

Discussion: Bronchiolitis obliterans organizing pneumonia (BOOP) is not a new disease, but it has been described as a distinct entity¹ with different clinical, radiographic, and prognostic features than the airway disorder bronchiolitis obliterans and the interstitial fibrotic lung disorder, usual interstitial pneumonia/idiopathic pulmonary fibrosis.² The main histological feature distinguishing BOOP from interstitial pneumonias is that the fibrosing process involves predominantly airspaces rather than interstitium. BOOP is characterized by polypoid endobronchial connective tissue masses composed of myxoid fibroblastic tissue resembling granulation tissue filling the lumens of terminal and respiratory bronchioles and extending in a continuous fashion into alveolar ducts and alveoli, representing an organizing pneumonia.³ BOOP is a restrictive lung disease with diffuse, bilateral patchy, radiographic infiltrates and a clinical onset that is often acute that mimics atypical pneumonia. BOOP is reversible with treatment (oral prednisone) in over 60% of cases,⁴ but it has the potential for progressing to irreversible pulmonary fibrosis and end-stage honeycomb lung.

We report on a case of BOOP in an African American man employed as a snack chip spicing technician. Unfortunately, we did not have access to the workplace or to the proprietary formula for the spices used in the spicing operation. However, the patient's description of the process suggested significant exposure to airborne spice dust. In our review of the medical literature, we found a long association of paprika (one of the spices to which the patient was exposed) causing occupational lung disease, specifically, hypersensitivity pneumonitis or allergic alveolitis. Paprika Splitter's Lung is caused from inhalation of organic material in the processing of the paprika fruit.⁵ It has been suggested that workers who developed Paprika Splitter's Lung were actually responding to a fungal element (*mucor*

stolonifer) associated with paprika rather than the paprika fruit itself.⁶ Paprika and other spices have also been associated with immunoglobulin E-mediated occupational lung disease causing immediate asthmatic responses in some patients.^{7,8} We found no reports supporting occupational BOOP in spice workers.

With this information, we questioned whether the patient may have had a component of hypersensitivity pneumonitis with secondary BOOP, and we obtained a second histopathological opinion at Duke Medical Center. The final opinion from the pulmonary pathologist commenting on the open lung biopsy tissue described, "A pattern of patchy acute pulmonary injury characterized by the presence of loose plugs and edematous connective tissue within alveolar ducts and terminal bronchioles [is] noted. No necrosis is seen. No significant interstitial fibrosis is present. The small airways also demonstrate moderate chronic inflammatory change. No granulomata are seen." Thus, the potential for BOOP in association with hypersensitivity pneumonia seemed to be ruled out.

BOOP has been observed following infectious illnesses, including chlamydia, legionella, mycoplasma, adenovirus, cytomegalovirus, influenza virus, malaria, pneumocystis, and cryptococcus. An infectious cause appears unlikely from the clinical workup. There was no evidence in the medical record for some of the other known causes of BOOP, including toxic fume inhalation, connective tissues disorder, adult respiratory distress syndrome, or aspiration pneumonitis, and the patient had not undergone organ transplantation. Our finding of what seems to be an occupation-associated BOOP in a spicing technician makes us question whether there are similar cases that have not been reported. In a telephone conversation with the National Institutes for Occupational Safety and Health (NIOSH) in Morgantown, we discovered that researchers are currently investigating cases of

bronchiolitis obliterans in another industry that uses spices. The following letter reports preliminary findings of the cases they have studied. Further research is needed to determine the exact agent(s) responsible for respiratory disease in spice industry workers.

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Rapidly Progressive, Fixed Airway Obstructive Disease in Popcorn Workers: A New Occupational Pulmonary Illness?

To the Editor: A number of former employees at a microwave popcorn packaging facility in Missouri presented in spring 2000 with severe pulmonary symptoms characterized

by fixed airway obstruction. Most had well-preserved carbon monoxide diffusing capacity of the lungs. These patients had seen numerous other practitioners but for the first time were recognized as all working in the same facility and as having been potentially exposed to the same occupational environment. The characteristics of Popcorn Packers' Lung seemed to be due to an environmental exposure to a workplace toxin that causes a unique and previously unrecognized form of rapidly progressive obstructive lung disease. We report the clinical cases here to increase awareness of the occupational medical providers in the hope that additional cases will be classified, hazardous workplaces will be identified, and primary preventive intervention will take place.

The facility, located in Missouri, received raw corn and produced packaged popcorn. The process consisted of mixing salt, oil, and flavoring; combining this with the popcorn; and packing it in single-serving packages for use in microwave ovens. The flavoring consisted of various spices, and a butterlike flavor was provided by the chemical diacetyl. Depending on where the employee worked in the plant, exposure to the flavoring components could vary by more than an order of magnitude.

Case 1: A 46-year-old woman was employed at a popcorn facility for 18 months and was responsible for bagging popcorn. Approximately 16 months after employment, she began to develop shortness of breath and a cough. This progressed rapidly, and she was admitted to the hospital with acute asthma and diagnosed with bronchitis. She was a life-long nonsmoker and had no prior symptoms of asthma.

The patient's pulmonary function demonstrated a forced vital capacity of 45%; a forced expiratory volume in 1 second (FEV₁) of 25%; and a forced expiratory flow, midexpiratory phase, of 10% of predicted. Her carbon dioxide diffusing capacity

was 80%, and her alpha₁-antitrypsin level was normal. She was evaluated at a referral medical center, where she was diagnosed with bronchiolitis obliterans on clinical presentation. An inspiratory computed tomographic scan of the chest demonstrated interstitial changes. The patient was evaluated, accepted for a lung transplant at a transplant center, and is currently on 3 L of oxygen per hour.

Case 2: A 26-year-old man was employed at popcorn factory as an oil mixer. Thirteen months after employment, he noted onset of symptoms so abrupt that in 1 day he went from being asymptomatic to being unable to climb up a single flight of stairs to his workplace. He began to have wheezing and chest pressure. The patient was initially diagnosed with pneumonia. Previously, he had smoked a pack of cigarettes a day for 8 years and had stopped 3 years before working at the popcorn factory. In addition, he was nonasthmatic.

The patient was employed at the facility for a total of 18 months. Approximately 2 months after initial symptoms, pulmonary function studies demonstrated a forced vital capacity of 41%; FEV₁ of 18%; and forced expiratory flow, midexpiratory phase, of 5% of predicted. He had a carbon monoxide diffusing capacity of 102% of predicted. His pulmonary function values have remained at this level over the past 2 years.

An inspiratory computed tomographic scan of the chest demonstrated changes consistent with mild diffuse bronchiectasis bilaterally. A ventilation perfusion scan demonstrated diffuse lung disease, and a right heart catheterization was normal. He was treated with Cytoxan and prednisone without affect. Laboratory studies were negative for alpha₁-antitrypsin deficiency. The patient was evaluated at a lung transplant center and was placed on the lung transplant list.

Case 3: A 54-year-old nonasthmatic nonsmoker had worked for 4

years in another microwave popcorn packaging facility, where his duties included mixing flavorings with oil and salt. One week after beginning to use a new artificial butter flavoring, he developed blurred vision from corneal ulcerations and worsening of his mild chronic cough, which was productive of white sputum. Bibasilar rales were apparent on auscultation of the chest. Pulmonary function tests at diagnosis showed mild airway obstruction with no improvement after albuterol inhalation. The diffusing capacity for carbon monoxide was normal. A computed tomographic scan of thorax with inspiratory and expiratory views was suggestive of mild air trapping.

The popcorn processing plant then closed for 2 weeks. During this time, the patient was treated with prednisone, 40 mg per day, for 14 days. One week after the first clinic visit, he reported improvement in his cough and his FEV₁ had increased from 2.55 L at initial presentation to 3.02 L. After the plant reopened, he returned to mixing the previous butter flavoring. When he was reassessed 6 weeks after diagnosis, his FEV₁ had increased to 3.22 L, his cough had resolved, and his corneal ulcerations had healed.

In summary, this employee of a microwave popcorn plant, who had been routinely exposed to an artificial butter flavoring, developed acute worsening of his mild chronic cough and corneal ulcerations after using a new artificial butter flavoring product in his work. There was significant improvement in his lung function and eye symptoms after exposure to this product ended and after corticosteroid therapy. These observations suggest that cessation of exposure is important for the treatment of this syndrome. Corticosteroids may also play a role in the management of this clinical problem.

Summary: Evaluation of these exposures and four others initially demonstrated an unusual concentration of bronchiolitis obliterans-type symptoms in a small popula-

tion. The longitudinal investigation is continuing under the aegis of the National Institute for Occupational Safety and Health (NIOSH). Recently, another case was diagnosed at a facility in northern Missouri where butter flavoring is manufactured. Suspicion of the causal agent being the flavoring was focused in an animal study performed using rats exposed for 24 hours to the flavorings, which produced severe upper and lower airway changes in the animals.¹

Diacyl (2,3-butanedione) is a commonly used food flavoring and also occurs naturally in butter, coffee, and bay oil. It forms the essential oil of butter and butter flavorings and has not previously been described as toxic when inhaled.² Diacyl is not listed in the most commonly used occupational guide to workplace chemical hazards, the *NIOSH Pocket Guide to Chemical Hazards*.³

Clearly, these early series of cases are of significance in inferring causality. The relative risk of a few former employees out of a total of approximately 400 is much higher than would be expected for the occurrence of bronchiolitis obliterans in the general population, which has been estimated to be between 1:40,000 and 1:100,000.⁴ The effect seems to be seen only in the current and former employees of a popcorn packaging facility and not in the general population of the surrounding county. There was consistency of results of testing by different and independent investigators. Furthermore, a temporal and physical correspondence and a biologic plausibility exist by both analogy of other chemicals and preliminary animal tests. Therefore, the Hill Criteria are fulfilled.⁵

We believe these cases represent a new and potentially lethal occupational pulmonary disease, Popcorn Packers' Workers' Lung. We would encourage all occupational health care providers to monitor employees who work in and around food flavorings by obtaining baseline and periodic values. Any eye, upper respira-

tory, and pulmonary symptoms among these workers require investigation. Unless exposure is stopped and therapy is initiated early on, the changes may be rapidly progressively and irreversible. Good industrial hygiene practices, including engineering projects to improve ventilation, provide personal protective equipment, and reduce exposure to the suspect agents should be urged. If any such cases are identified, the state public health department and NIOSH should be notified immediately.

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A Follow-Up: High Level of Dioxin Contamination in Vietnamese From Agent Orange, Three Decades After the End of Spraying

To the Editor: This is an update of our findings of current dioxin contamination of Vietnamese from Agent Orange phenoxyherbicide, last applied over 30 years ago. Agent

Orange, half 2,4-D and half 2,4,5-T phenoxyherbicides, contaminated with an average of 3 parts-per million (ppm) of 2,3,7,8-tetrachlorodibenzo-p-dioxin, or TCDD, was very heavily sprayed in the south of Vietnam between 1962 and 1971 during the US-Vietnam war, with the heaviest spraying between 1967 and 1971.^{1,2} The blood from 43-Bien Hoa residents sampled between 1999 and 2001 in the heavily sprayed southern Vietnamese city of Bien Hoa (population 390,000; located 35 km north of Saigon which is now known as Ho Chi Minh City) has now been analyzed for dioxins. These were from a convenience sample of men and women aged 16 to 71 years who were willing to donate over 60 mL of whole blood as part of a Vietnam Red Cross dioxin survey. Comparison blood from Hanoi, where no Agent Orange was used, was also analyzed ($n = 105$). Except for the dioxin contaminant characteristic of Agent Orange, 2,3,7,8-TCDD, no other dioxins or dioxin-like chemicals were elevated. In the case of TCDD, elevated levels were defined as above 5.0 ppt, lipid-normalized. Of the 43 persons, 41 (95%) had elevated TCDD. Comparison blood from Hanoi had an average level of approximately 2 parts per trillion (ppt) TCDD, whereas the range in Bien Hoa varied from 2.4 to a very high 413 parts per trillion (ppt), with a median of 67 ppt, as shown in Table 1. The high value (413 ppt) represents a 206-fold increase above the Hanoi TCDD baseline level. Although Agent Orange was sprayed in Vietnam between 1962 and 1971, an underground spill of Agent Orange also occurred in 1971 at the nearby storage facility at Bien Hoa Air Base. Elevated TCDD was found in children and adults born in this southern region of Vietnam and in northern Vietnamese who recently moved to the area.

Because almost all dioxin body burden comes from ingestion of contaminated animal fat, the findings are almost certainly attributable to the