported in a 2006 article (Kanwal et al. 2006). "Ever-mixers"

[1] Although mixers at the Agrilink plant were exposed to 30 times less butter flavoring than was measured at Gilster, and there were only one-third the number of workers at the plant, the authors claimed to have generated just as many suspected cases of BO as Gilster (ten at Agrilink and nine at Gilster-Mary Lee) and even reported on more lung biopsies (six compared to three) (Kanwal et al. 2006). All of those initially biopsied at Agrilink were smokers, and only one of the biopsies was reported to show signs of constrictive bronchiolitis, and not one of the pathology reports was described (NIOSH 2003a). Combining this with the cases identified through the questionable spirometry data and other noninvasive studies, NIOSH claimed a total of ten workers "may have bronchiolitis obliterans" out of 41 studied (NIOSH 2003a).

Table 1 Comparing diseases

Patient data	Constrictive bronchiolitis	COP/BOOP	Severe asthma	Hypersensitivity pneumonitis
Clinical complaint	Shortness of breath, easy fatiguability	Shortness of breath, easy fatiguability	Acute difficulty breathing, often related to environmental trigger	Cough and dyspnea, associated with exposure to a particular antigen
Pulmonary exam: Wheezing	Rare	Rare	Signature finding when patient having active complaints	Infrequent, but may occur during acute challenges to reactive agents
Pulmonary Function Testing	"Fixed obstructive" pattern (unresponsive to bronchodilators)	Restrictive pattern	Obstructive pattern, usually responding to bronchodilators	Restrictive during acute presentation
Chest X-ray	Often normal, or signs of hyperinflation	Diffuse patchy infiltrates	Normal or signs of hyperinflation	Nodular infiltrates
High resolution CT scanning of chest	Air trapping, bronchial wall thickening, "mosaic pattern"	Peripheral increased densities	Air trapping, bronchial wall thickening, "mosaic pattern"	Multiple rounded opacities, patchy airspace opacification; may progress to diffuse fibrosis in chronic state
Open lung biopsy findings	Patchy, concentric, subepithelial fibrous obstruction of small airways, sometimes leading to "obliterated" airways; "temporal heterogeneity"	Highly cellular interstitial infiltrate, "organizing pneumonia," obstruction of distal airways with "granulation polyps"	Thickening of basement membrane, submucosal gland hypertrophy, subepithelial fibrosis, hypertrophy of smooth muscle	Highly cellular interstitial infiltrate, granulomas usually seen in acute and subacute states; interstitial fibrosis prevalent in chronic state
Response to steroid therapy	Rare	Frequent (80%)	Usually positive, mainstay of treatment during flareups	Often helpful, particularly if pulmonary fibrosis not present
Clinical course	Usually gradual deterioration, leading to lung transplant or death	Most experience complete or partial recovery; mortality is unusual	Disease usually not progressive, but death can occur in severe attacks	Gradual recovery with removal of exposure to inciting agent

had an incidence of obstructive spirometry changes of 11.6%, compared with a rate of 10.7% in "never-mixers." If the claim being made is that mixers constitute a higher risk group with significantly greater exposure to butter flavoring, this minimal difference should not be seen as particularly striking.[2]

The human population represented by NHANES is not a proper comparison group for a worker population with domestic and occupational exposures to dusts, molds and pesticides. NHANES divides up the United States into "primary sampling units," and requires minimum population sizes for an area to be evaluated; a strategy that would tend to lessen the attention on agrarian communities with low population densities (National Center for Health Statistics Analytic and reporting guidelines: the National Health and Nutrition Examination Survey 2005). A more fair and appropriate comparison would be with a regional agrarian population without exposure to microwave popcorn, reflecting the fact that farmers and agricultural workers in general tend to have a higher incidence of respiratory disorders (Mobed et al. 1992; Schenker 2005).

From the NIOSH worker questionnaires, it is known that a majority of the Gilster workers (57%) reported having had exposures outside the popcorn packing plant to known environmental risk factors for lung disease. Specifically, they reported farming activities (40%), exposures to grain dust (32%), to irritant gases (14%), and to nitrogen oxides (8%) (NIOSH 2006). NIOSH, in using the NHANES data as the comparison group for evaluating Midwestern popcorn packaging workers, did not account for the high expected background incidence of respiratory ailments in the regional population. Incorrect inferences regarding disease incidence are thus a distinct possibility.

Of the former eight workers at this plant who were reported to have symptoms "consistent with" BO, only four worked in the mixing room. The other four worked in the packaging area where much lower levels of exposure were measured. Indeed, it was reported that none of these packagers had ever worked in the mixing room (NIOSH 2006). Thus, half of the eight cases had little to no exposure to butter flavoring, while the other half had relatively high exposure, which seems unusual in the context of a traditional dose–response relationship. These excessive obstructive respiratory findings in packaging workers were not duplicated in the NIOSH reports of any other popcorn facility studied.

Akpinar-Elci study of popcorn production workers (2004)

NIOSH summarized the medical, radiographic and histologic findings from workers at the index plant in Missouri. In their series of nine patients, three of whom underwent lung biopsy, and eight of whom had high resolution CT scans of the chest performed, they determined that:

- Five of the nine individuals had some degree of exposure to mixed butter flavorings.
- Shortness of breath and wheezing started on average 18 months after beginning employment.
- All cases were noted to have a decreased FEV1.
- All eight CT scans showed bronchial wall thickening and areas of decreased attenuation with air trapping.
- After leaving employment, "nearly all cases experienced stabilization of their lung function within 2 years" (Akpinar-Elci et al. 2004).

NIOSH concluded that "astute clinicians can help identify new causes of airways obstruction by alerting public health authorities to unexplained disease cases occurring in groups of workers" (Akpinar-Elci et al. 2004).

Limitations of the Akpinar-Elci 2004 Paper

Bronchiolitis obliterans syndrome (BOS) has its nosologic origin from the International Society for Heart and Lung Transplantation (ISHLT), who attempted to create a classification system for patients with airway disease following lung transplantation. The application of BOS was limited to transplant patients, an accepted high-risk group for developing BO, and was never intended to be used to describe patients with other respiratory conditions.

> "Definition of BOS: We use the term *bronchiolitis obliterans syndrome* to connote graft deterioration secondary to persistent airflow obstruction…BOS does not necessarily require histologic confirmation; in contrast, the term *bronchiolitis obliterans* is used for a histologically proven diagnosis" (Estenne et al. 2002).

Thus, the implicit assumption by NIOSH that all patients suspected to have BO can be accurately diagnosed noninvasively has never been adequately tested, nor should patients on chronic immunosuppression automatically be considered to be at similar risk to develop BOS compared with a non-transplant population. Indeed, "This (BOS) terminology has not yet been adopted outside the field of lung transplantation" (Cordier 2007).

In the eight cases described by the NIOSH authors, only three had lung biopsy results reported. A brief summary of one (Case 9) indicated no correlation with findings expected in cases of BO. Instead, the authors described "mild emphysema, unilateral pleural changes consistent with recurrent pneumothoraces and subpleural interstitial fibrosis" (Akpinar-Elci et al. 2004). Another biopsy (Case

[2] The findings have an associated *P* value of 0.8; that is, there is an 80% probability that the data could have occurred by chance.

3) was described as "consistent with bronchiolitis obliterans" (Akpinar-Elci et al. 2004). However, the finding of tissue granulomas in this specimen introduced the possibility that a hypersensitivity pneumonitis or other granulomatous process could be responsible (Markopoulou et al. 2002). The last biopsy specimen (Case 1) was pictured and does display many features seen in CB. The presence of active inflammation seen in the interstitial and peribronchiolar tissues may also be consistent with a cellular bronchiolitis, where mural and peribronchiolar fibrosis is also common. Thus, we believe that only this last biopsy can be considered suggestive of BO. The authors themselves state that two of the three biopsies "were not diagnostic of bronchiolitis" but attributed this to "a recognized sampling problem" (Akpinar-Elci et al. 2004).

What is even more problematic, however, is the lack of biopsy data for the other six cases alleged to have BO. Without a definitive tissue diagnosis, one might suspect BO, but claims of a specific rare disease outbreak should be linked to clear evidence of that disease. Questionnaire responses and PFTs are important data, but overly broad in their approach. Also, HRCT findings of mild mosaic pattern seen on expiration can frequently be seen in normal patients and in diseases such as asthma and emphysema, and is noted to occur in BO only about 50% of the time (Jensen et al. 2002).

Other HRCT findings should also be interpreted with caution due to overlap with more common disease processes.

> "Computed tomography is more sensitive than the chest radiograph in detecting the changes of hypersensitivity pneumonitis. A characteristic pattern is of ground-glass shadowing with areas of decreased attenuation and air trapping on expiratory scans" (Bourke et al. 2001).

As a result of relying upon scant lung biopsies with poorly correlated findings, and assuming that the HRCT changes observed could not represent alternative pulmonary processes, NIOSH appears to have acted prematurely in designating this group of nine workers as having BOS, a syndrome which has not been defined in a non-transplant population.

California Department of Health Services Report of May 15, 2006

Cases of BO were stated to have occurred in two workers at food flavoring companies in California. Both of these workers performed mixing of dry powders to make various flavoring substances, including butter flavoring (Harrison et al. 2006).

Case 1, a 32-year-old man, was described as having intermittent wheezing and a productive cough. He had been diagnosed with bronchitis and allergic rhinitis. After complaining of progressive dyspnea, HRCT scanning showed "scattered peribronchial ground glass opacities," findings that are not commonly associated with BO, but rather with a variety of other, primarily interstitial, lung disorders.[3]

Pulmonary function testings revealed the worker to have an FEV1 of 28% of predicted. A second HRCT scan was done several months later showing "subtle areas of mosaic attenuation." No lung biopsy was performed to validate the minor HRCT findings, and over the succeeding 18 months, the patient experienced no further deterioration. It was not noted if the patient required continuous supplemental oxygen therapy, or what his level of functioning had been; nor were any courses or effects of therapy revealed, other than receiving antibiotics for an initial diagnosis of bronchitis and rhinitis.

Case 2 was a 43-year-old woman, who again complained initially of an upper respiratory infection that was treated with antibiotics. She also complained of worsening dyspnea, and was found to have an HRCT study that showed "several small areas of patchy ground glass opacities throughout the lung fields." Again, this finding is consistent primarily with interstitial lung processes, not airway-related lung diseases. This was confirmed after the patient underwent a wedge resection, which showed histologic findings of "inflammatory infiltrates in the peribronchial and interstitial areas" as well as "non-caseating type granulomas with giant cells." These findings are supportive of extrinsic allergic alveolitis, as well as a number of other granulomatous lung diseases, but are not characteristic of BO. Also, histologic findings that one would expect to find in BO were not described, such as submucosal bronchiolar fibrosis, obliteration of small airways, or heavy elastin staining. We assume if these features were present, they would have been described. It is also interesting that the CDHS relied upon total body plethysmography to produce findings that are interpreted as "consistent with air trapping," when her HRCT study should have provided evidence of air trapping, if in fact it were present.

Thus, after reviewing the CDHS diagnoses in these two cases, it appears that other compelling explanations for their conditions have been overlooked. We do not doubt that significant respiratory conditions are present; however, the leap to making the diagnosis of BO appears to us to be premature and without sufficient basis.

[3] Examples include extrinsic allergic alveolitis, nonspecific interstitial pneumonia, follicular bronchiolitis and lymphocytic interstitial pneumonia.

Discussion

Suspicions of BO should be characterized as such, and spirometry data, normal chest X-rays, subjective questionnaire results, and other studies where findings may exhibit considerable overlap with other conditions should not be described as "consistent with" a rare disease, implying that diagnostic certainty has been attained. Characterizing individuals as having this rare disease should ideally only occur after a definitive biopsy has been performed. We do realize, however, that there are circumstances where different disease definitions may be appropriate. For example, epidemiology studies looking at the incidence of severe respiratory disease in a given industry may well be interested in less strict criteria for BO. In these circumstances, the less certain nature of the diagnosis should be openly acknowledged, as well as alternative diseases that may be in the differential. Since even in experienced hands the diagnosis of BO can be difficult to make, standards should be adopted to ensure accurate and consistent histopathologic readings of lung biopsy specimens in exposed workers going forward, improving the chances that appropriate medical treatment will be provided.

The animal studies that have been performed subsequent to the initial NIOSH plant evaluations are inadequate for defining the nature of the responsible agent for respiratory complaints (Hubbs et al. 2002, 2004). Animal studies that relate to the types of exposures actually experienced in an occupational setting should be designed and performed to better understand the mechanism of disease. Also, the chemical properties of diacetyl, often cited as the causative agent for "popcorn lung," do not appear to be consistent with a disease process known to target the deep lung. As Hubbs et al. (Hubbs et al. 2002) noted: "In particular, water-reactive and water-soluble vapors tend to accumulate in nasal tissues". No mechanism has yet been described that would explain how diacetyl exposure could lead to deep lung damage or other chronic health effects.

Heated soybean oil may itself be a risk factor, in light of recent studies showing the deleterious effects of oleic acid in the lungs of dogs (Li et al. 2006). Oleic and linoleic acid, fatty acids present to a significant degree in soybean oil, have been shown to be respiratory irritants (Khan et al. 1991) and have been suggested as models for BOOP and BO in humans. Other constituents of butter flavoring may also be useful to examine (NIOSH 2003d).

Conclusion

NIOSH scientists have used the example of the microwave popcorn manufacturing plants as a demonstration of unrecognized occupational health risks leading to severe disease in workers. Their investigations and reports have led to significant changes in the policies and procedures for these manufacturing plants, and have undoubtedly reduced chemical exposures for many workers in these facilities. However, in our view, they have been unable to provide sufficient evidence to support their claims of an outbreak of BO in the worker populations studied, and the agent(s) responsible for the incidence of severe respiratory disease remains unclear.

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