History of a new illness

- Jasper, Missouri popcorn facility
- Biology of the lung
- Initial Clinical Cases
- Epidemiology
- NIOSH Investigation
- Chemistry
- Brochiolitis Obliterans Syndrome

Jasper, Missouri

Small facility located in SW Missouri, packs popcorn. Initially in 1980s, packed for home popping in jars. In early 1990s, began packaging microwave packets.

Occupational Medicine

- Prevent occupational illness and injury
- Treat occupational illness and injury
- Dedicated to promoting the health of workers through preventive medicine, clinical care, research, and education
BUT FIRST…

• A quick review of human/mammalian respiratory physiology

• Out goes the bad air, in comes the good…

The airways decrease in individual size, increase in total cross section

Upper Airway  Trachea  Bronchus  Bronchiole  Alveolus
bone structure  cartilage rings  muscular tubes  sacs
2 cm² 100m²

Pulmonary Functions

<table>
<thead>
<tr>
<th>Volume</th>
<th>Time</th>
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<td>Tidal Volume</td>
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Forced Vital Capacity (FVC) in Litres

Forced Expiratory Volume in One Second (FEV₁) in Litres

Forced Expiratory Flow from the 25th to 75th Percentile (FEF25-75) in Litres per second

And Diffusing Capacity (DLCO)

Initial Cases

• Early 1990s, workers began noting difficulty breathing, particularly with certain product lines.

• Several became too ill to work and developed asthma, respiratory illnesses of various sorts.

• Consultations at specialty centers did not provide a definitive diagnosis to individuals
Initial investigation

- An attorney interviewed several former employees, multiple diagnoses, multiple treating physicians.
- Cases presented for medical review.

Holy Smokes! There’s an Epidemic of Bronchiolitis Obliterans in Jasper.

- Background incidence (rate of new cases per year) of Bronchiolitis Obliterans ~1/40,000 people per year
- Rate in Jasper ~50/10,000 people/yr
- Epidemics are defined as excessive rate of disease
- So there is an epidemic in Jasper

Patient Characteristics

- Aged 29-50
- 5 Female/4 Male
- 8 Non-Smokers
- Employed few months to several years
- Worked in various places and positions around the plant
- No time of year specified for onset

Patient 1

- 40 y/o F, employed 6 months on packing line.
- Non-smoker
- FVC=57% FEV\textsubscript{1}=21% FEF\textsubscript{25-75}=6%
- DLCO=51%

Patient 7

- 50 y/o M, employed 18 months as an oil mixer.
- Ex-smoker: 12 pk-yrs (stopped 15 years)
- FVC=40% FEV\textsubscript{1}=19% FEF\textsubscript{25-75}=8%
- Additional exams: Developed allergic dermatitis due to diacetyl, per KUMC. Claim denied.

Epidemiology

- May, 2000-Missouri Department of Health contacted.
- August, 2000-MDH, NIOSH meet with and discuss investigation.
- August, 2000-March, 2001-NIOSH site investigation.
- August, 2001-Interim Report
### Pulmonary Findings in Popcorn Workers: Index Cases

- **PFTs**
  - Severe fixed airway obstruction in 6 of 8
  - Well-preserved DLCO in 7 of 8
- Chest X-rays unremarkable in all
- Initial diagnoses: bronchitis, pneumonia, asthma, emphysema
  - NIOSH Workshop Summary 8/25/01

- Wedge lung biopsy from 1 subject showed granulomatous bronchiolitis/pneumonitis
  - This person had a normal BAL
  - Is this a hypersensitivity response?
- 1/2 given Cytoxan had objective improvement
- 0/8 responded to corticosteroids
- 4 are listed for lung transplantation
  - NIOSH Workshop Summary 8/25/01

### Pulmonary Findings in Popcorn Workers

- **What exposure(s) caused these findings?**
  - Exposures at this plant consist of salt, flavorings, oil and popcorn kernels
  - Flavorings used include a butter flavoring containing diacetyl
    - Diacetyl is the predominant ketone in butter flavoring
  - NIOSH Workshop Summary 8/25/01

- Have these exposures been associated with lung disease in other settings?
  - J. Lockey described a food flavoring plant employee with fixed airway obstruction, air trapping and normal DLCO on PFTs with bronchiolitis obliterans on open lung biopsy, later published as 5 cases.

### Other Findings

- Eye irritation
- Dermatitis
- Infertility association

### Pulmonary Findings in Popcorn Workers

- Gross lung specimens notable for focal nodules, failure to deflate in the expected time after biopsy is taken
- Histologic appearance is that of organizing fibroblastic polyps
  - Usually extend from one side wall of a respiratory or terminal bronchiole, sometimes into an adjacent alveolar duct or sac
Bronchiolitis Obliterans

- Lymphocytes and plasma cells sometimes present
- Need a specimen obtained by VATS or open biopsy to make the dx in a definitive manner
- HRCT very useful

Bronchiolitis Obliterans Differential Diagnosis

- **Inhalation of toxic fumes, gases, dusts**
  - Cigarette smoke, irritant gases such as chlorine, silica, grain dust etc.
- **Infection**
  - Influenza, CMV, RSV, other viruses
  - Fungi
  - Bacteria
    - *Bordetella pertussis*
    - *Mycoplasma*

High Resolution CT Findings in Bronchiolitis Obliterans

- Inspiratory film: areas of low attenuation
- Expiratory film: areas of air trapping, distinct from normal areas of increased attenuation seen at end expiration

Pulmonary Findings in Popcorn Workers

- Is there supportive data from animal studies?
  - Rats exposed to vapors from a butter flavoring by NIOSH scientists developed necrosis of airway epithelium from the nasal cavity to the lung
    - NIOSH Workshop Summary 8/25/01
    - Hubbs 1-2002, Hubbs 2-2004

Nebraska Popcorn Worker with Cough

- 50+ yo popcorn packing facility manager who developed corneal ulcerations, worsening of his mild chronic cough 1 wk after starting to use a new low-fat butter flavoring (with more butter flavoring than usual recipe)
- Non-smoking, no history of asthma
- 4 year work history, with duties including mixing of flavorings
**Popcorn Worker with Cough**

- Eye exam confirmed the corneal ulcerations
- Hoarseness
- Bibasilar rales on chest exam
- Inspiratory/expiratory high resolution CT: normal vs. mild air trapping
- PFT's showed mild fixed airway obstruction

**Nebraska Popcorn Worker**

- The plant was shut down for 2 weeks
- He developed *Herpes zoster* and was treated with prednisone 40 mg/day
- 1 week later, he had resolution of his blurred vision and his cough was decreasing in severity
- 6 weeks later, he denied pulmonary and eye symptoms and had returned to full-time work at the popcorn packing facility

**Nebraska Popcorn Worker: Important Features**

- Had acute onset with exposure to a new flavoring
- Unique physical findings included corneal ulcerations, hoarseness
- Rapid improvement with change in exposure, corticosteroids

**Popcorn Worker’s Lung: Summary/Conclusions**

- Syndrome seen in workers who package microwave popcorn
  - Those who mix flavoring, pack at highest risk
- Airway obstruction (mild to very severe)
  - Not reversible with bronchodilator therapy
  - Air trapping on inspiratory-expiratory high resolution CT scan
  - PFTs stabilize with cessation of exposure

**Popcorn Worker’s Lung: Summary/Conclusions**

- Radiographs and PFTs c/w bronchiolitis obliterans but we do not yet fully understand the histology
- Evidence points to flavoring agents containing diacetyl as a causative agent
  - Diacetyl used widely as a butter flavoring, is present in butter
  - Await results of industrial hygiene studies, animal experiments

**Popcorn Worker’s Lung**

- The microwave popcorn industry needs to control exposure to fumes from artificial butter flavorings
  - NIOSH is working with this industry to address the problem using industrial hygiene measures and use of PPE
Interim Report

• 87% of employees evaluated by survey, spirometry, chest x-rays.
• Ees had 2.6 times rate of expected chronic cough compared to national average. 3.3 times rate of chronic bronchitis.
• Non-smoking Ees had 5 times rate of expected chronic cough compared to national average, 10.8 times rate of chronic bronchitis.
• Average loss of lung volume 200 ml/yr compared to national average of 30 ml/yr.

Animal Exposure Study

• Rats inhalation exposed to butter seasoning at increasing doses.
• Deaths occur at 1/3 workplace maximums.
• Suspect chemical: Diacetyl (2,2-Butanedione)
  \[ \text{C}_4\text{H}_6\text{O}_2 \]
  Naturally occurring ketone in butter, coffee, bay oils.
  FDA lists as GRAS

The Suspects:

• Diacetyl (2,2-Butanedione)
  \[ \text{C}_4\text{H}_6\text{O}_2 \]
• Acetaldehyde
  \[ \text{C}_2\text{H}_4\text{O} \]
• Acrolein (2-propenal)
  \[ \text{C}_3\text{H}_4\text{O} \]

Diacetyl was once used to treat recurrent pneumothorax by causing pleural scarring: Laforet & Hering, Intrapleural Insufflation of Diacetyl Phosphate to Promote Pleural Symphysis, *Chest*, 1963;44:505-508.

NIOSH Summary

• Work Related Brochiolitis Obliterans Syndrome in Relation to exposures arising in the mixing room but widely disseminated throughout other areas of the plant.
• Recommend extensive primary, secondary and tertiary prevention efforts for all current and former workers.

Diacetyl in other Industry?

• Flavor manufacturing
• Candy
• Pastries
• Butter flavored oils
• Coffee?

Timeline-diacetyl in butter flavor

• 1987 Two workers develop brochiolitis obliterans in baking factory.
• 1989 First of eight employees develops BO at flavoring manufacturer. She dies.
• 1989-Test rats die after 4 hour exposure
• 1994-Manufacturer’s employees into full respirators
• 1995-Manufacturer investigates workers’ compensation claims. Decides not to inform government, workers or customers of risks.
• 1997-Manufacturers conference on Bronchiolitis Obliterans
• 2004-OSHA calls for safety guidelines governing flavoring additives. Regulations still pending.
• 2005-Manufacturers change Material Safety Data Sheets to reflect hazards of inhalation of diacetyl.
Finding Disease is Just Luck!

- Serendipity?
- Many highly qualified clinicians saw these patients, some as early as 1993. No public health issue raised until 2000.
- OR

The dose makes the poison
Paracelsus, 1567

What do we need to know?

- What is the biological effect of diacetyl, acetaldehyde and related chemicals?
  - Basic toxicity testing in lab animals
  - The lab rat problem and other animal models
  - Protective effect of nicotine?
  - Understanding the biochemistry and binding sites
- What are safe levels for workers?
  - How do we sample the chemicals?
  - Engineering protection-ventilation, respirators?
  - Surveillance of the workplace and workers?
  - Long term health studies needed.
- Are there hazards to consumers?
  - Needs large scale statistical studies

What is this?

- Bronchiolitis obliterans?
- Bronchiolitis obliterans syndrome (King, 2001)
- Diacetyl induced BO (DIBO), (Harber, 2007)
- Flavoring induced BO (FIBO)

Bronchiolitis Obliterans Syndrome

First Trial $20M

Federal (IN)Action 2007:
April Congressional Hearings: Mr. Foulke, Secretary of OSHA stated, “the science is murky”.

“People at OSHA have no interest in running a regulatory agency,” said Dr. David Michaels, an occupational health expert at George Washington University.

There are currently trials pending and cases in California, Illinois, Indiana, Iowa, Kentucky, Ohio, Missouri, Montana, Nebraska and North Carolina.

New York Times, Page 1, April 27, 2007
References

• Joplin Globe extensive reporting for individual trials and cases.