Reactive Airways Dysfunction Syndrome (RADS)*
Persistent Asthma Syndrome after High Level Irritant Exposures

Stuart M. Brooks, M.D., F.C.C.P.; Mark A. Weiss, M.D.; and I. L. Bernstein, M.D.

Ten individuals developed an asthma-like illness after a single exposure to high levels of an irritating vapor, fume, or smoke. In most instances, the high level exposure was the result of an accident occurring in the workplace or a situation where there was poor ventilation and limited air exchange in the area. In all cases, symptoms developed within a few hours and often minutes after exposure. We have designated the illness as reactive airway dysfunction syndrome (RADS) because a consistent physiologic accompaniment was airways hyperreactivity. When tested, all subjects showed positive methacholine challenge tests. No documented preexisting respiratory illness was identified nor did subjects relate past respiratory complaints. In two subjects, atopy was documented, but in all others, no evidence of allergy was identified. In the majority of the cases, there was persistence of respiratory symptoms and continuation of airways hyperreactivity for more than one year and often several years after the incident. The incriminated etiologic agent varied, but all shared a common characteristic of being irritant in nature. In two cases, bronchial biopsy specimens were available, and an airways inflammatory response was noted. This investigation suggests acute high level, uncontrolled irritant exposures may cause an asthma-like syndrome in some individuals which is different from typical occupational asthma. It can lead to long-term sequelae and chronic airways disease. Nonimmunologic mechanisms seem operative in the pathogenesis of this syndrome.

Environmental agents, such as ozone, nitrogen dioxide, and sulfur dioxide; occupational pollutants, including polyvinyl chloride pyrolysis emissions, grain dust, red cedar; and certain respiratory infections can cause increases in airways reactivity.1-8 Studies which demonstrate these changes in airways responsiveness are generally performed in controlled laboratory settings with subjects inhaling relatively low and acceptable concentrations of the pollutant. In most instances, the airways hyperreactivity induced by the agent is transient.9 There are no studies where very high and unacceptable levels of a pollutant are inhaled and then airways reactivity is tested. It is not clear, for instance, whether induced airways hyperreactivity is a dose-effect phenomenon and whether a high level exposure causes a more prolonged or intense airways response.

Over the past several years, a number of patients evaluated at the University of Cincinnati Occupational Health facility were observed to have an illness develop after a single excessively high environmental or occupational exposure. While the illness clinically simulated bronchial asthma and was associated with airways hyperreactivity, we consider it different from typical occupational asthma because of its rapid onset, specific relationship to a single environmental exposure, and no apparent preexisting period for sensitization to occur with the apparent lack of an allergic or immunologic etiology. We have termed this illness reactive airways dysfunction syndrome, or RADS, because the characteristic finding is hyperreactivity of the airways. This report describes observations on this entity.

Methods

The study population consisted of persons examined at the occupational health facility at the University of Cincinnati Medical Center between the years 1975 and 1982. During this period, there were approximately 2,000 new cases examined in the Occupational Health Clinic. About 25 percent of these cases were patients with apparent bronchial asthma, mostly suspected of being occupational or environmental in origin. Among the approximate 500 cases of asthma, there were 30 with suspected RADS. Twenty of these RADS cases did not have complete past histories or medical information or lacked some of the clinical criteria listed in Table 1. The final population for reporting consisted of ten subjects who fulfilled the specific criteria listed in Table 1.

Subjects were evaluated in the Occupational Health Clinic. A detailed medical and occupational history was obtained, and a physical examination performed by the same examiner in all cases (SMB). The history was obtained by traditional methods using direct questioning and not by an administered questionnaire. In all sub-

*From the Department of Environmental Health, Department of Pathology, and Department of Medicine, University of Cincinnati College of Medicine, Cincinnati.
This study was supported by NIEHS Center grant 5F30ES00159, CCBC grant MOL-BB-0069, and NHLBI grant HL22415.
Manuscript received January 24; revision accepted March 25.
Reprint requests: Dr. Brooks, 117 Kettering Laboratory, University of Cincinnati Department of Environmental Health, Cincinnati 45221.
Methacholine chloride was combined with sodium chloride and sodium bicarbonate to produce a solution with the same molarity as isotonic saline. The methacholine solution was prepared in accordance with published procedures,16 dispensed into 40 ml aliquots, and frozen until immediately prior to use.

Baseline pulmonary function studies were performed according to accepted criteria using the dry rolling seal spirometer (calibrated daily) connected to a microprocessor.19 The subject was then given a 30-second isotonic saline challenge followed by repeat spirometry two minutes after challenge. Providing there was no reaction to saline, the first dose of methacholine was then given (usually 100 to 200 μg) followed by pulmonary function tests two minutes after exposure. The test was considered positive when there was a 20 percent or greater fall in FEV1. Otherwise, additional methacholine was administered until the total cumulative dose of 2,000 μg was given. Following each methacholine dose, pulmonary function studies were performed until the two best FEV1 values were within 5 percent. The best FEV1 for each dose was used to calculate percent fall. The provocative dose corresponding to a 20 percent fall in FEV1 (ie, the PD20) was calculated by performing a log dose transformation of the data and performing a linear regression against the percent fall in FEV1. Experience in our laboratory has shown that most asthmatic patients respond to less than 1,000 μg methacholine using the generation system described above. In some cases studied before 1982, a modification of this challenge procedure was used.49 Posteroanterior chest x-ray films were obtained in each case. In two subjects, pathologic material from fiberoptic bronchial biopsies was available and reviewed. Consultations with subjects’ private treating physicians and copies of past medical records and hospitalizations were collected. Details of the chemical characterization of exposures were documented as completely as possible by communicating with manufacturers or industrial concerns. The majority of patients was examined on several occasions; some were followed for several years with serial tests and clinical examinations.

RESULTS

The patients with RADS consisted of seven men and three women whose mean age was 36.4 years (Table 2). There were six cigarette smokers with an average cigarette smoking consumption of 15.7 pack/year. Pulmonary function tests were considered normal in three of the ten subjects. There was airway obstruction with FEV1/FVC <70% in four and FEF25-75 <70% predicted in seven subjects. Table 3 lists clinical symptoms and shows cough (ten subjects), dyspnea (nine subjects), and wheezing (six subjects) pre-

### Table 1—Clinical Criteria for the Diagnosis of Reactive Airways Dysfunction Syndrome (RADS)

1. A documented absence of preceding respiratory complaints.
2. The onset of symptoms occurred after a single specific exposure incident or accident.
3. The exposure was to a gas, smoke, fume or vapor which was present in very high concentrations and had irritant qualities to its nature.
4. The onset of symptoms occurred within 24 hours after the exposure and persisted for at least three months.
5. Symptoms simulated asthma with cough, wheezing and dyspnea predominating.
6. Pulmonary function tests may show airflow obstruction.
7. Methacholine challenge testing was positive.
8. Other types of pulmonary diseases were ruled out.

### Table 2—Demographic and Spirometric Results in Subjects with RADS

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Smoking (pk/ys)</th>
<th>Atopy</th>
<th>Exposure</th>
<th>% Predicted</th>
<th>Methacholine Challenge</th>
<th>Chest X-ray Film</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>FVC</td>
<td>FEV1</td>
<td>FEF25-75</td>
</tr>
<tr>
<td>1</td>
<td>53</td>
<td>M</td>
<td>30</td>
<td></td>
<td>Uranium hexafluoride</td>
<td>110</td>
<td>69</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>19</td>
<td>M</td>
<td>0</td>
<td>–</td>
<td>Floor sealant</td>
<td>96</td>
<td>102</td>
<td>103</td>
</tr>
<tr>
<td>3</td>
<td>41</td>
<td>M</td>
<td>21</td>
<td>–</td>
<td>Spray paint</td>
<td>93</td>
<td>79</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>45</td>
<td>M</td>
<td>0</td>
<td>–</td>
<td>Spray paint</td>
<td>67</td>
<td>60</td>
<td>32</td>
</tr>
<tr>
<td>5</td>
<td>39</td>
<td>M</td>
<td>20</td>
<td>–</td>
<td>35% hydrazine</td>
<td>100</td>
<td>80</td>
<td>35</td>
</tr>
<tr>
<td>6</td>
<td>32</td>
<td>M</td>
<td>9</td>
<td>–</td>
<td>Spray paint</td>
<td>92</td>
<td>75</td>
<td>43</td>
</tr>
<tr>
<td>7</td>
<td>31</td>
<td>M</td>
<td>7</td>
<td>–</td>
<td>Heated acid</td>
<td>72</td>
<td>56</td>
<td>25</td>
</tr>
<tr>
<td>8</td>
<td>24</td>
<td>F</td>
<td>0</td>
<td>+</td>
<td>Fumigating fog</td>
<td>97</td>
<td>100</td>
<td>118</td>
</tr>
<tr>
<td>9</td>
<td>34</td>
<td>F</td>
<td>7</td>
<td>–</td>
<td>Metal coat remover</td>
<td>107</td>
<td>89</td>
<td>57</td>
</tr>
<tr>
<td>10</td>
<td>46</td>
<td>F</td>
<td>0</td>
<td>+</td>
<td>Fire/smoke</td>
<td>101</td>
<td>103</td>
<td>97</td>
</tr>
</tbody>
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**CHEST / 88 / 3 / SEPTEMBER, 1984**

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dominating. Chest x-ray films at time of evaluation were normal in all persons except for signs of hyperinflation in two patients. Methacholine challenge tests were positive in all cases. Two subjects were considered to be atopic as determined by skin testing to a variety of aeroallergens. Each had preexisting upper respiratory tract allergic rhinitis symptoms, but absence of asthma symptoms. The information obtained from past medical records, private physician interviews, and discussion with patients indicated no subjects had evidence of preexisting pulmonary disease. Table 3 provides temporal information related to patient studies. This information was obtained from the patient’s interview, and corroborated by medical records obtained at the time of the injury and by discussions with persons familiar with the incident. In each case, there was a specific incident where a very high exposure occurred, either by accident or because there was very poor workplace ventilation. The duration of exposure to the provoking pollutant ranged from just a few minutes to as long as 12 hours. In five subjects, the duration of exposure lasted 15 minutes or less; it lasted two hours or more in another five affected persons (Table 3). Generally, there was some time interval between the end of exposure and when the person first reported RADS symptoms. In three subjects, symptoms were reported almost immediately or within a few minutes. In the other seven individuals, several hours passed before symptoms were observed (mean 8.9 hours). There were no differences in clinical, physiologic, or prognostic parameters among persons with immediate compared to delayed onset of symptoms.

An important consideration of RADS was persistence of symptoms after termination of exposure and treatment of the acute episode. It was documented to be present for one year or more in seven cases and less than one year in three. For the total ten subjects, the mean duration of RADS was estimated to be almost three years (35.8 months). In three individuals RADS persisted for four years or more; one person had symptoms for almost 12 years. Only two of ten patients were not receiving medication, either a theophylline preparation, beta agonist aerosol, cromolyn, or intermittent corticosteroids when examined.

A variety of offending agents were incriminated (Table 2). In several cases, the exposure was to a mixture and the exact chemical exposures could not be determined. Also, exact concentrations of the incriminating agent were not available, since the incident where the exposure occurred was unusual and unexpected. Most high exposures were related to an accident or occurred after an improper work practice was employed. In each case, the exposure was characterized toxicologically as being irritant in nature and present in high concentrations. Efforts were made to identify any known sensitizing agents in the exposures, but none could be incriminated.

**Pathologic Findings**

Bronchial biopsies were available in two cases and showed respiratory epithelial injury with a chronic unspecific airway inflammatory response (Fig 1 and 2). Mild inflammatory infiltrates in bronchial and bronchiolar walls consisted mainly of lymphocytes and plasma cells. Desquamation of respiratory epithelium was present in one biopsy (case 7), and mucus (goblet cell) hyperplasia in another (case 6). Adherent mucus was present in one bronchial biopsy (case 6). In neither of the biopsies was there significant eosinophilic infiltrate or exudate, mucus gland hyperplasia, basement membrane thickening or smooth muscle hypertrophy.

**Case Reports**

**Case 1**

A 53-year-old chemical worker had an accidental exposure to
uranium hexafluoride gas at work in a chemical plant on Nov 12, 1968. He was not wearing a respiratory protective device and breathed uranium hexafluoride vapors for about 15 minutes. He immediately developed shortness of breath and cough and was subsequently taken to an emergency room where because of severe respiratory distress, an emergency tracheotomy was performed. He was discharged from the hospital after four days, but noted persistent dyspnea and increased airway excitability after exposure to non-specific irritants or stimuli such as marked temperature change, dusts, and a variety of fumes and vapors. He was evaluated at UC Medical Center approximately 140 months after his accident on July 8, 1980.

CASE 2

This 19-year-old grocery clerk was previously in good health until Sept 22, 1978, when he was exposed to fumes from a concrete floor sealant used to coat a stockroom floor. The floor sealant was documented to contain several aromatic hydrocarbons, including Decane, ethylbenzene, toluene, xyle, and chlorohydrin. It did not contain isocyanates or anhydrides. He had never performed this type of work before, and in the room in which he worked was small and poorly ventilated. The work involved taking a 15-gallon drum of sealant, pouring it on the floor, and spreading the sealant with a mop. He noted the sealant smelled like “glue” or “varnish.” He worked in the enclosed space approximately 2% hours without respiratory protection. He developed dizziness, watery eyes, severe headache, and facial flushing and later, cough and dyspnea. The next day, he felt better but his symptoms did not completely abate. Three days later, he continued having symptoms but used the sealant again for 3½ hours in a similar operation working without respiratory protection. His dyspnea and cough worsened. A physical examination by a private physician a few days after the incident reported a mild conjunctivitis, inflamed throat, and runny eyes. Chest x-ray film was reported to be within normal limits. He was evaluated at the UC Medical Center 14 months later on Dec 4, 1979, describing exertional dyspnea, chest tightness, and wheezing after running a short distance.

CASES 3 AND 4

A 41-year-old painter and his partner, a 45-year-old man, both previously healthy and with no known respiratory illness, were working together, spray painting a new apartment. Because the weather was cold, the windows of the room were covered with heavy plastic material with duct tape placed around the edges to insure a seal, and the main entrance to the apartment was also covered to conserve heat. The ventilation in the work area was extremely poor. The painters did not wear appropriate respiratory protective devices but wore only paper masks over their nose and mouth while they spray painted. The paint used, a one-stage vinyl latex primer, was a rapid drying type, and contained 25 percent ammonia, 16.6 percent aluminum chlorohydrate, and a number of other additives. There were no isocyanates or anhydrides. Each individual worked only as a painter in the past, one for 20 years and the other 25 years. Each stated he never previously spray painted under the environmental conditions as in this instance.

After spray painting a total of 12 hours each, both simultaneously noted the onset of generalized weakness, nausea, cough, shortness of breath, paint taste in their mouths, chest tightness, and wheezing. Both subjects were subsequently hospitalized for about two weeks with provisional diagnoses of “acute chemical bronchitis.” Initial chest x-ray film in one subject was interpreted as showing increased bronchovascular markings consistent with “chemical pneumonitis.” The other x-ray film findings were normal. After discharge from hospital, each subject continued to note persistent wheezing, cough, exertional dyspnea, and each reported aggravation of symptoms after exposure to nonspecific stimuli such as cold air, dusts, aerosol sprays, smoke, and fumes. Each painter consulted different private physicians, and both were treated with prednisone, theophylline preparations, and aerosol bronchodilators. They were examined at the University of Cincinnati on March 4, 1982, four months after the incident.

CASE 5

This 39-year-old power plant utility worker had a heavy exposure to a 35 percent hydrazine solution while at work on Dec 18, 1979, while transporting a 55-gallon drum containing hydrazine solution. The drum overturned and a large quantity of the solution spilled on him. He was pinned down by the drum for about five minutes and could not call for help because of pressure on his chest. The hydrazine solution flowed onto his face, mouth, neck, chest, arms, abdomen, and urogenital areas. He denied eye exposure, but he stated he reflexively swallowed some of the solution. Eventually, a co-worker noted his dilemma and assisted in his removal. Two hours later, he felt a “prickly,” pins and needles sensation on his face, neck, and anterior chest. A workmate noted he had a facial rash. He later became disoriented to time and place and was sent to a hospital emergency room. Within five hours from the time of the incident, he noted neck pain, respiratory symptoms, nausea, diarrhea, and abdominal cramping which persisted until the next day when he returned to the hospital and was told he had “the flu.” He described wheezing and chest tightness, paroxysmal nonproductive cough, and muscle aching which persisted. He received intermittent injections of corticosteroids over the next three weeks for these complaints. Over the next five to six months, he lost many days of work because of persistent respiratory symptoms, and musculoskeletal weakness which necessitated treatment with short courses of prednisone, albuterol inhaler, and a theophylline preparation. He developed severe episodes of bronchospasm at work after exposures to airborne irritants such as from a mixture of caustic soda and hydrochloric acid or sulfuric acid. He was examined at the University of Cincinnati on Oct 19, 1982, 34 months later.

CASE 6

This 32-year-old painter, evaluated on May 13, 1980, complained of “breathing problems” since Sept 3, 1975, when he was exposed to excessive paint fumes while working in an enclosed area. On this day, he was working in a spray painting operation for several hours without respiratory protection, and he inhaled “large amounts” of paint fumes of an oil-base enamel paint. At the end of the work day, he noted shortness of breath, cough, and a feeling of having to “force air into his lungs.” He described wheezing that night. Subsequently, he noted problems being around any type of paint fumes which necessitated his leaving the painting occupation and becoming a construction supervisor with limited exposure to irritants (Fig 1). A bronchial lung biopsy was performed in Feb 1981 because of persistent symptoms. He was examined 56 months later, on May 13, 1980, at the University of Cincinnati.

CASE 7

In mid-June 1974, this 32-year-old welder of 13 years, was welding a tank which previously contained acid. He used a stainless steel rod for this welding which consisted of 0.06 percent carbon, 20.5 percent chromium, 9.5 percent nickel, 0.6 percent manganese, and 0.5 percent silicon. The flux was lime and titanium coated. Significant fumes evolved from the welding process causing him to cough. Seven to eight hours later, he noted worsening cough, wheezing, and shortness of breath which persisted. A workup by an allergist was negative. In March 1977, bronchoscopy showed patent bronchi but hypertrophic mucosa and some bloody secretions in the lower lobes (Fig 2). A bronchial biopsy was performed. He was examined at the UC Medical Center 48 months after the incident on March 16, 1978.
CASE

This 46-year-old patient was inside a bookstore on Dec 16, 1982, when an airplane crashed into the building setting it on fire. She was knocked down because of the impact of the crash, and was inside the building for about 15 minutes. Books, papers, furniture, upholstery, and paint burst into flames, and she breathed in the smoke, fumes, combustion and pyrolysis products generated by the fire. When she got outside, she did not recall any specific symptoms, but was very frightened. She noted a cough and "feeling well" the next day. Later, she developed worsening cough with paroxysms, shortness of breath, wheezing, and chest discomfort. She had a past history of allergic rhinitis and had received allergy injections for about two years but was well documented not to have asthma or respiratory symptoms before the incident. Her husband is a physician. She was evaluated at the UC Medical Center on Nov 17, 1983, 11 months after the accident.

DISCUSSION

The case histories described in this report have similar clinical presentations with each affected person developing an asthma-like illness after an exposure to a high level of an irritant vapor, fume, or smoke. Review of the past medical records of the subjects revealed a number of different diagnoses were initially entertained including "chemical bronchitis," "bronchitis," "chemical pneumonitis," "mild pulmonary edema," and "asthma." When the subjects were evaluated four to 140 months after the incident, a consistent physiologic alteration was airways hyperreactivity with all subjects showing positive methacholine challenge tests. The incriminated etiologic agents all shared a common toxicologic characteristic of being irritant in nature. In some cases, the agent was present as a gas, such as the case of uranium hexafluoride. In other situations, the toxic inhalant was an aerosol as with the spray painting or the fumigating fog exposure. In two instances, it was due to heating or combustion; one case was fire and smoke inhalation, and one case was due to inhalation of heated acid vapors and fumes during welding. While exposures to hydrazine or stainless steel welding could involve sensitization and asthma, to the best of our knowledge, allergic sensitization was not a factor in the pathogenesis of the illness because the onset of the illness began after a first time exposure with no period of sensitization possible.

Mechanisms to explain the development of RADS must focus on the toxic effects of the irritant exposure on the airways. This conclusion is only speculative and not substantiated. Our investigation is retrospective and highly dependent on the recollection of and clini-
suggested hyperreactivity was a frequent sequela of high level SO\(_2\) exposure and that airways hyperreactivity could persist for several years after SO\(_2\) injury. Seven mine workers were involved in a pyrite dust explosion and had SO\(_2\)-induced lung injury. The exact concentration of the gas exposure was estimated between 300 and 1,600 ppm. The seven workers had examinations before the accident and subsequently had six periodic examinations over a four-year period. In six individuals, an “obstructive” pattern was noted, while in one person, a “restrictive” pattern was seen. Four years after the accident, reversible obstructive airways disease persisted in three individuals. Four subjects reacted positively to histamine challenge; two did not respond to bronchodilators or histamine. For another SO\(_2\) exposure, Charan and co-workers\(^{18}\) described five cases of accidental high levels of SO\(_2\) exposure with three survivors developing severe and another showing mild airways obstruction. Flury et al\(^ {14}\) described a 50-year-old man who inhaled substantial quantities of concentrated ammonia fumes. Serial pulmonary function studies over the next five years documented development of airways obstruction. Although a methacholine challenge test was not performed, the authors indicated hyperreactive airways were present and likely the direct result of the inhalation injury.

Donham et al\(^{11}\) described an acute toxic exposure to high levels of hydrogen sulfide after agitation of liquid manure. One survivor had respiratory symptoms persisting for over two months after the incident. In a study on 28 patients with thermal injury and smoke inhalation, prolonged airway obstruction was seen in some persons more than a year after injury.\(^ {12}\)

Murphy et al\(^{10}\) reported a subject who developed severe airway obstruction after inhaling fumes liberated from mixing several drain cleaning agents. Hasan et al\(^ {14}\) studied 18 subjects after acute chlorine exposure and noted airway obstruction in all individuals immediately after exposure. The obstructive abnormality resolved within one week in 12 subjects, but a slower resolution occurred in six subjects whose initial chief complaint was dyspnea. In this group, expiratory flow rates were still decreased two weeks after exposure. Kaufman and Bukon\(^ {15}\) found acute chlorine exposure caused an obstructive defect which cleared within three months. A study by Kowitz et al\(^ {16}\) reported 115 longshoremen accidentally exposed to chlorine gas. There were 11 subjects hospitalized because of respiratory distress who showed persistent airways obstruction over a two- to three-year period.

Axford et al\(^ {17}\) reported a majority of individuals developed respiratory symptoms within 24 hours after a single severe exposure to toluene diisocyanate (TDI). Almost four years later, 20 men described persistent respiratory symptoms. Another report by Mastromatteo\(^ {18}\) involved 24 individuals exposed to a single TDI
spill with six requiring hospitalization. Convalescence in these patients was extremely slow with at least one individual developing an asthma-like syndrome persisting for several months.

The exact pathologic change induced after inhalation injuries is not known, but bronchiolitis obliterans has been proposed as a lesion occurring after some toxic gases and fumes inhalation. Ladue reported an employee of a shoe shining parlor using a liquid dye with an acrid and irritating odor who developed a respiratory illness which pathologically was shown to be bronchiolitis obliterans. While patients with bronchiolitis obliterans may describe symptoms which simulate asthma, pulmonary function tests show airflow limitation, shift of pressure-volume curve upward with a normal slope, and normal or reduced lung volumes and CO diffusion. Methacholine bronchial challenges have not been reported in this condition. While it is possible some RADS patients have bronchiolitis obliterans, the clinical and physiologic course of their illness mitigates against this diagnosis.

We believe the hyperreactive airway noted in our patients is likely due to an inhalation injury. Mechanisms of importance reported for explaining induced airway hyperresponsiveness include altered neural tone and vagal reflexes; modified beta-adrenergic sympathetic tone; and influences of a variety of mediators including both lipoxygenase and cyclooxygenase products of arachidonate metabolism. Increased airways responsiveness occurs after recovery from the adult respiratory distress syndrome, after certain viral respiratory infections and after exposure to occupational and environmental agents. A common pathologic accompaniment of all these varied entities is pulmonary inflammation. Our pathologic material showed airways inflammation and we speculate this bronchial inflammatory reaction was due to the inhaled toxic agent. There are a number of studies documenting the inflammatory nature of irritant exposure such as with phosgene and chlorine which can persist for months. Hinson et al demonstrated the importance of pulmonary inflammation on the airway response to aerosol histamine. When granulocyte depletion was induced in sheep after hydroxyurea administration, a reduced bronchial response to histamine aerosol was noted. This suggested the pulmonary inflammation was responsible for the change in histamine responsiveness, perhaps by augmenting bronchial smooth muscle response to histamine. Because subepithelial irritant receptors are superficial in location, they could be affected by an extensive bronchial inflammatory response which might occur after heavy irritant exposure. Subsequent reepithelialization and probable reinervation of bronchial mucosa might drastically alter the threshold of the receptors and cause airways hyperreactivity. Another possibility is bronchial epithelial damage leads to increased epithelial permeability causing hyperreactivity airways on this basis. Biopsy material from our patients showed bronchial/bronchiolar epithelial desquamation and mucus cell hyperplasia. Other inflammatory mediators or biochemical correlates might also play a role in the hyperresponsive change of the airways.

The present study documents a clinical syndrome we feel has not previously been well emphasized. RADS might be similar to an asthma syndrome such as "intrinsic asthma," an entity where in most cases, no specific etiologic factor is documented. It differs from typical occupational asthma because of the absence of a preceding period for sensitization to occur and the onset of the illness after a single, first time exposure. Because the incriminated agents are not sensitizers, low level exposures are not expected to cause asthmatic attacks. Instead, there was clinical increased non-specific bronchial reactivity to a number of irritants. Thus, the typical work-related preoccupation of symptoms was absent and individuals reported symptoms both at home and at work. Whether RADS differs from typical adult onset intrinsic asthma cannot be determined, but its relationship to a specific environmental agent and its clinical course suggests it may be one of a number of clinical asthma variants. More careful investigation into events preceding the development of forms of adult-onset asthma might better demonstrate the influences of environmental or occupational factors in its etiology. While our definition of RADS is restrictive and requires the presence of a high level exposure, it is conceivable that a low level chronic exposure could cause a similar type process in some individuals. An important consideration of RADS is once it develops, there may be long-term sequelae and chronic airways disease occurring. Further investigations into the role of nonimmunologic environmental and occupational factors in the pathogenesis of asthma syndromes and airways hyperreactivity seem warranted.

ACKNOWLEDGMENT: Drs. William Krall, Sidney Peerless, and Eugene Saenger referred patients; Mary Ann Brockman and Marilyn Clark prepared the manuscript; and Dr. Raymond Suskind reviewed the manuscript.

REFERENCES


Downloaded From: http://journal.publications.chestnet.org/pdaccess.ashx?url=/data/journals/chest/21486/ on 06/27/2017
5 Boushey HA, Empey DW, Laitinen LA. Meat wrapper's asthma: effect of fumes of polyvinyl chloride on airways function. Physiologist 1975; 18:148
7 Cockcroft DW, Cotton DJ, Mink JT. Nonspecific bronchial hyperreactivity after exposure to Western red cedar. Am Rev Respir Dis 1979, 119:505-10
16 Makino S. Clinical significance of bronchial sensitivity to acetylcholine and histamine in bronchial asthma. J Allerg 1966; 38: 127-42
23 Murphy DMF, Fairman RP, Lapp NL, Morgan WKC. Severe airway disease due to inhalation of fumes from cleaning agents. Chest 1987; 69:372-76
32 Yockey CC, Eden BM, Byrd RB. The McConnel missile accident. JAMA 1980; 244:1221-23
33 Egler GB, Colby TV. The spectrum of bronchiolitis obliterans. Chest 1983; 83:161-62
43 Durlacher SH, Bunting H. Pulmonary changes following exposure to phosgene. Am J Pathol 1947; 23:679-93
46 Haggard HW. Action of irritating gases upon the respiratory tract. J Indus Hyg 1924; 5:390-98
49 Creese BR, Bock MK. Hyperreactivity of Airways smooth muscle produced in vitro by leukotrienes. Prostagland Leukot Med 1983; 161-69

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Downloaded From: http://journal.publications.chestnet.org/pdffaccess.aspx?url=/data/journals/chest/21486/ on 06/27/2017
52 Kolb WP, Kolb LN, Wetsel RA, Rogers WR, Shaw JO. Quantitation and stability of the fifth component of complement (C5) in bronchoalveolar lavage fluids obtained from non-human primates. Am Rev Respir Dis 1981; 123:226-31
55 Auty RA. Pharmacologic modulation of bronchial hyperreactivity. Immunol Allerg Prac 1983; 5:47-54
57 Harries MG, Packes PEG, Lessof MH, Orr TSC. Role of bronchial irritant receptors in asthma. Lancet 1981; 1:5-7