

# Occupational Asthma: A Case of Baker's Asthma

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## ABSTRACT

*Asthma is one of the most prominent respiratory diseases worldwide. It is defined by airflow limitation and/or airway hyperresponsiveness and can be exacerbated by a number of environmental allergens. When allergic asthma exacerbations are attributed to stimuli in a particular work environment, then occupational asthma must be considered. Incidence estimates vary, but in 1999 the Surveillance of Work-Related and Occupational Respiratory Disease in the United Kingdom estimated 4293 incident cases of occupational respiratory disease, an increase of 1427 cases over the previous year. Occupational asthma represented 26% of these cases. Baker's asthma is one of the most frequently reported types of occupational asthma in several countries. Diagnostic steps include thorough history, careful exam, and demonstration of functional reversible airflow obstruction. Treatment modalities used for occupational asthma are similar to those used in the management of other forms of asthma, with particular attention to reducing the level of exposure to the inciting allergen. (Allergy and Asthma Proc 25:151-156, 2004)*

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## CASE REPORT

A 35-year-old male business owner presented with a complaint of sneezing and nasal congestion for 8 years. Symptoms were worse at home and at night while indoors, and upper respiratory tract infections exacerbated his symptoms. The patient denied any past history of asthma, hay fever, or eczema. He had never taken regular medications of any sort. His social history included business ownership since the age of 27 years and he had a 15-pack-year smoking history that concluded 1 year ago. Physical exam was significant only for edema and pallor of the nasal turbinates. Pulmonary function test revealed a forced expiratory volume in 1 second (FEV<sub>1</sub>) of 2.03 L (52% predicted), a forced vital capacity of 3.71 L (75% predicted), an FEV<sub>1</sub>/forced vital capacity ratio equal to 0.55, and a forced expiratory flow at 25–75% of 1.13 L/s. The  $\beta_2$ -agonist administration reversed his FEV<sub>1</sub> to 2.30 L. Skin testing to environmental allergens showed local reactions to grass pollen, tree pollens, and dust mites. Chest x ray showed no abnormality. Additional history revealed he was a bagel-store owner and was involved directly with the baking process. This prompted additional laboratory investigation. The patient's eosinophil count was 360 cells/ $\mu$ L (normal, 100–300 cells/ $\mu$ L), immunoglobulin E (IgE) was 212 IU/mL (normal, 0–150 IU/mL), and  $\alpha$ -1-antitrypsin was 147 mg/dL (normal, 140–320 mg/dL). Special testing revealed allergen-specific IgE antibody to be very positive to wheat (class V) and strongly positive to rye grain (class IV). Specific antibody to baker's yeast and brewer's yeast were negative. He was diagnosed with allergic rhinitis and baker's asthma.

## DEFINITION

Asthma is one of the most prominent respiratory diseases encountered by allergists and physicians in general with an increasing worldwide prevalence. In the United States alone, the prevalence in 1994 was estimated at 5.6% of the general population or 14.6 million persons.<sup>1</sup> Induction of reactive airways disease involves interaction between environment and intrinsic susceptibility. The workplace can be a significant contributor to inflammatory airway disease. Occupational asthma has been defined classically as a "disease characterized by variable airflow limitation and/or airway hyperresponsiveness due to causes and conditions attributable to a particular occupational environment and not to stimuli encountered outside the workplace."<sup>2</sup> Within this definition of occupational asthma there are two pathogenic types, namely "immunologic"<sup>2</sup> and "nonimmunologic."<sup>2</sup> These can be distinguished from one another based on a latency period that exists in immunologically based occupational asthma but is absent in non-immunologically based occupational asthma.

## EPIDEMIOLOGY

Incidence estimates have used a number of voluntary reporting surveillance schemes including sentinel-based and medicolegal data. One of best-known programs is the Surveillance of Work-Related and Occupational Respiratory Disease, which collects reports from British specialists in occupational or respiratory diseases on newly diagnosed occupational lung disease. There were an estimated 4293 incident cases of occupational respiratory disease reported in the United Kingdom in 1999, an increase of 1427 cases over the previous year. Occupational asthma represented 26% of these cases.<sup>3</sup> This occupational asthma incidence was stable with some changes in the responsible agents. There was an increase in the number of cases among nurses, construction and mine workers, and bakers, with a decrease among hairdressers and laboratory technicians.<sup>4</sup> In the United States, the Sentinel Event Notification System for Occupational Risks identifies potentially dangerous sentinel cases at work. Between the years of 1993 and 1995, the Sentinel Event Notification System for Occupational Risks surveillance in California, Massachusetts, Michigan, and New Jersey identified 1101 people with occupational asthma, including 210 people with work-aggravated asthma and 891 new-onset diagnoses.<sup>5</sup>

Occupational asthma prevalence is said to range between 2 and 6% of the asthmatic population.<sup>6</sup> Epidemiological evidence suggests occupational asthma is underdiagnosed.<sup>7,8</sup> A New England health maintenance organization contributed data to a prospective cohort study that revealed only 7% of health care practitioners record job exposures in new-onset asthma cases, among whom almost three-quarters had asthma associated with work.<sup>9</sup> Epidemiological studies encounter what is referred to as the healthy worker

effect whereby workers developing occupational asthma quit without reporting their illness, leaving behind an asymptomatic, "healthy" population. Nonetheless, prevalence studies have their place and remain useful for the examination of workforces exposed to newly recognized agents.<sup>10</sup>

## RISK FACTORS

The reason one worker succumbs to occupational asthma while a coworker in identical conditions does not is most likely because of personal risk factors. Atopy, defined by skin test positivity to common aeroallergens, is a risk factor for occupational asthma,<sup>11</sup> but only in workers exposed to high molecular weight antigens. Examples of cross-sectional studies in which a greater prevalence of occupational asthma was seen in atopic groups include health care workers with allergy to latex, detergent workers with allergy to microbial enzymes, and laboratory handlers allergic to animal proteins.<sup>12-14</sup> There was no increased prevalence of atopy among patients who have asthma and respond to the low molecular weight antigen found in the western red cedar.<sup>15</sup> Previous studies do not support atopy as a risk factor for workers with occupational asthma from reactive chemicals.<sup>11</sup> Smoking tobacco has been shown to increase the likelihood for development of IgE-specific antibody and asthma at work. In a group of workers exposed to tetrachlorophthalic anhydride (TCPA), a greater proportion of workers with allergen-specific IgE antibody to TCPA were smokers compared with workers who did not have the allergen-specific IgE.<sup>16</sup> In addition to greater risk of allergic sensitization to TCPA among smokers, smoking was found to be more common in salmon-processing workers,<sup>17</sup> enzyme-related workers, and snow crab workers.<sup>18</sup> The relation of smoking to occupational asthma has been thought to be protective for red cedar asthma workers, because 94% of affected workers were nonsmokers or former smokers. This discrepancy illustrates the need for continued study of particular risk factors in occupational allergy. To date, no risk factors should strictly preclude a person from entering a particular occupation, but risk associations should alert the physician to possible confounding factors leading to the development of occupational asthma.

## GENETIC FACTORS

Reports on allergic diseases have suggested a genetic liability to the environment as high as 40%.<sup>19</sup> Both genetics and environment make occupational asthma a heterogeneous and multifactorial condition. Consequently, no single study has yet examined the complex interaction of genes and environment perfectly. Although studies of human leukocyte antigen-associated polymorphisms focusing primarily on class II polymorphism have shown associations with exposure to some low molecular weight agents,<sup>20,21</sup> most lack consistently reproducible results.<sup>22</sup>

TABLE I

## Common Agents Causing Occupational Asthma and Workers at Risk

| Agent                        | Workers at Risk                                                                           |
|------------------------------|-------------------------------------------------------------------------------------------|
| High molecular weight agents |                                                                                           |
| Animal-derived allergens     | Animal handlers                                                                           |
| Cereals                      | Bakers, millers                                                                           |
| Enzymes                      | Bakers, detergent users, pharmaceutical workers                                           |
| Gums                         | Carpet makers, pharmaceutical workers                                                     |
| Latex                        | Health professionals                                                                      |
| Seafood                      | Seafood processors                                                                        |
| Low molecular weight agents  |                                                                                           |
| Acrylate                     | Adhesive handlers                                                                         |
| Amines                       | Lacquer and shellac handlers, solderers                                                   |
| Anhydrides                   | Epoxy resins, plastic users                                                               |
| Chloramine-T                 | Cleaners, janitors                                                                        |
| Drugs                        | Health professionals, pharmaceutical workers                                              |
| Dyes                         | Textile worker                                                                            |
| Formaldehyde, glutaraldehyde | Hospital workers                                                                          |
| Isocyanates                  | Manufacturers of foam, synthetic rubbers, plastics; insulation installers, spray painters |
| Metals                       | Refiners, solderers                                                                       |
| Persulfate                   | Hairdressers                                                                              |
| Wood dusts                   | Cabinet makers, carpenters, foresters                                                     |

Source: Ref. 25.

Linkage studies have been used to identify regions where a disease-associated gene may reside. Promise has been greatest in regions 5q31–33, 6p21, 11q13, 12q, 13q, and 16p12 linking asthma and atopy.<sup>23</sup> Linkage-disequilibrium-mapping technology using single nucleotide polymorphisms may be a useful means to understand the pathophysiology of asthma.<sup>24</sup> Additional investigative schemes are underway currently. Advances in genetic understanding have contributed significantly to innumerable other disease states. Occupational asthma certainly will be no exception.

## CAUSATIVE AGENTS

More than 250 agents are considered major inducers of occupational asthma. Most agents have been categorized broadly according to their molecular weight and the associated occupations at risk are known (Table I).<sup>25</sup>

## PATHOGENESIS

Common agents causing occupational asthma have been identified and are implicated in both immunologic and nonimmunologic types of occupational asthma.

Immunologic types of occupational asthma are more common and typically depend on the molecular weight of the inciting agent. High molecular weight allergens such as animal protein, fish and shellfish proteins, arthropods, plant-derived proteins, and enzyme components are large enough to act as complete antigens and can induce production of allergen-specific IgE antibodies. Cross-linking of surface-bound IgE on mast cells, basophils, and perhaps eosinophils and macrophages leads to activation of these inflammatory cells, with synthesis and release of inflammatory mediators that cause an inflammatory reaction in the airways.<sup>26–28</sup> Low molecular weight agents typically are highly reactive electrophilic compounds that first haptenate with hydroxyl, amino, or thiol functionality of autologous or heterologous airway proteins to form functional antigen capable of acting *via* an IgE-mediated mechanism.<sup>29,30</sup> Platinum salts, tri-metallic anhydride and other acid anhydrides can produce allergenic epitopes after such conjugation, and specific antibodies against these chemicals correlate with the presence of occupational asthma.<sup>31–33</sup> Some low molecular weight agents, including isocyanates and plicatic acid, cause occupational asthma by non-IgE-mediated means. Allergen-specific IgG antibodies have been reported to play an important role in asthma induced by diisocyanates such as hexamethylene diisocyanate and diphenylmethalene-4'-4'-diisocyanate.<sup>34</sup> Allergen-specific IgE antibodies were found in only 20% of asthma patients who reacted to plicatic acid from western red cedar.<sup>35</sup> Depending on the exposure, detection of IgE or IgG allergen-specific antibodies to high molecular weight and some low molecular weight compounds can be useful in the diagnosis of occupational asthma.

Nonimmunologic types of occupational asthma, also known as irritant-induced asthma, are less common and follow workplace exposure to concentrated irritant gases, fumes, or chemicals on one or several occasions.<sup>36</sup> The underlying mechanism by which nonspecific irritants lead to reactive airways disease is not known. It is thought denuding of the respiratory epithelium leads airway inflammation by eosinophil and T-cell infiltration, neurogenic inflammation *via* axon reflexes, and nonspecific activation of mast cells with subsequent release of their preformed, proinflammatory mediators and cytokines.<sup>37</sup>

## PATHOPHYSIOLOGY

The pathological airway changes in occupational asthmatic subjects are the same, regardless of the cause, and similar to other forms of asthma.<sup>38</sup> Desquamation of the epithelium, epithelial cell ciliary abnormalities, smooth muscle hyperplasia, and subepithelial fibrosis; increase in

inflammatory cells; and obstruction of the airway by exudates or mucus are involved.<sup>2</sup> These changes were found in the airways in a patient who died of isocyanate-induced asthma<sup>39</sup> and in bronchial biopsy specimens from occupational asthma patients.<sup>40,41</sup> Additionally, in isocyanate-induced asthmatic bronchial specimens, mast cells were found localized in the epithelium, and an increase in activated T-lymphocytes and eosinophils in the mucosal and submucosal layers was noted.<sup>42</sup> In those with toluene diisocyanate-associated asthma, a reduction of bronchial subepithelial fibrosis occurred 5–12 months after cessation of exposure, but the inflammatory cell infiltrate persisted.<sup>43</sup>

## DIAGNOSIS

**A**n important element in diagnosis of any form of asthma is a thorough history. This should include complete medical history to confirm the diagnosis of asthma and its relation of asthma symptoms to work. Special investigation should be made into the extent and mode of any work-related exposures in both past and present occupations because the duration of illness can be prolonged. Epidemiological studies have supported the level of exposure as the most important determinant of occupational asthma. Even differences in the mode of exposure to the same high molecular weight agent can give different patterns of IgE response.<sup>44</sup> A suggestive symptom history of occupational asthma may include cough, wheezing, shortness of breath, and chest tightness that worsens at work and improves away from work during weekends or vacation. Questions regarding nasal, ocular, or urticarial contact symptoms are important as well. Allergic rhinitis may precede or appear concurrently with the development of allergic asthma and may be a manifestation of the same disease entity.<sup>45,46</sup>

If the history is consistent with occupational exposure and a positive response to bronchodilators shows reversibility, then it is important to determine the possible causative agents. Employee health records, material safety data sheets, and product labels may be useful. Computerized data lists of occupational agents and associated workplaces are available.<sup>47</sup> Appropriate skin testing assays for allergen-specific IgE can be helpful if available. Skin reactivity or increased allergen-specific IgE or IgG antibodies may reflect exposure or sensitization but may not imply allergen effect on the airway. This difference in target organ susceptibility has been shown for occupational allergens including isocyanates, psyllium, and snow crab.<sup>34,48,49</sup> Negative skin tests make occupational asthma unlikely with high molecular weight chemicals such as cereal or psyllium.<sup>50</sup> The standardization and reliability of each test must be assessed before interpreting any test results.

Determination of peak expiratory flow rates and bronchial responsiveness to nonallergic stimuli is a critical step in diagnosis. Peak expiratory flow assessed prospectively using specific inhalational challenge as the gold standard

revealed a sensitivity and a specificity of 81–89% and 74–89%, respectively.<sup>51,52</sup> These relatively low values may be related to a number of factors including effort dependence and improper estimation of peak expiratory flow assessed during FEV<sub>1</sub> determinations. If the patient is at work and does not show any decrement in pulmonary function, occupational asthma is virtually excluded. Positive tests require additional laboratory and workplace challenges. Unfortunately, combining peak expiratory flow rate with serial determinations of bronchial hyperresponsiveness both away from work and at work is no more sensitive or specific than peak flow monitoring alone.<sup>51</sup> If peak flow results suggest occupational asthma, a medical technician can attend the patient's workplace to monitor FEV<sub>1</sub> values before work and at hourly intervals while at work.<sup>53</sup> If a question still remains, controlled specific inhalational challenge tests simulating occupational exposure may be devised whereby patients are monitored during slowly increasing doses of the agent believed to be the cause of the occupational asthma. This may be dangerous and one must proceed with caution. Positive tests establish the diagnosis of occupational allergy.<sup>37</sup> If challenges are negative or specialized testing is not available, the patient may return to work with close monitoring.

Diagnosis of nonimmunologic, irritant-induced occupational asthma is based solely on clinical history and demonstration of airway obstruction and/or hyperresponsiveness. A history of respiratory symptoms appearing shortly after a workplace exposure to an irritant on one or several occasions should exist.<sup>54</sup>

## DIFFERENTIAL DIAGNOSIS

**W**hen a worker presents with symptoms of asthma and is confirmed to have reversible airflow obstruction, the diagnosis of asthma should be considered. Occupational asthma can not be diagnosed unless there is convincing proof that the symptoms are attributed only to the workplace. If evidence is lacking, an alternative diagnosis should be considered.<sup>55</sup> The most obvious is nonoccupational asthma. Some other disease states may be confused with asthma including chronic obstructive pulmonary disease, hypersensitivity pneumonitis, cystic fibrosis, bronchiectasis, bronchitis obliterans, gastroesophageal reflux disease, and central or extrathoracic airway obstruction. Less common considerations are pulmonary infiltration with eosinophilia, systemic mastocytosis, carcinoid syndrome, lymphangioleiomyomatosis, and amyloidosis.<sup>56</sup> A broad differential is necessary because asthma symptoms may masquerade as other diseases and treatments of these vary greatly.

## TREATMENT

**T**he treatment of occupational asthma is similar to the management of other forms of asthma with particular attention to reducing the level of exposure. For example,

bakeries have established permissible exposure limit concentrations of  $0.2 \mu\text{g}/\text{m}^3$  for wheat allergen or  $0.5 \text{ mg}/\text{m}^3$  for dust exposure during a work shift to achieve considerable risk reduction for sensitization to wheat flour.<sup>57</sup> Other industries should establish exposure limits because once occupational asthma occurs, the level of exposure required to react may be lower. Removal from exposure altogether is ideal. A study comparing the outcome of toluene diisocyanate-induced asthma patients revealed that workers with persistent potential exposures experienced more symptoms, required more medication, and were considered more medically unstable than workers whose exposure discontinued. Compared with those no longer exposed, some workers exposed with only occasional risk showed decrements in FEV<sub>1</sub> and PC15, the concentration of agent in broncho-provocation challenge testing required for 15% fall in FEV<sub>1</sub>. Workers exposed to isocyanates for >10 years or who continued to work for >3 years after asthma onset failed to recover.<sup>58</sup> Respiratory masks should not be considered acceptable protection, especially in the already sensitized occupational asthmatic patient. Masks may increase work of breathing, resistance to the flow of air, and dead space ventilation.<sup>59</sup> Immunotherapy has been reported to be successful but needs additional evaluation.<sup>60</sup> The importance of removing the occupational asthma patient from the aggravating exposure can not be overemphasized.

## CASE DISCUSSION

**B**aker's asthma is among the most frequently reported types of occupational asthma in several countries. According to Surveillance of Work-Related and Occupational Respiratory Disease, from 1989 to 1994, the annual incidence in Britain was estimated between 290 and 450 cases per million population.<sup>3</sup> Allergen-specific IgE antibodies in bakers are found most often against wheat, rye, or barley. There are as many as 40 flour proteins with allergenic capacity and because of their taxonomic relation, one-half cross-react with rye.<sup>61–63</sup> Cross-reactivity occurs less with oats, corn, and rice. In addition to grain, other additives besides grain also can cause baker's asthma, including the dough-conditioning food enzyme additives  $\alpha$ -amylase, hemicellulase, and papain,<sup>64</sup> and contaminant mold spores *Aspergillus* and *Alternaria*.<sup>65</sup> Dust mites and storage mites in grain also can cause asthma. Nasal and ocular symptoms almost always precede the onset of asthma, and the latency period can last from months to even years before the onset of asthma.<sup>11</sup> As with other forms of allergic asthma, avoidance is the key. The amount of allergen exposure required to exacerbate baker's asthma is so small that discontinuance of the job may be necessary. In this case, the patient improved when he sold the bakery and found an alternative, unrelated profession. As his symptoms and pulmonary function improved with time away from work, his symptomatic therapy has decreased.

## REFERENCES

1. Adams PF, and Marano MA. Current estimates from the National Health Interview Survey, 1994. *Vital Health Stat* 10:94, 1995.
2. Bernstein IL, Chan-Yeung M, Malo JL, and Bernstein DI (Eds.). *Asthma in the Workplace*, 2nd ed. New York: Marcel Dekker, Inc., 1999. pp 1–3.
3. Meyer JD. SWORD '99: Surveillance of work-related and occupational respiratory disease in the UK. *Occup Med* 51:204–208, 2001.
4. McDonald JC, Keynes HL, and Meredith SK. Reported incidence of occupational asthma in the United Kingdom, 1989–1997. *Occup Environ Med* 57:823–829, 2000.
5. Jajosky RAR, Harrison R, Reinisch F, et al. Surveillance of work-related asthma in selected U.S. states using surveillance guidelines for state health departments: California, Massachusetts, Michigan, and New Jersey, 1993–1995. *MMWR CDC Surveill Summ* 48:1–20, 1999.
6. Halperin WE (Ed.). *Public Health Surveillance*. New York: Van Nostrand Reinhold, 1992.
7. Baker EL, Melius MJ, Millar JD. Surveillance of occupational illness and injury in the United States: Current perspectives and future directions. *J Public Health Policy* 9:198–221, 1988.
8. Sama SR, Hunt PR, Cirillo PA, et al. Identification of adult onset asthma among HMO members. *Am J Respir Crit Care Med* 163: A161, 2001.
9. Meredith S, and Nordman H. Occupational asthma: Measures of frequency from four countries. *Thorax* 51:435–440, 1996.
10. Gautrin D, Newman-Taylor AJ, Nordman H, and Malo JL. Controversies in epidemiology of occupational asthma. *Eur Respir J* 22: 551–559, 2003.
11. Bernstein DI, Bernstein IL, Middleton E Jr. Occupational asthma. *Allergy* 963–980, 1998.
12. Bernstein DI, and Malo JL. High molecular weight agents. In *Asthma in the Workplace*. Bernstein IL (Ed). New York: Marcel Dekker, 1993.
13. Venables KM, Dally MB, Nunn AJ, et al. Smoking and occupational allergy in workers in a platinum refinery. *Br Med J* 299:939–942, 1989.
14. Slovak AJM, and Hill RN. Does atopy have any predictive value for laboratory animal allergy? A comparison of different concepts of atopy. *Br J Ind Med* 44:129–132, 1987.
15. Chan-Yeung M, Lam S, and Koener S. Clinical features and natural history of occupational asthma due to Western red cedar. *Am J Med* 72:411–415, 1982.
16. Venables KM, Topping MD, Howe W, et al. Interaction of smoking and atopy in producing specific IgE antibody against a hapten protein conjugate. *Br Med J* 290:201–204, 1985.
17. Douglas JD. Occupational asthma caused by automated salmon processing. *Lancet* 346:737, 1995.
18. Venables KM. Low molecular weight chemicals, hypersensitivity, and direct toxicity: The acid anhydrides. *Br J Ind Med* 46:222, 1989.
19. Duffy DL, Martin NG, Battistutta D, et al. Genetics of asthma and hay fever in Australian twins. *Am Rev Respir Dis* 142:1351–1358, 1990.
20. Mapp CE. The role of genetic factors in occupational asthma. *Eur Respir J* 22:173–178, 2003.
21. Newman A, Cullinan P, Lympay PA, et al. Interaction of HLS phenotype and exposure intensity in sensitization to complex platinum salts. *Am J Respir Crit Care Med* 160:435–438, 1999.
22. Mapp CE, DeMarzo N, Jovine L, et al. Association between HLA genes and susceptibility to toluene diisocyanate induced asthma. *Clin Exp Allergy* 5:651–656, 2000.
23. Heinzmann A, and Deichmann KA. Genes for atopy and asthma. *Curr Opin Allergy Clin Immunol* 1:387–392, 2001.

24. Palmer LJ, and Cookson WOCM. Using single nucleotide polymorphisms (SNPs) as a means to understanding the pathophysiology of asthma. *Respir Med* 2:102–112, 2001.
25. Chan-Yeung M, and Malo JL. Current concepts: Occupational asthma. *N Engl J Med* 333:107–112, 1995.
26. Malo JL, and Chan-Leung M. Occupational asthma. In *Current Reviews of Allergy and Clinical Immunology*. St. Louis, MO: Mosby, Inc., 2001.
27. Galli SJ. New concepts about the mast cells. *N Engl J Med* 328:257–265, 1993.
28. Holgate S. Mediator and cytokine mechanism in asthma. *Thorax* 48:103–109, 1993.
29. Mapp CE. The genetic susceptibility to occupational asthma. *Eur Respir J* 22:173–178, 2003.
30. Mapp CE, Sactta M, and Maestrelli P. Mechanisms and pathology of occupational asthma. *Eur Respir J* 7:544–554, 1994.
31. Venables KM, Topping MD, Nunn AJ, et al. Immunologic and functional consequences of chemical (tetrachlorophthalic anhydride)-induced asthma after four years of avoidance of exposure. *J Allergy Clin Immunol* 80:212–218, 1987.
32. Zeiss CR, Wolkonsky P, Pruzansky JJ, et al. Clinical and immunologic evaluation of trimellitic anhydride workers in multiple industrial settings. *J Allergy Clin Immunol* 70:15–18, 1982.
33. Bernstein DI, Gallagher JS, D'Souza L, et al. Heterogeneity of specific IgE responses in workers sensitized to acid anhydride compounds. *J Allergy Clin Immunol* 74:794–801, 1984.
34. Cartier A, Grammer L, Malo JL, et al. Specific serum antibodies against isocyanates: Association with occupational asthma. *J Allergy Clin Immunol* 8:507–514, 1989.
35. Frew AJ, Chan H, Dryden P, et al. Immunological studies of the mechanisms of occupational asthma due to Western red cedar. *J Allergy Clin Immunol* 92:466–478, 1993.
36. Brooks SM, Weiss MA, and Bernstein IL. Reactive airways dysfunction syndrome (RADS): Persistent asthma syndrome after high level irritant exposures. *Chest* 88:376–384, 1985.
37. Sama S, Christiani D, and Milton D. Diagnosis and management of occupational asthma. *Immunol Allergy Clin North Am* 22:791–806, 2002.
38. Boulet LP, Boutet M, Laviolette M, et al. Airway inflammation after removal from the causal agent in occupational asthma due to high and low molecular weight agents. *Eur Respir J* 7:1567–1575, 1994.
39. Fabbri LM, Danieli D, Crescioli S, et al. Fatal asthma in a subject sensitized to toluene diisocyanate. *Am Rev Respir Dis* 137:1494–1498, 1988.
40. Sactta M, Maestrelli P, DiStefano A, et al. Airway mucosal inflammation in occupational asthma induced by toluene diisocyanate. *Am Rev Respir Dis* 145:160–168, 1992.
41. Lam S, LeRiche J, Phillips D, and Chan-Yeung M. Cellular and protein changes in bronchial lavage fluid after late asthmatic reaction in patients with red cedar asthma. *J Allergy Clin Immunol* 80:44–50, 1987.
42. Sactta M, Maestrelli P, DiStefano A, et al. Effect of cessation of exposure to toluene diisocyanate (TDI) on bronchial mucosa of subjects with TDI-induced asthma. *Am Rev Respir Dis* 137:1444–1448, 1988.
43. Bentley AM, Maestrelli P, Sactta M, et al. Activated T-lymphocytes and eosinophils in the bronchial mucosa in isocyanate-induced asthma. *J Allergy Clin Immunol* 89:821–829, 1992.
44. Sastre J, Vandenplas O, and Park HS. Pathogenesis of occupational asthma. *Eur Respir J* 22:364–373, 2003.
45. Linneberg A, Nielsen NH, Frolund L, et al. The link between allergic rhinitis and allergic asthma. A prospective population-based study. *Allergy* 57:1048–1052, 2002.
46. Lundblad L. Allergic rhinitis and allergic asthma: A uniform airway disease? *Allergy* 57:969–971, 2002.
47. Chan-Yeung M, and Malo JL. Aetiologic agents in occupational asthma. *Eur Respir J* 7:346–371, 1994.
48. Bardy JD, Malo JL, Seguin P, et al. Occupational asthma and IgE sensitization in a pharmaceutical company processing psyllium. *Am Rev Respir Dis* 135:1033–1038, 1987.
49. Cartier A, Malo JL, Ghezzi H, et al. IgE sensitization in snow crab-processing workers. *J Allergy Clin Immunol* 78:344–348, 1986.
50. Cartier A. Definition and diagnosis of occupational asthma. *Eur Respir J* 7:153–160, 1994.
51. Cote J, Kennedy S, and Chan-Yeung M. Sensitivity and specificity of PC20 and peak expiratory flow rate in cedar asthma. *J Allergy Clin Immunol* 85:592–698, 1990.
52. Perrin B, Lagier F, L'Archeveque J, et al. Occupational asthma: Validity of monitoring of peak expiratory flow rates and nonallergic bronchial responsiveness as compared to specific inhalational challenge. *Eur Respir J* 5:40–48, 1992.
53. Chan-Yeung M, and Malo JL. Occupational asthma. *N Engl J Med* 333:107–112, 1995.
54. Malo JL, and Chan-Yeung M. Occupational asthma. *J Allergy Clin Immunol* 108; 3:317–328, 2001.
55. Malo JL, and Chan-Yeung M. Occupational agents. In *Asthma*. Barnes PJ, Grunstein MM, Leff AR, and Woolcock AJ (Eds). Philadelphia: Lipincott-Raven, 2143–2156, 1997.
56. Tilles SA, and Nelson HS. Asthma diagnosis and differential diagnosis. In *Current Review of Asthma*. Kaliner (Ed). Philadelphia: Current Medicine, Inc., 41–50, 2003.
57. Houba R, Doekes G, and Heederik D. Occupational respiratory allergy in bakery workers: A review of the literature. *Am J Ind Med* 34:529–546, 1998.
58. Pisati G, Baruffini A, and Zedda S. Toluene diisocyanate induced asthma: Outcome according to persistence or cessation of exposure. *Br J Ind Med* 50:60–64, 1993.
59. Newman L. Occupational asthma: Diagnosis, management, and prevention. *Clin Chest Med* 16:4:621–636, 1995.
60. Brisman J. Baker's asthma. *Occup Environ Med* 59:498–502, 2002.
61. Blands J, Diamant B, Kallos-Deffner L, et al. Flour allergy in bakers: Identification of allergenic fractions in flour and comparison of diagnostic methods. *Int Arch Allergy Appl Immunol* 52:392–406, 1976.
62. Sutton R, Skeritt JH, Baldo BA, et al. The diversity of allergens involved in baker's asthma. *Clin Allergy* 14:93–107, 1984.
63. Williams N, Skoulas S, and Merriman JE. Exposure to grain dust. I. A survey of the effects. *J Occup Med* 6:319–329, 1964.
64. Chan-Yeung M, Schulzer M, MacLean L, et al. Epidemiologic health survey of grain elevator workers in British Columbia. *Am Rev Respir Dis* 121:329–338, 1980.
65. Klaustermeyer WB, Bardana EJ Jr, and Hale FC. Pulmonary hypersensitivity to *Alternaria* and *Aspergillus* in baker's asthma. *Clin Allergy* 7:227, 1977. □

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