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Reactive Airways Dysfunction Syndrome and Irritant-Induced Asthma

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INTRODUCTION

Although irritant-induced nonimmunological asthma without a latency period had previously been reported, the acronym for this form of occupational asthma (OA) was first derived from the descriptive term "reactive airways dysfunction syndrome" (RADS) in 1985 (1). It was originally defined as asthma occurring after a single exposure to high levels of an irritating vapor, fume, or smoke. Although the term "irritant-induced asthma (IIA) disease" is more consistent with the definitions of OA described in chapter 1, the RADS terminology was retained by the editors because of the high recognition index that it has engendered among the occupational health community as well as the specific diagnostic criteria, which distinguish it from other forms of IIA. Initial symptoms developed within minutes or hours after exposure. In the majority of cases there was continuation of obstructive symptoms and persistent airway hyperresponsiveness for more than one year. The condition is defined here as nonimmunological OA, and, according to this definition, it should be distinguished from other nonimmunological OA entities occurring after longer latent periods of exposure (e.g., meat wrappers' asthma and potroom asthma) and/or fixed obstructive disorders, such as bronchiolitis or bronchiolitis obliterans, resulting from chemical inhalation injury (Chapter 28). As more investigators recognize RADS as a unique form of OA, in future it will be most likely referred as a special phenotype of IIA (2).

CLINICAL DESCRIPTION OF THE SYNDROME

The initial report included 10 individuals who developed a persistent asthma-like illness after a single exposure to high levels of an irritant vapor, fume, gas, or smoke. Respiratory symptomatology and continued presence of nonspecific bronchial hyperresponsiveness (NSBH) were documented in all the subjects for a mean follow-up of three years. In one person, the persistence of disease was documented to have lasted for at least 12 years. Generally, the incremental exposure was short lived, often lasting just a few minutes, but sometimes lasted for 12 hours. Usually, there was a time interval between the exposure and the development of symptoms; this time period was immediate in three subjects, but several hours in the other seven subjects (mean of nine hours). In almost all instances, the exposure was because of an accident or a situation in the work area where there was very poor ventilation and limited air exchange. All the causal etiological agents, although varied in each case, were irritants and included uranium hexafluoride gas, floor sealant, spray paint containing significant concentrations of ammonia, heated acid, 35% hydrazine, fumigating fog, metal coating remover, and smoke inhalation. When tested, all subjects displayed a positive result for methacholine challenge test. There was no identifiable evidence of preexisting respiratory complaints in any of the patients studied. Two subjects were found to be atopic, but in all others no evidence of allergy was identified. Pulmonary function was normal in 3 of 10 subjects and showed airflow limitation in seven.

Typical Courses of Two Sentinel Cases

A previously healthy 41-year-old painter and his partner, a 45-year-old man, worked together spray painting a poorly ventilated apartment during the late fall when the weather was cold. The room was sealed and there was poor fresh air recirculation; the windows were covered with a heavy plastic material, duct tape was placed around the edges to ensure a seal, and the main entrance to the apartment was covered to conserve heat. The painters did not wear approved respiratory protective devices, but only paper masks covering their nose and mouth while they worked. The paint used was a one-stage vinyl latex primer, reported to be rapid-drying, and said to contain 25% ammonia, 16.6% aluminum chlorohydrate, and other additives, many of which were documented irritants.

Both men spray-painted for a total of 12 hours, that is, four hours the first day and eight hours the second. Both of them noted the appearance of an illness beginning at the end of the second day of work, with symptoms of nausea, cough, shortness of breath, paint taste in the mouth, chest tightness, wheezing, and generalized weakness of the limbs. Each worker was subsequently hospitalized for about two weeks with the provisional diagnosis of "chemical bronchitis." A chest roentgenogram of one patient showed "increased bronchovascular markings" consistent with "chemical pneumonitis." After being discharged from the hospital, both painters consulted private physicians and were eventually treated with prednisone, oral theophylline, and aerosol beta2-adrenergic bronchodilators.

On evaluation four months later, there remained persistent symptomatology of wheezing, cough, and exertional dyspnea; in one painter there was also chest discomfort. Separately, each reported newly developed bronchial irritability symptoms, that is, respiratory manifestations after exposure to many and varied nonspecific stimuli such as cold air, dusts, aerosol sprays, smoke, and fumes. The bronchial irritability symptoms were not present before the heavy exposure. Each painter denied a past history of asthma, allergies, rhinitis, frequent colds, dyspnea, or other respiratory symptoms. One of the painters recalled a transient episode of bronchitis 11 years previously without recurrence. Each worker denied a family history of allergy, asthma, or previous respiratory problems. Both had worked only as painters in the past, one for 20 years and the other for 25 years. Both stated that they had never previously spray-painted under the environmental conditions similar to that of the inciting incident. One subject was a cigarette smoker with a 21-year history; the other person was essentially a nonsmoker, having smoked only 20 to 40 cigarettes in his life. A physical examination in one worker disclosed expiratory rhonchi. Laboratory tests of the subjects included normal complete blood counts with 5% eosinophilia in one, normal chest roentgenograms, and negative in vitro battery for common airborne allergens. Pulmonary function testing showed mild airways obstruction; forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) was 67.7% in one person and 70.3% in the other; forced expiratory flow at the midportion of FVC $(FEF)_{25-75}$ was 39.8% and 31.7% of that predicted, respectively.

Over the next year, the two men were followed up with serial clinical evaluations, lung function testing, and methacholine bronchial challenges. The persistence of asthmatic symptoms and airway hyper-responsiveness was noted. Results of methacholine challenges shown in Table 1 demonstrate that NSBH persisted for at least one year in both workers. Because one of the painters reported spray-painting with a polyurethane-based paint several years before, the possibility of isocyanate-induced airway disease was considered. Response to subsequent toluene diisocyanate (TDI) bronchial challenge testing in this person was negative. When last evaluated about 16 to 17 months after the incident, both continued to experience symptoms and had not returned to the painting occupation.

OTHER CASE AND SERIES REPORTS OF RADS

Prior to the 1985 description of RADS, there were a number of reports of workers developing asthma after exposure to high levels of irritants. Although these workers demonstrated evidence of airflow obstruction and symptoms of airway hyperresponsiveness for varying periods after the challenge, they differed from subjects with RADS because the airway hyperresponsiveness was not documented by methacholine or histamine challenge tests. Charan et al. (3) described five victims of accidental inhalation of high levels of SO_2 with three survivors developing severe and others showing mild airway obstruction. Flury et al. (4) described a 50-year-old man who inhaled substantial quantities of concentrated ammonia vapors. Over the next four years serial pulmonary function testing documented the development of

Table 1 Methacholine Reactivity[a]

Date	Subject 1	Subject 2
March 4, 1982	15 inhalation units	29 inhalation units
March 25, 1982	30 inhalation units	28 inhalation units
March 1, 1983	232 μg	52 μg
April 15, 1983	232 μg	–

[a]Positive tests are defined by methacholine doses of <200 inhalation units of 750 μg methacholine.

an obstructive lung disorder. Although methacholine challenges were not performed, the authors indicated that hyperresponsive airways were present and likely the direct result of the inhalation injury. Donham et al. (5) described an acute toxic exposure to high levels of hydrogen sulfide after agitation of liquid manure. One survivor had respiratory symptoms persisting more than two months after the incident. Harkonen et al. (6) followed seven mineworkers who were involved in a pyrite dust explosion and sustained SO_2-induced lung injury. Four years after the accident, an asthma-like condition characterized by reversible airway obstruction was observed in three persons; four workers showed positive histamine challenges, whereas two subjects responded neither to histamine nor to bronchodilators. The authors concluded that NSBH was a frequent sequel of high-level SO_2 exposure and could persist for years.

Subsequent to the original RADS report, other occurrences of RADS were reported. Several of these investigators modified the original criteria of RADS, thereby creating another phenotype of IIA, low-intensity chronic exposure dysfunction syndrome (LICEDS). Tarlo and Broder (2) performed a retrospective review of the files of 154 consecutive workers assessed for OA. Of 59 subjects considered having OA, a subset of 10 persons (and possibly an additional 15) with asthma symptoms for an average of five years were characterized by disease initiated by an exposure to high concentrations of an irritant. The RADS clinical criteria were modified in this study, and exposure was not limited to just a single accident or incident at work. It was concluded that "irritant-induced" OA is not uncommon in a population referred for the assessment of possible OA. The prevalence was estimated to be 6% for definite IIA and 10% for those with a possible diagnosis. Boulet (7) implied that there was prolonged induction of NSBH after the inhalation of high concentrations of irritants in four "normal" subjects and an aggravation of airway hyperresponsiveness in another person with "mild" preexisting asthma. Two of the persons were believed to have developed hyperresponsiveness following an intense short-term exposure alone. Gilbert and Auchincloss (8) reported a case of RADS occurring after a single massive silo dust exposure. In addition to objective evidence of NSBH, flow volume loops revealed a mixed obstructive/restrictive pattern in this worker, presumably on the basis of constriction of bronchioles or alveolar ducts. Other case examples reported as RADS included the following: (i) three Philadelphia police officers exposed to "toxic fumes" from a roadside truck accident (9); (ii) a female computer operator exposed to a floor sealant (10); (iii) workers exposed to TDI (11); (iv) possible exposures to acetic acid (12). Moisan (13) described RADS after smoke inhalation in three subjects. Bernstein et al. (14) evaluated four previously healthy, nonatopic men after acute exposure to toxic levels of anhydrous ammonia fumes. All of these workers exhibited obstructive symptoms, decreases in airway caliber, and persistent NSBH. Many other cases and case series have been reported. By the mid 1990s both the number of case reports and irritant agents have expanded.

Accidental inhalations reported by surveillance of work-related and occupational respiratory disease (SWORD) in the United Kingdom were most commonly caused by chlorine, smoke, and oxides of nitrogen (15). However, an extensive list of agents has been associated with RADS and/or IIA, as shown in Table 2.

RADS cases were identified by the four American states (i.e., California, Massachusetts, Michigan, and New Jersey) that conducted surveillance for work-related asthma (WRA) during the period 1993 to 2003 as part of the Sentinel Event Notification Systems for Occupational Risks (SENSOR). In this sampling period, a total of 445 RADS cases were documented by SENSOR (Chapter 14, Table 1).

Table 2 Agents Associated with RADS and/or Irritant-Induced Asthma

Agent	Type of study	Evidence	References
Acetic acid	Case report	H, S, P	(12)
	Epidemiological	H, S, BHR	(16)
Acids (various)	Case report	H, S, BHR	(2)
	Case report	H, S, BHR, P	(17)
Acid (heated) (+ welding fumes)	Case report	H, S, BHR, P	(1)
Ammonia	Case report	H, S	(4)
		H, S, BHR, P	(14)
		H, S, P	(18)
Bleaching agent	Case report	H, S, BHR	(7)
Calcium oxide	Case report	H, S, BHR	(2)
Chlorine	Case report	H, S, BHR	(2)
	Case report	H, S, BHR, P	(19)
	Epidemiological	H, S, BHR	(20)
Chloropicrin	Experimental	P	(21)
Cleaning agents	Case report	H, S	(22)
Diesel exhaust	Case reports	H, S, BHR	(23)
Diethylaminoethanol	Epidemiological	H, S	(24)
Epichlorohydrin	Experimental	P	(21)
Ethylene oxide	Case report	H, S, BHR, P	(25)
Floor sealant (aromatic hydrocarbons)	Case report	H, S, BHR	(1)
Formalin	Case report	H, S	(26)
Fumigating agent	Case report	H, S, BHR	(1)
Hydrazine	Case report	H, S, BHR	(1)
Hydrochloric acid	Case reports	H, S, BHR	(2,7,9)
Isocyanates	Case report	H, S	(11)
	Case reports	H, S, BHR	(2,27)
	Case report	H, S, BHR, P	(28)
	Experimental	S	(29)
Metal coat remover	Case report	H, S, BHR	(1)
Metam sodium	Epidemiological	H, S, BHR	(30)
Spray paint	Case report	H, S, BHR, P	(1)
Paint (fumes)	Case report	H, S, BHR	(2)
Perchloroethylene	Case report	H, S, BHR	(7)
Phthalic anhydride	Case report	H, S, BHR	(31)
Sulfur dioxide	Case reports	H, S, BHR, P	(6)
	Case report	H, S, BHR	(2)
	Case reports	H, P	(32)
Sulfuric acid	Case report	H, S, BHR	(2,7)
Uranium hexafluoride	Case report	H, S, BHR	(1)
Urea fumes	Case report	H, S, BHR, P	(33)
Fire/smoke (pyrolysis products)	Case report	H, S, BHR	(1)
	Case reports	H, S	(13)
Gases (chlorine, phosgene, mustard, etc.)	Case reports	H, P	(34)
	Case reports	H, S, BHR	(2)

Abbreviations: H, clinical history; S, spirometry; BHR, bronchial hyperresponsiveness; P, pathology.
Source: From Ref. 35.

In Table 3, the most common causal agents of RADS according to the SENSOR data are compared to asthma inducers of new-onset asthma (36). As expected, the two lists differ. Cleaning materials and chemicals not otherwise specified (NOS) lead the RADS list, whereas diisocyanates and lubricants (NOS) are most common for other WRA cases. The authors reported that RADS cases represented 14% of all new-onset WRA cases identified by SENSOR. As shown in Table 4, comparable figures from other studies and surveillance systems ranged from 5% to 18% (36).

PRESENCE OR ABSENCE OF RADS AFTER HIGH-LEVEL IRRITANT EXPOSURES DURING DISASTERS

Exposure to Irritant Gases During War

Thousands of military and civilian personnel experienced high-level exposures to irritants when mustard gas was used as a chemical weapon during the 20th century. On exposure to mustard gas, vesicant, cell damage occurs by the addition of an alkyl group to DNA and the initiation of cytokine-mediated inflammation. Mustard gas was used during World War I and, later by Iraq, during the Iran–Iraq war from 1980 to 1988 (37). One study examined the health of 34,000 Iranians, 13 to 20 years after they had survived exposure to mustard gas in the 1980s. The researchers determined that 42.5% had persistent medical problems of the lungs, defined as FEV_1 or FVC less than 80% of predicted and abnormal lung sounds (37). In another study, researchers identified an elevated prevalence of several lung disorders among 197 Iranian military veterans who had experienced heavy mustard gas exposure 10 years earlier: (*i*) 8.6% diffuse bronchiectasis; (*ii*) 9.6% airway narrowing due to scarring caused by granulation tissue; (*iii*) 10.7% asthma; (*iv*) 12.2% pulmonary fibrosis; and (*v*) 58.9% chronic bronchitis (38). The only respiratory problem among a comparison

Table 3 The Seven Most Frequently Reported Agents for Both Work-Related RADS and Other WRA Cases

RADS		Other WRA	
Agents[a]	No. (%)[b]	Agents[a]	No. (%)[b]
Cleaning materials	18 (15)	Diisocyanates	102 (39)
Chemicals NOS	10 (8)	Lubricants NOS[c]	46 (15)
Chlorine	8 (7)	Formaldehyde	24 (8)
Solvents NOS	8 (7)	Natural rubber latex	22 (7)
Acids, bases, and oxidizers NOS	7 (6)	Glutaraldehyde	19 (6)
Smoke NOS	7 (6)	Epoxy resins	16 (5)
Diesel exhaust	7 (6)	Acrylates NOS	10 (3)

[a]The agent categories are based on a scheme developed by Hunting and McDonald. We created two inclusive agent categories: "cleaning materials" included bleach, cleaning materials NOS, and metal polish; "diisocyanates" included toluene diisocyanate, methylene diisocyanate, naphthalene diisocyanate, hexamethylene diisocyanate, and diisocyanate NOS.

[b]For RADS, the percentages are of the 123 cases. For other WRA, the percentages are of the 301 cases.

[c]This category includes metalworking fluids.

Abbreviations: NOS, not otherwise specified; WRA, work-related asthma.

Sources: From Refs. 36, 40.

Table 4 Percentage of WRA Attributed to RADS or Irritant Asthma, from Surveillance in Four Countries

References	Country (state, province, or region)	Years	Surveillance program (how cases identified)	% RADS or irritant asthma
Henneberger et al. (36)	United States (California, Massachusetts, Michigan, New Jersey)	1993–1995	SENSOR (MD, HDD, WCC)	14% RADS (123/891)
Reilly et al. (41)	United States (Michigan and New Jersey)	1988–1992	SENSOR (MD, HDD, WCC)	8% RADS[a] (42/498)
Rosenman et al. (42)	United States (Michigan)	1988–1994	SENSOR (MD, HDD, WCC)	10% RADS[a] (69/672)
Reinisch et al. (43)	United States (California)	1993–1996	Doctors first reports (MD)	9% RADS (27/290)[b]
Provencher et al. (44)	Canada (Quebec)	1992–1993	PROPULSE (MD)	5% RADS (14/301)[c]
Chatkin et al. (45) Tarlo et al. (46)	Canada (Ontario)	1984–1988	Ontario Worker Compensation Board (WCC)	5% RADS (12/235)
Ross et al. (47)	United Kingdom	1994	SWORD (MD)	9% RADS/irritant asthma (93/1034)[d]
Gannon et al. (48)	United Kingdom (West Midlands Region)	1989–1991	SHIELD (MD)	18% irritant asthma
Hnizdo et al. (49)	South Africa	1996–1998	SORDSA (MD, PR, OHN)	13% irritant asthma (30/225)[e]

[a]The cases from the Michigan SENSOR program are included in Refs. Reilly et al. (38) and Rosenman et al. (39). Some of the cases from Rosenman et al. (39) were included in Henneberger et al. (36).

[b]The 290 cases of WRA were the new-onset cases who were interviewed and could be classified. These cases included 24 RADS and 28 other WRA cases from California that were included in Henneberger et al. (36).

[c]There were 287 cases of OA and 14 cases of inhalation accident/RADS. The combination of these two groups equals 301 cases and 14/301 = 5% RADS.

[d]There were 280 cases of work-related inhalation accidents reported to SWORD in 1994. Based on an earlier study, the researchers estimated that about one-third of the inhalation cases were either asthma or RADS, chiefly because of chemical irritants (215). Thus, about 1/3 × 280 = 93 RADS/irritant asthma cases. With the RADS/irritant asthma cases and other OA cases combined (93 + 941 = 1034), the RADS/irritant asthma cases represented 9% of the total (93/1034 = 9%).

[e]There were 195 cases of OA with latency and 30 cases of asthma induced by irritants. Thus, the percentage of asthma induced by irritants was 30/225 = 13%.

Abbreviations: WRA, work-related asthma; RADS, reactive airways dysfunction syndrome; MD, reports from physicians; HDD, hospital discharge data; WCC, worker compensation claims; PR, reports from provincial representatives; OHN, reports from occupational health nurses; OA, occupational asthma.

Source: From Ref. 36.

group of 86 unexposed veterans was one case of chronic bronchitis. Whether asthma was a direct consequence of RADS in these veterans was not determined.

The Bhopal Industrial Disaster: Chemical Accident

In December 1994, thousands of people were exposed to toxic levels of the irritant methyl isocyanate as the result of an accidental leak at the Union Carbide plant in Bhopal, India. Medical surveys of survivors have identified a variety of adverse respiratory outcomes (50). For example, decrements in FEF_{25-75} were observed at 2 and 10 years after the accident, suggesting persistent small-airways obstruction (51,52). Survivors were not systematically screened with histamine or methacholine challenge to determine whether they were at an increased risk for RADS or other forms of IIA (50,53). However, investigators conducted spirometry before and after administering bronchodilators, which provided some information about whether those tested had fixed or variable obstruction. For example, 11.6% of those tested shortly after the accident responded to a bronchodilator with an improvement of 11% to 20% in FEV_1, and 8.9% had an improvement of over 20% (51). By the third month, these percentages had declined to 7.7% and 8.8%, respectively. The authors concluded that there was no increase in "asthmatic tendency" related to the Bhopal methyl isocyanate exposure (51). Other investigators conducted spirometry before and after inhalation of 200 μg of salbutamol as part of the 10-year follow-up of 74 Bhopal survivors (52). Only 2 of the 74 participants responded to salbutamol. The investigators concluded that IIA was not a common disorder among survivors of the Bhopal accident (52). It would appear that further systematic assessments of the health effects of this industrial accident in larger numbers of survivors are still needed (54,55).

WTC RADS and WTC Cough

On September 11, 2001, terrorist operatives of Osama Bin Laden's Al-Qaida commandeered four U.S. commercial airplanes and initiated an attack on the United States. Two of the planes were flown into the World Trade Center (WTC) towers causing their collapse. The destruction and collapse of the towers generated an intense, short-term exposure to inorganic dust, pyrolysis products, and other respirable materials (56). Nearly 3000 people died and an estimated 250,000 to 400,000 people in the vicinity of the WTC collapse were exposed to the dust, debris, smoke, and chemicals (57). Firefighters and other rescue workers were also exposed to the high levels of the dust and other particulate materials especially during the first few days after the WTC collapse.

WTC Exposures

The specific content of the dust was later measured by the United States Geological Survey (USGS), which collected dust samples from various WTC areas and from steel girder coatings of the WTC debris (58). Most samples were obtained after September 17, 2001, when substantial settling of the dust had already occurred. The composition of the dust was shown to be made up of silicon, aluminum, calcium, magnesium, sodium, and other elements like gypsum; concrete and aggregates (containing calcium and aluminum hydroxides and a variety of silicate minerals containing silicon, calcium, potassium, sodium, and magnesium); particles rich in iron, aluminum, titanium, and other metals that had been used in building construction; and particles of other components, such as computers. Organic carbon in the dusts was most likely from paper, wallboard binder, and other organic materials. The leachate solutions developed alkaline pH values of between 8.2 and 11.8, likely a result of the dissolution of concrete, glass fibers, gypsum, and other material in the dusts. Metals present in relatively high concentrations in the leachate were aluminum, chromium, antimony, molybdenum, barium, manganese, copper, and zinc. The Centers for Disease Control and Prevention (CDC) concluded from an evaluation of environmental data that the level of exposure to most substances did not exceed limits set by the National Institute for Occupational Safety and Health or the Occupational Safety and Health Administration, with concentrations of airborne and respirable particulates ranging up to 2.3 and 0.3 mg/m^3, respectively (59). Fractionations of airborne dust samples revealed that 0.4% to 2% of particulates were respirable (56).

Respiratory Disorders Following WTC Collapse

Following the WTC collapse, several respiratory illnesses were described among rescue workers, including what has been called "WTC cough," persistent hyperresponsiveness/RADS, and acute eosinophilic pneumonia (56,60,61). There were discussions and controversies concerning these conditions (62–65). A high prevalence of rhinitis/sinusitis and gastroesophageal reflux disorders was also noted (56,61).

WTC Cough. The WTC cough was defined as a new/worsening persistent cough that developed after the exposure to the WTC site and was accompanied by respiratory symptoms severe enough to require medical leave for at least four weeks (56). The exposure categories were derived retrospectively from the questionnaire data. Although no direct personal exposure profiles were established, there was some confirmation obtained from work records. High exposure was assigned to Fire Department of New York (FDNY) firefighters who reported to the WTC site on the morning of the collapse (<24 hours); a moderate exposure for FDNY workers arriving within two days; low exposure for FDNY workers arriving between three and seven days after the collapse. No exposure was assigned for FDNY officers if they were not at the site for at least two weeks during the rescue operation.

The specific diagnosis of WTC cough was not formally confirmed until one month after the collapse. In the first medical examination, 332 of 10,116 firefighters (3.3%) met the diagnostic criteria for WTC cough. Within 24 hours after exposure, all 332 FDNY workers with WTC cough reported having a productive cough with black/gray-colored sputum that was "infiltrated with pebbles or particles" (56). WTC cough was more common (8%; 128/1636) in firefighters in the highest exposure category, but cough also developed in 3% (187/6958) with a moderate exposure and 1% (17/1320) with a low exposure. Methacholine challenge testing was performed in about 60% of the WTC cough workers (196/332), and NSBH (as defined by PC_{20} of <16 mg/mL) was present in 24% (47/196); approximately 19% (20/103) of workers without severe cough also showed NSBH (56). Significant numbers of firefighters described dyspnea, chest discomfort, gastroesophageal reflux disease, and upper-airway symptoms. Although the WTC cough cohort had reductions in FVC and FEV_1, they were similar in magnitude with no change from the FEV_1/FVC% determined before exposure. However, 16% (53/332) showed FEV_1/FVC% of <75%. Among those tested, NSBH was noted in about 25% of the firefighters with high levels of exposure, whether or not they had WTC cough.

Airway Hyperresponsiveness and WTC RADS. A cohort of firefighters received a follow-up examination six months after the WTC collapse, and the findings were a basis for a second publication describing persistent hyperresponsiveness and RADS (61). RADS was defined as NSBH ($PC_{20} \leq 8$ mg/mL) in conjunction with respiratory symptoms six months post-WTC collapse (61). Subjects designated as having RADS did not include subjects previously identified as suffering from WTC cough reported in the first paper (Prezant, personal communication). However, the authors noted that 13% (19/151) of exposed subjects (mostly in the highly exposed group) subsequently developed "WTC cough" after study enrollment. Of this group, only half (9/18) of the WTC cough group qualified for the diagnosis of RADS (symptoms and NSBH). While it is somewhat difficult to precisely extract numbers from the descriptions provided in the article, at six months there were 16% (20/123) of all exposed study subjects (representing 2% of the population of firefighters) who fulfilled the long-term criteria for the diagnosis of RADS (NSBH).

Significance of WTC Cough, Airway Hyperresponsiveness, and RADS. There were obviously tremendous amounts of dust generated with the fall of the WTC, as most television observers of that fatal day in September can attest. Retrospectively, most firefighters were not exposed to what might be characterized as a massive level of dust exposure by the time they arrived on site or in the days following the collapse of the towers. While not a disqualifying factor, dust exposures have not previously been described for RADS (1). The CDC concluded that the level of WTC dust exposures (0.3–2.3 mg/m^3) when measured several days later did not exceed governmental threshold limit values (15 mg/m^3) or permissible exposure limits (59). Most of the dust consisted of large-sized particles, a small proportion of which (0.4–2%) was respirable (56). Perhaps most of the cough that developed could be attributed to upper airway effects. Sinobronchial disease and rhinitis were prevalent, and these conditions are common causes of cough. In addition, gastroesophageal reflux, another important cause of cough, was also common. One of the features of the dust, which was said to be a characteristic of its irritancy, was its alkalinity ($pH > 10$) (58,61). However, inhalation of alkaline aerosols does not necessarily cause adverse responses, as determined by Gross et al. (66) who studied 24 asthmatic volunteers exposed to the alkaline aerosols generated during automobile airbag deployment from sodium azide oxidation (67).

The criteria for RADS, as defined by Banauch, were different from the original definition and criteria of RADS described by Brooks et al. (1,68,64). The diagnosis of RADS in the firefighters was established at the six-month evaluation; the subjects were not evaluated within 24 hours of the exposure. In support of the latter point, there was no reporting of inordinate numbers of firefighters visiting emergency rooms within the first 24 hours of the collapse. Of course, firefighters are dedicated professionals who felt an obligation to save as many lives as possible so they chose to work at the site for long hours during the first several days and weeks following the collapse of the towers. Even so, with a severe airway injury of sufficient magnitude to cause classical RADS, emergency medical care is usually necessary (69).

The number of firefighters tested, as compared to the total population at risk, was small with only about 3% of the surveyed firefighters undergoing methacholine challenges. Airway hyperresponsiveness at the six month examination was documented in about 28% of the highly exposed and 8% of the moderately exposed workers, a statistically significant difference. Testing only a fraction of the population may be misleading. As many as one-third of asymptomatic persons in the general population demonstrate a positive methacholine challenge test (70), and approximately 10% of workers with no respiratory symptoms demonstrate methacholine $PC_{20} \leq 8$ mg/mL (71). The sensitivity of methacholine hyperresponsiveness for confirming cases of OA may often be less than 100%, particularly when subjects are no longer exposed to the offending agent (72).

RADS diagnosis requires ruling out preexisting asthma. To qualify for employment as a firefighter, there must be no past history of asthma; this disqualifying fact could possibly have precluded firefighters from mentioning a past history of asthma on their entrance examination (Dorsett Smith, personal communication). Persons with asymptomatic airway hyperresponsiveness are at an increased risk for future development of asthma. On longitudinal follow-up, as many as 45% of asymptomatic persons with bronchial hyperresponsiveness develop asthma during a two- to three-year period (73). The measurements for NSBH show good reproducibility over months to years and may precede the onset of symptomatic clinical asthma by several years (74,75). The finding of a positive methacholine challenge does not necessarily signify disease or asthma. In fact, there is often difficulty in reaching the definitive diagnosis of asthma because of its complex nature and characteristics (76). Although most subjects with active OA show airway hyperresponsiveness (62), this characteristic must be put in context of asthma, which is a dynamic disease, the clinical course of which depends on numerous factors including the lapsed time period since cessation of exposure and treatment (19,77).

Susceptibility (Personal Determinants) for IIA

Even though there were uncertainties about the interpretation of the observed data for firefighters exposed to WTC exposures, the dust does not appear to have the potential for causing lung injury (60). The firefighters with asthma and NSBH presented with new-onset symptoms and findings. How can this observation be interpreted? One explanation may come from the study of Brooks et al. (1) who described two types of IIA that presented as new-onset asthma. The first type was characterized by an intense exposure followed by sudden-onset IIA that corresponded to RADS. The clinical manifestations began within 24 hours. The affected individual was immediately ill and required prompt medical care. In this scenario, RADS was a response to a very excessive (usually brief) accidental exposure to an irritant gas, vapor, or fume. Because of the enormity of the exposure, there was extensive airway damage, which induced bronchial mucosal inflammation; these outcomes led to NSBH and clinical asthma manifestations (78,79). An atopic status was not operative in the pathogenesis of RADS. Likely, the original description of RADS exemplified the extreme end of the spectrum of an irritant effect on the airways (80,81).

In the second phenotype of IIA, a longer onset time (e.g., >24 hours) occurred because the exposure did not involve massive concentrations and the subjects were able to tolerate the exposure for a longer period of time. In this chapter, this form of IIA will be termed LICEDS. Why does an irritant exposure, not considered to be massive or of high level, produce sufficient airway injury to create persistent airway inflammation and airway hyperresponsiveness? Alternative mechanisms other than persistent airway damage caused by massive exposure must be considered. In fact, most acute inhalation injuries clear without residual lung damage.

There may be a susceptibility or risk factor(s) that puts a person at increased risk for developing an acute asthmatic process from this type of exposure. Host susceptibility, such as preexisting asthma or atopy, with its associated inherent biochemical and pathological consequences, is a consideration (82). While subjects with RADS do not show a greater prevalence of allergy/atopy predisposition, a higher percentage (88%) of individuals with the more slowly evolving onset type asthma were atopic (82). Additionally, 40% of persons who presented a new-onset IIA reported a preexisting asthmatic state that was in remission (82); usually, the remission was present for years before the exposure occurred. Persons with asthma in remission may be relatively asymptomatic and do not require medications (70,83–85). Therefore, allergy/atopy status and preexisting asthma may be important risk factors for developing asthma from moderate-level irritant exposures. Whether these or other unknown risk factors for IIA were present in WTC firefighters is unknown, but firefighters might not have mentioned previous atopy or asthma during their childhood or in the distant past, to qualify for employment.

PATHOLOGY

The first descriptions of the pathological features of RADS were mostly those of the chronic stage of the syndrome (1). Brooks and co-workers were the first to perform bronchial biopsies in patients with RADS. Later, bronchial biopsy data reported by Bernstein et al. (14) revealed typical histopathological features of asthma including marked denuded epithelium, submucosal chronic inflammation, and collagen proliferation below the basement membrane. The latter finding had developed in one anhydrous ammonia–exposed patient who had a bronchial biopsy within two weeks after the acute exposure (14).

Deschamps et al. (17,25) performed biopsies on two subjects, the first case three years after exposure to toxic concentrations of ethylene oxide, the second several months after inhalation of a mixture of sodium hypochlorite and hydrochloric acid. They reported severe injury of the epithelial layer as well as inflammatory infiltrates containing lymphocytes. Electron microscopic examination of these biopsy specimens revealed a thickening of connective tissue with collagen fibers. There was no thickening of the basement membrane itself. Histopathological changes in the case of IIA secondary to multiple exposures to an irritant agent have also been described at the chronic stage of the disease. In five workers studied by Gautrin et al. (78) two years after cessation of repeated exposure to high concentrations of chlorine, desquamation of bronchial epithelium and squamous cell metaplasia as well as inflammatory infiltrates consisting of lymphocytes and polynuclear cells with reticulo-collagenic fibrosis in the bronchial wall and thickening of the basement membrane were found. The biopsy specimens of four subjects with IIA and RADS have been examined with immunohistochemical techniques to characterize structural changes further (M. Boulet, personal communication, 1995). Collagen types I, III, IV, and VII, fibronectin, desmin, and laminin beneath the basement membrane, between smooth muscle fibers, and around nerves were observed. These findings indicate marked airway remodeling. Three workers with IIA were investigated by Chan-Yeung et al. (86) five months to one year after exposure to sulfur dioxide, hydrogen peroxide, and acetic acid, respectively; thickening of the basement membrane and cellular infiltration in the mucosa and submucosa were present. In contrast to earlier findings, the inflammatory infiltrates consisted of eosinophils, shown on immunohistology to be activated, and a few T lymphocytes (both CD8+ and CD4+). Two subjects suffering from RADS after a single exposure to toxic fumes were studied by Lemiere et al. (33,28). Bronchial biopsies were performed 46 days and 60 days after the event, respectively.

Immunohistochemical stains revealed that most inflammatory cells were T lymphocytes; no degranulated eosinophils were detected.

Table 5 summarizes the time course of changes in the pathophysiological features in two cases of RADS immediately following the accidental inhalation of chlorine and isocyanates, respectively (Figs. 1 and 2) (19,28). Briefly, there was rapid denudation of the mucosa with fibrinohemorrhagic exudates in the submucosa followed by signs of regeneration of the epithelial layer with proliferation of basal and parabasal cells and subepithelial edema. Five months after the inhalation accident and three months after treatment with inhaled corticosteroids, regeneration of the bronchial epithelium was complete in the first case but only partial in the second case. The time course of the pathological features in these two cases suggests that histological injuries of RADS could be almost completely reversible. Yet, in the specimens described by Brooks et al. (1) from biopsies performed several years after the offending exposure, injuries of the epithelial layer and inflammatory infiltrate were still present. An important difference in the series of cases investigated by Brooks et al. (1) and those by Lemiere et al. (19,28) is the medical management. In the latter series, both subjects were prescribed inhaled corticosteroids after the first bronchoscopy at day 3 and day 45 after exposure to chlorine and isocyanates, respectively. It can be hypothesized that early institution of inhaled corticosteroid treatment may have enhanced the regeneration of bronchial epithelium and reduced the inflammatory reaction (87).

The acute changes of RADS were confirmed in a model in which rats were exposed to high concentrations of chlorine (88). Histological evaluation revealed epithelial flattening, necrosis, and evidence of epithelial regeneration. Bronchoalveolar lavage (BAL) showed an increased number of neutrophils. Maximal abnormality in the appearance of the epithelium occurred between days 1 and 3 and corresponded to the timing of maximal functional changes in lung resistance and NSBH (Fig. 3) (88). Although the functional and pathological abnormalities were resolved in the majority of animals after a variable period, some animals were left with persisting epithelial abnormalities. So, in the animal model of RADS it was shown that institution of parenteral steroids for one week significantly reduced the increased percentage of neutrophils in BAL and had partial beneficial effects on airway wall damage as evidenced by the decrease in the extent of epithelial changes (epithelial flattening, necrosis, and stratification) in goblet cell number and in the amount of smooth muscle (89).

A mouse model (A/J mice) was used recently by Martin et al. (90) to investigate the link between functional changes and the inflammatory response following exposure to chlorine and to explore the possibility that oxidative mechanisms are involved in the injury caused by chlorine. Airway responsiveness to methacholine was measured and inflammation was assessed by lung lavage and histology 24 hours after a five-minute exposure to 100, 200, 400, or 800 ppm chlorine. The presence of tissue oxidation was evaluated by immunostaining with 3-nitrotyrosine (3-NT) in lung lavage cells and pulmonary tissues. Epithelial cells and alveolar macrophages from mice exposed to 800 ppm of chlorine stained for 3-NT residues. Specific inhibition of nitric oxide synthase with an experimental inhibitor (1400 W; 1 mg/kg) suppressed the chlorine-induced changes in responsiveness. These results support the hypothesis that some of the functional and pathological changes in the airways caused by chlorine exposure are associated with oxidative stress and show that inducible NOS is involved in the induction of changes in response to methacholine.

Table 5 Time Course of Histological Lesions After Accidental Inhalation

Interval after accidental inhalation			
Case 1: Exposure to toxic concentrations of chlorine (19)			
60 hours	15 days	60 days	150 days
Superficial fibrinohemorrhagic layer replacing bronchial epithelium that is sloughed; degeneration of connective tissue	Persistence of superficial hemorrhage; bronchial epithelial sloughing	Regeneration of the epithelial cells (basal, parabasal); collagen degeneration	Complete regeneration of the epithelium layer
	Increased deposition of collagen	Spots of lymphocytes	Numerous basal cells indicating regeneration
		Few polynuclear cells Increase in collagen of basement membrane	
Case 2: Exposure to toxic concentrations of solvents and isocyanates (28)			
45 days		98 days	
Severe damage of the epithelial layer with few remaining basal cells Subepithelial edema with inflammatory cells underneath the basement membrane		Incomplete regeneration of the epithelial layer with few ciliated cells Inflammatory cells persisting in epithelium and connective tissue	

Source: From Ref. 87.

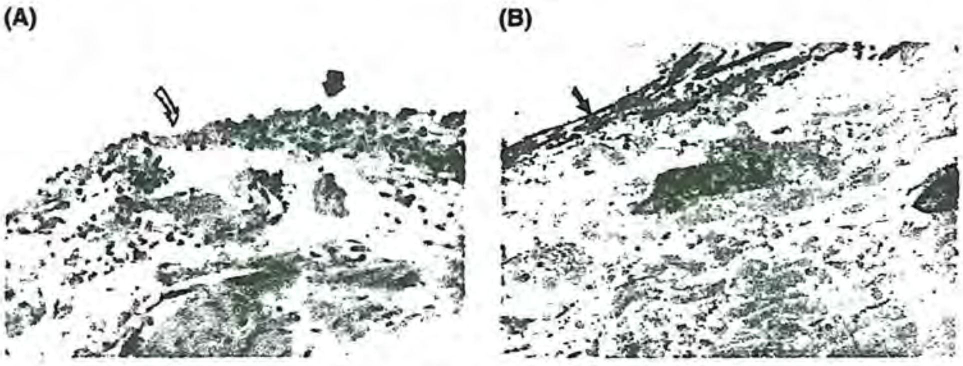

Figure 1 (A) Light micrograph of bronchial biopsy 46 days after single massive exposure to isocyanates. Severe loss of epithelial cells (*open arrow*) with few remaining basal cells (*shaded arrow*). Subepithelial edema with inflammatory cells (mainly lymphocytes) underneath basement membrane (hematoxylin-eosin (H-E) stain ×250). (**B**) Electron micrograph of first biopsy. Epithelial cell loss at luminal surface with fibrin deposition and intrafibrillar edema (*arrow*). Epon-embedded material stained with uranyl acetate and lead citrate (×2700). *Source*: From Ref. 28.

HYPOTHESIS OF PATHOGENETIC MECHANISMS

The pathogenesis of RADS is entirely speculative, primarily because the clinical descriptions of the syndrome thus far have been retrospective. Although airway damage in the animal models described earlier appears to confirm the acute changes occurring in RADS, it does not address the diversity of the causative agents and the uncertainties concerning individual susceptibility and risk factors. Moreover, since the initial clinical cases were observed only after high-level irritant exposures, it cannot yet be claimed that the asthma-like reactions caused by low-level respiratory irritants (i.e., LICEDS) are equivalent to RADS. From the currently available meager amount of bronchial biopsy histopathological data, it appears that the

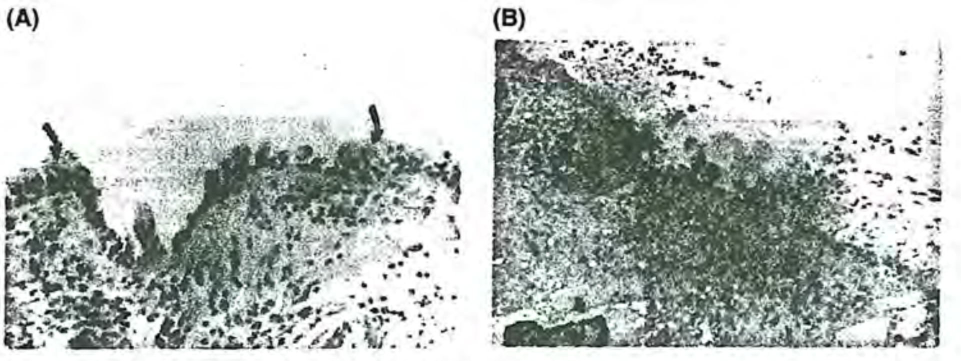

Figure 2 (A) Light micrograph of second bronchial biopsy 98 days after isocyanate exposure. Incomplete regeneration of epithelial layer with few ciliated cells (*arrows*). Inflammatory cells (mainly lymphocytes) persist in epithelia and connective tissue (H-E stain ×250). (**B**) Electron micrograph of second biopsy. Epithelial cells with incomplete cilia genesis and dilatation of smooth endoplasmic reticulum. Lymphocytes at bottom (*arrow*) (uranyl acetate and lead citrate staining, ×2700). *Source*: From Ref. 28.

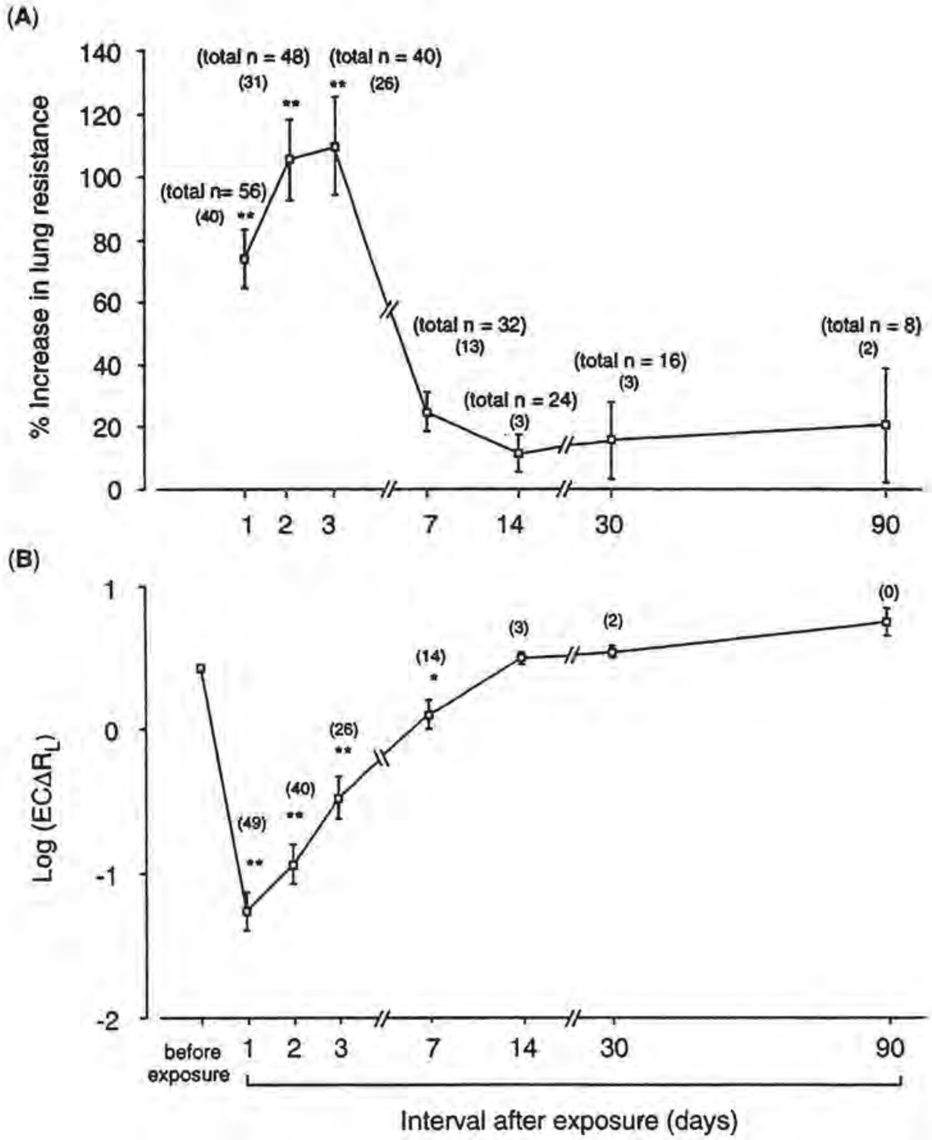

Figure 3 (**A**) Time course of lung resistance changes after acutre chlorine exposure; (**B**) time-course of the effective concentration of methacholine required to induce an increase in R_L of 0.20 cmH_2O mL/sec from postsaline inhalation value (EC ΔR_L). Data are expressed as mean ± SEM. Statistically significant differences between measured value and baseline value are expressed as $**p < 0.01$, $*p < 0.05$. The total number of rats included and the number of rats with abnormal findings (*in brackets*) are given at each time interval. *Source*: From Ref. 88.

micropathological outcome of RADS is similar to asthma. It may therefore be appropriate to propose a pathogenetic hypothesis commensurate with current knowledge about naturally occurring asthma.

Assuming that RADS is a "big bang" event occurring after a high concentration, and often accidental, single exposure to an irritant gas, vapor, or fume, the high

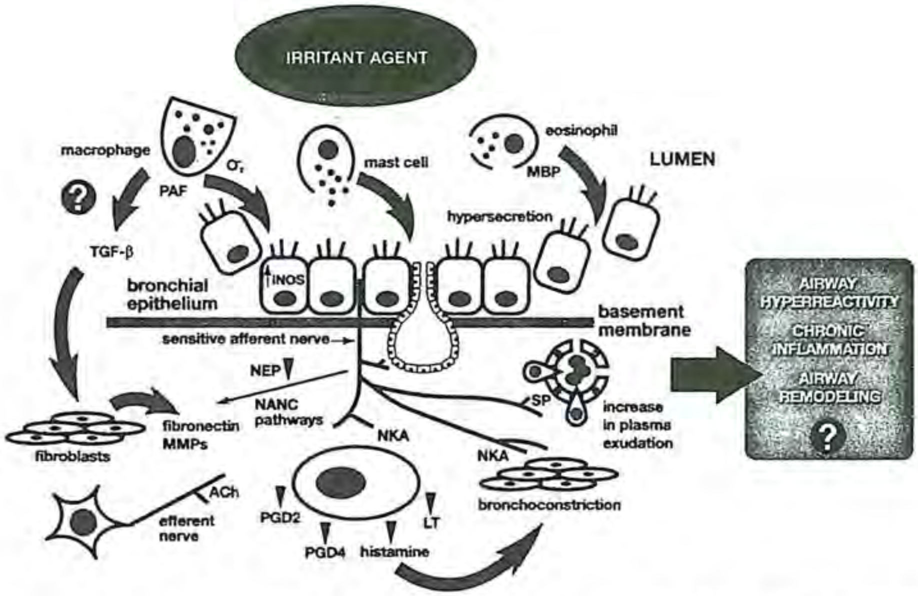

Figure 4 Pathophysiological hypothesis in RADS. *Abbreviations*: Ach, acetylcholine; iNOS, inducible nitric oxide synthase; LT, leukotriene; MBP, major basic protein; MMPs, matrix metalloproteinases: NANC, nonadrenergic, noncholinergic; NEP, neutral endopeptidase; NKA, neurokinin A; PAF, platelet-activating factor; PGD, prostaglandin; SP, substance P; TGF-β, transforming growth factor. *Source*: From Ref. 87.

levels of such irritant exposures will initiate massive airway injury (Fig. 4). The sequelae of the severe epithelial damage may lead to a cascade of changes that include airway inflammation and remodeling. The airway epithelial damage may also lead to direct activation of nonadrenergic, noncholinergic (NANC) pathways via axon reflexes and resultant neurogenic inflammation. Nonspecific macrophage activation and mast cell degranulation may also occur with the release of proinflammatory chemotactic and toxic mediators. Secondary recruitment of inflammatory cells will then enhance the subsequent profound inflammatory response. Subepithelial fibrosis, changes in mucous glands smooth muscle structure, and other changes of remodeling may then ensue.

The important inaugural event involves initiation of bronchial epithelial injury. What exactly transpires is not completely understood, but the injury in some way impairs intrinsic respiratory epithelial function (i.e., loss of ciliary activity, reduced neutral endopeptidase activity, decreased availability of epithelial-derived relaxing factor) and also initiates epithelial cell release of inflammatory mediators with subsequent activation of NANC nerves and transmitter release (neurokinins A and B, substance P, etc.). These combined effects not only induce changes in microvascular permeability but also cause increased mucus cell secretion. The chronic inflammatory process observed in bronchial wall biopsies is probably the end result of secretions from the major effector cells: alveolar macrophages, mast cells, and eosinophils. Many of the inflammatory mediators released by these cells are directly toxic. Others lead to lymphocyte recruitment and subsequent release of a complex cascade of cytokines, which enhance the inflammatory response. It is therefore not surprising that a chronic state of NSBH occurs as an aftermath of RADS.

During the recovery process there may be resolution of inflammation, epithelial cell repair, neural activity inhibition, and improvement of vascular integrity. However, the greater the degree and extent of the initial injury, the more unlikely that a complete recovery will occur. Under the latter conditions there may be deposition of type III collagen under the basement membrane, and such changes may be irreversible. In most cases of RADS due to high-level irritant exposure, the sequelae of the inflammatory response are obviously severe enough to cause chronic persistent asthma with concurrent NSBH.

The importance of airway remodeling in the pathogenesis of RADS (and other types of IIA) is supported by an investigation of workers exposed to repeated accidental inhalations of high and low concentrations of chlorine. Studies were performed to determine if airway obstruction and NSBH were associated with airway remodeling (91). In a prospective cohort of workers from a metal-processing plant, 32 workers were assessed at beginning of employment and five years after. Spirometry and bronchial challenges were performed on both occasions. At follow-up, sputum induction was also performed. Gelatinase (MMP-9) and collagenase (MPP-1) activities were assessed. Increase in bronchial hyperresponsiveness (BHR) (>2 dose decrement in PC_{20}) and/or decrease in FEV_1 (>11%) were present in 13 subjects (40.7%). These workers had reported more accidental chlorine puffs per year in comparison with the other 19 workers (40.1 + 28.5 vs. 10.6 + 3.8 puffs). Gelatinase activities in activated sputum samples from workers with changes in lung function were significantly higher than in those with no such changes; collagenase activities in nonactivated samples were similar in both groups. These findings suggest that functional decreases associated with repeated exposures to chlorine may be related to airway remodeling. Further studies are needed to identify and quantify the gelatinase subclass involved (MMP-2 or -9).

Several risk or susceptibility factors have been suggested for RADS or LICEDS. Patients with preexistent NSBH (e.g., asthma patients in long-term remission, rhinitis patients with asymptomatic NSBH, and some otherwise normal persons in the general population) might be expected to have underlying pathologic features that would be augmented and worsened by a sudden proinflammatory airway exposure.

What are the possible mechanisms to explain "new-onset" IIA in an individual with an atopy/allergy status? Perhaps atopic persons and possibly individuals with a genetic tendency for allergies (but without overt atopic manifestations) are unique in their responses to irritants. It is known that atopic individuals are at an increased risk for developing asthma, are more likely to show serial accelerated declines in lung function tests, and display exaggerated responses to irritants (39,92–96). Furthermore, IgE, paramount to the atopic state, seems linked to NSBH (97,98).

The roles of bronchial epithelial cells and barrier protection should be considered. Bronchial epithelial cells of atopic subjects react differently to irritant exposures because IgE is bound to their surfaces (99). A further possibility is that a preceding irritant exposure enhances bronchial mucosal permeability which could facilitate sensitization (100,101). The enhanced bronchial mucosal permeability leads to greater penetration of common airborne environmental aeroallergens into the airway mucosa. Previous sensitization to these aeroallergens could then lead to increased allergy/IgE/mast cell interactions and more pronounced mediator release, eventuating into clinically new-onset asthma. An irritant exposure might lead directly to mediator release from various airway cells (e.g., mast cells and bronchial

Table 6 Cardinal Diagnostic Features of RADS

Identification of date, time(s), frequency, and extent of exposure; the latter may be a single high exposure, multiple high exposures, or multiple somewhat high exposures (yet still higher than either TLV or PEL concentrations)
Symptoms appear within 24 hrs
No latency period between exposure and symptoms
Symptoms less likely to improve away from work
Objective (pulmonary function) tests demonstrate obstruction
Presence and persistence of nonspecific bronchial hyperresponsiveness (as measured by methacholine or histamine challenge tests)

Abbreviations: RADS, reactive ariways dysfunction syndrome; TLV threshold limit value; PEL, permissible exposure level.

epithelial cells) and an accentuated airway inflammatory response and NSBH (7). Airway sensitivity to an allergen could be augmented by nonallergic irritant exposure. This has been demonstrated in humans after preexposure to low-levels of ozone and diesel fumes (102,103). In most likelihood, there is also a complex interplay between IIA injury, preexisting airway inflammation, IgE-mediated mechanisms, and genetic factors about which much is not known.

DIAGNOSIS OF RADS

The clinical criteria for confirming the diagnosis of RADS are listed in Table 6. They are determined after a thorough medical and occupational history, abnormal pulmonary function tests, and objective evidence of NSBH.

History and Symptoms

Although there are no rigorous validity data about the predictive value of history, there is no question that it is crucial for the diagnosis of RADS. In contrast to other forms of OA, where the onset of the illness cannot be precisely determined, the onset of RADS usually can be specifically dated. The patient may even be able to identify the exact time of the day that the illness began. The reason for this clear-cut time discrimination is that RADS is a dramatic event, generally following an accident or an unusual precipitous incident. The details remain vividly clear in the subject's mind. The exposure is an irritant and generally a vapor or gas, but on occasion a high-level smoke or dust exposure may be responsible. The original criteria have been modified to encompass both single high-toxic exposures and repetitive exposures to either high toxic or somewhat lower concentrations—yet still above permissible exposure levels of the same irritant. Multiple exposures to low levels of irritants are not included in the original case definition of RADS. Moreover, the terminology of "RADS-consistent symptoms" cannot be rigorously defined and should be discouraged.

A prerequisite of RADS is documenting the onset of a totally new respiratory process. Persons considered to have RADS must not suffer from reactivation of a previously quiescent asthma. RADS is not applicable for the patient with preexisting asthma that worsens with the irritant exposure. Besides preexisting asthma, other entities, such as bronchiolitis obliterans and vocal cord dysfunction, must be considered. In particular, the latter is often falsely considered as RADS. Meticulous review of relevant medical records and careful history taking are imperative to rule out previous respiratory disease.

It is important to document details of the onset with the exact date and time and to distinguish initial severity of disease using objective findings. The documentation may consist of emergency room notes that describe wheezing, reduced arterial oxygen saturation, a reduced FEV_1, a decreased peak flow rate, or a positive methacholine challenge test. The reason for documenting early manifestations (within 24 hours of the exposure) is that individuals with RADS may pursue litigation options. Such patients are examined by several physicians over succeeding months or years. Consequently, reliance solely upon the retrospective description by the patient makes the diagnosis debatable. Acute reported symptomatology could simply be an acute irritant response, and not actual asthma. Therefore, it is essential to document the evolution of serious airway injury in close proximity (e.g., within 24 hours) to the exposure.

The most important historical feature that distinguishes RADS from immunological OA is the presence of a latency period between the initial exposure and disease onset. Therefore, complete knowledge about the suspected etiological agent, the time of exposure, and the subsequent onset of symptoms is essential for an acceptable diagnosis of RADS. Confusion may occur after a single massive exposure to an agent known to cause immunological OA in certain cases (104). For example, although workers with exposures to one or more large spills of TDI are more likely to report asthma symptoms or show changes in lung function tests, an immune mechanism may or may not be demonstrated in such cases (105,106).

Similar to other types of OA, the symptoms of cough, dyspnea, and wheezing may occur. Characteristically, cough is a predominant symptom and may lead to an incorrect diagnosis of "acute bronchitis." Some RADS patients develop an intractable cough, which even interferes with the medical interview and precludes proper spirometric measurements.

The response of symptoms to removal from work may not have the same significance for RADS patients as it does for other types of OA. Workers with RADS are less likely to improve away from work, at least for several months after the first appearance of symptoms. Symptoms usually do not improve over a two-day weekend or an occasional day off, but might gradually taper off within a period of months. Some workers with RADS may note improvement away from work because their newly induced hyperresponsiveness makes them more susceptible to other low-level irritants and physical stimuli in the workplace.

Objective Tests

Changes in airway caliber and airway reversibility are variable in RADS. Abnormalities usually can be demonstrated soon after the initial exposure event. Long-term persistence of airflow limitation depends upon the inciting agent and the initial duration of exposure, both of which determine the degree of epithelial damage and subsequent inflammatory response. Resolution of airways obstruction depends upon the quality and efficiency of the recovery process. Thus, if the recovery is complete, the spirometric tests should become normal. When a RADS patient is well enough to return to work, cross-shift changes in FEV_1 or other obstructive parameters should not be expected to vary, because the industrial event that originally caused RADS is no longer an inciting risk factor for the worker. Thus, in contrast to other forms of OA (both immunological and nonimmunological), pulmonary function tests in RADS workers usually do not vary significantly at or away from work. However, during the active phases of RADS, exaggerated diurnal variation of spirometric values will be present just as in other types of asthma. Therefore, serial peak expiratory flow rate tests are particularly useful in this group of patients for prognosis of the obstructive process (107–109).

Testing for the presence of NSBH in RADS workers is vital for following the course of the disease (110,111). As airway obstruction may resolve within a matter of months, a finding of increased NSBH may be the only objective finding in such patients. In the reported cases that have been followed up, significant NSBH, as measured by methacholine or histamine challenge tests, may be demonstrated for years after the initial inhalation episode (14). The waning or disappearance of NSBH is a good harbinger of recovery (112).

Potentially Novel Diagnostic Techniques for RADS

In recent years, several innovative approaches to the assessment of lower airway inflammation have emerged. These techniques have been evaluated in a number of studies of occupational immunologic asthma but as yet there have been no systemic or prospective investigations of them in IIA.

Total cell and differential counts in sputum samples induced by hypertonic saline have been utilized in several recent OA reports. In general, the presence of increased sputum eosinophils tends to occur more often in immunologic asthma induced by high-molecular-weight compounds, although elevated sputum eosinophils can also be found in asthma due to low-molecular-weight compounds (113). In contrast, Di et al. (114) observed high levels of neutrophil and lower eosinophil counts in the airways of subjects with asthma induced by low-molecular-weight compounds. In the same study, induced sputum results in these subjects were significantly different than in patients with OA due to the action of high-molecular-weight agents which caused increased eosinophils in induced sputum samples. High levels of eosinophils in induced sputum samples may also be found in patients with chronic cough without asthma. Under these conditions, this syndrome is further defined as eosinophilic bronchitis without evidence of variable airflow obstruction or NSBH (115). Since the first report of occupationally induced eosinophilic bronchitis by Maestrelli et al. (116), other case reports have appeared (117–119). OA primarily associated with sputum neutrophils has been reported in workers exposed to metal working fluids and cleaning workers of a swine containment room (120). However, in another report of swine containment workers with a history of asthma, only macrophages were elevated in induced sputum samples (121). It is not clear whether any of the current reports that equate induced sputum measurements as surrogates of airway inflammation can be applied directly to IIA; further research is needed in this area. Of related interest is that several studies have also assayed proinflammatory cytokines, such as IL-6 and IL-8, but no general conclusions can be drawn from such random and uncontrolled studies.

Measurement of exhaled gases, such as hydrogen peroxide and nitric oxide (NO), has been suggested as a surrogate marker for lower airway inflammation. Thus far, most investigators have focused attention primarily on nitric oxide. So far, the chief utility of this test in nonoccupational asthma appears to be its ability to detect changes in mild asthmatic patients and to confirm the ameliorative effects of corticosteroid treatment. In performing the tests, it is essential to exclude nasal NO, which has high concentrations relative to the lower respiratory tract. This can be accomplished by exhalation against resistance which closes the velum during expiration. Because expiratory NO levels are markedly flow dependent, a constant expiratory flow rate is required for reliable measurement. These preconditions may therefore limit the interpretation of the tests in certain subjects. A further possible limiting factor is a recent finding that exhaled NO is increased in patients with chronic obstructive pulmonary disease. This increase was most likely influenced by tobacco-induced lung damage in these patients (122).

The application of exhaled nitric NO as an indicator of airway inflammation secondary to occupational exposure has not been investigated widely, either in immunologic or nonimmunologic asthma. Obata et al. (123) reported that levels of exhaled NO increased 24 hours after challenge with plicatic acid in both responders and nonresponders, and was significant only in nonresponders. Further, no correlations were found between increase in NO and the magnitude of functional changes in the airways. Allmers et al. (124) found no clear relationship between bronchial response and increased NO levels in patients with immunologic asthma. It has been suggested that patients with preexisting atopy may exhibit elevated levels of NO when they have been recently exposed to a relevant allergen (125). Thus, among paper mill workers exposed to bleach, asthmatic workers with preceding atopic problems had higher levels of exhaled NO. In a subsequent report, it was demonstrated that workers exposed to an unusual ozone peak not only developed asthma symptoms but also had higher median concentrations of exhaled NO in comparison with those workers who did not experience such gassing effects (126). Exhaled NO has also been evaluated in patients before and 24 hours after specific bronchial challenge tests to occupational agents (127). In positive challenges which induced bronchoconstriction, a significant increase in exhaled NO was noted. It was particularly accentuated if responding patients had normal or only slightly increased basal NO levels (<14.5 ppb basal NO). On the other hand, patients with both high basal NO levels (>14.5 ppb) and significant bronchoconstriction after challenge did not show significant NO elevations.

Recently, the diagnostic potential of exhaled NO has been assessed in workers exposed to various irritants at work that ultimately cause asthma or asthma-like syndromes. Thus, workers exposed to high concentrations of sulfur dioxide during the process of apricot sulfurization developed asthma-like symptoms with decrements in FEV_1 and FEF_{25-75} (128). Concentrations of serum proinflammatory cytokines, direct nitrite, total nitrite, and nitrate were significantly higher in workers exposed to the sulfurization process than in a normal control cohort (129). These investigators postulated that TNFα, IL-1β, IL-6, IL-8, and NO may play a role in the pathogenesis of bronchoconstriction and asthma-like syndromes occurring after the sulfur dioxide exposure. Unfortunately, exhaled NO was not directly evaluated in this study. Swine confinement workers, who reported wheezing, cough, and sinusitis symptoms, were more likely to have small increments in mean exhaled NO than normal controls (121). In a recent study of 218 aluminum smelter workers, 17% of the potroom workers developed asthma-like symptoms. Exhaled NO concentrations in nonsmoking potroom workers were 63% higher than in nonsmoking control subjects evaluated in the same plant. It was interesting that no differences in exhaled NO were found between smoking potroom workers and controls. This most likely was due to known decreases in exhaled NO in chronic cigarette smokers, one of the limitations of the method. Overall, these results are consistent with the notion that increased concentrations of NO in exhaled air in potroom workers may reflect a subclinical degree of airway inflammation caused by exposure to pollutants in the

Table 7 Similarities and Differences Between OA with a Latency Period and RADS

	OA with a latency period	RADS
Latency period	Present	Absent
Diagnosis	Various: PEF monitoring; SIC	History; functional
Pathology	Like asthma	Acute: more epithelial shedding hemorrhage; chronic: more connective tissue
Functional	Better reversibility to BDT	Less reversibility to BDT
Treatment	Steroids useful	Steroids useful

Abbreviations: OA, occupational asthma; BDT, bronchodilator; PEF, peak expiratory flow; SIC, specific inhalation challenge; RADS, reactive airways dysfunction syndrome.
Source: From Ref. 35.

smelting environment (130). Exhaled NO was also studied in synthetic leather workers exposed to organic solvents, such as toluene, xylene, and ketones. Under workplace exposure conditions, the solvent concentrations were high but within permissible exposure levels. Exhaled NO was evaluated at baseline and at the end of the work shift. Exhaled NO increased by 40% in the leather workers at the end of a working day as compared to controls. None of these workers had developed respiratory symptoms. The authors concluded that exhaled NO may be a sensitive tool to monitor possible subclinical effects of occupational proinflammatory substances (131).

Although measurement of exhaled NO may ultimately provide a novel way of estimating lower airway inflammation, it has not yet been investigated on a prospective basis in classical cases of IIA. Such investigations are required before this test can be recommended as part of the current algorithmic approach to IIA.

COMPARISON BETWEEN RADS AND OTHER FORMS OF OA

Common and distinguishing features of RADS and other types of OA are listed in Table 7. From a histopathological point of view, desquamation of the epithelium is found in both conditions. In the acute stage, desquamation is much more extensive in RADS; consequently, regeneration of basal cells is prominent in RADS. The inflammatory exudate, on the other hand, is less intense in RADS. Neutrophils are found in BAL at least in the acute stage of RADS. Lymphocytes are encountered in both types of OA, although they are more numerous in nonoccupational asthma. Eosinophils are commonly found in both natural and OA. However, their presence in RADS has only been reported in two series of cases (78,86). Thickening of the basement membrane is common in both conditions but is more pronounced in RADS. Subepithelial fibrosis is much more pronounced in RADS (78).

From a functional point of view, if airway obstruction is present, it is less responsive to bronchodilators in the case of RADS. Gautrin et al. (78) compared 15 subjects with RADS and 30 subjects with OA with a latency period, all with a FEV_1 of <80% of predicted normal and with similar intervals from the end of exposure. The mean improvement in FEV_1 after administering a bronchodilator was close to 20% in OA with a latency period, but only 10% in subjects with RADS. As in OA with a latency period, there may be improvement in NSBH for up to two to three years after cessation of exposure (132). Finally, clinical evidence (19) coupled with experimental findings (89) suggests that corticosteroids can improve airway caliber and NSBH in RADS similar to their effects in both OA with a latency period and natural asthma.

EPIDEMIOLOGIC STUDIES

Incidence

It is difficult to estimate the incidence of RADS or a syndrome similar to RADS because of variability in the target populations: i.e., nonoccupational exposure to an accidental spill (133,134) with populations subsequently reporting to a poison control medical center (135) or a worker population (16). In the former instance, a true incidence rate for RADS cannot be calculated because only those self-reporting to a poison or a medical center are evaluated (136). Similarly, in worker populations, NSBH has not been objectively assessed in the entire exposed population but only among subjects consenting to the test (16) or among selected groups of workers at risk of developing RADS (20). Nonetheless, Kern provided an estimate of the incidence of RADS following a single accidental exposure of 56 hospital employees to high concentrations of glacial acetic acid, of whom 51 were assessed within 2.5 hours after the accident (16). Eight workers (16%), with no history of asthma, reported symptoms consistent with RADS within 24 hours after the accident and symptomatic status was related to the degree of exposure. Among the 24 workers who accepted a bronchial challenge test, RADS was confirmed in four subjects and a dose–response relationship was seen corresponding to the degree of acetic acid exposure.

In the United Kingdom, the SWORD data offer a basis for estimating the incidence and outcome of inhalation accidents (137). Between 1990 and 1994, 1180 inhalation accidents were reported; this represented 10% of all work-related lung diseases reported, the fifth most common category. The highest rates were among chemical processors (163.5/million/year), followed by engineers and electricians (32.1/million/year). An investigation of over 700 inhalation accidents (1990–1993) indicated that symptoms lasted for one month or more in 26% of cases, including 9% with asthma or RADS (15). Quantitative SENSOR data for RADS between 1993 and 2003 were discussed above.

Persistence of RADS

Some epidemiological studies addressing the question of the persistence of RADS, or a syndrome with similar features, are summarized in Table 8; for this review, the authors gave preference to studies in which NSBH was assessed. More often than not, there was a lack of information on duration of exposure and concentrations of an irritant agent after an accident. Levels of exposure have been assessed only indirectly through a description of location and employee's movements during the episode (138) or through an analysis of the characteristics of the site (16). In some instances, exposure has been estimated through self-reporting or first-aid reports (139–141). In the absence of estimates of exposure, clinical changes (i.e., dyspnea) associated with accidental inhalations have been used as predictors of lung diseases (138,142).

From the workforce-based studies, there is some evidence that accidental inhalation to high concentrations of irritants leads to persistent symptoms and/or

Table 8 Workforce-Based Surveys of Reactive Airways Dysfunction Syndrome: Long-Term Effects of High-Level Irritant Exposure

No. studied/ population	Type of population	Longest follow-up period	Outcome			Persistence of effects (%)	Type of irritant exposure; estimated level	Host factors: smoking, personal, asthma	References
			Symptoms	Functional tests	Bronchial responsiveness				
59/150 exposed	Longshoremen	2 yrs	Dyspnea: 35% vs. 0%	VC 91% vs. 99.8%; W_{el} 2.7 vs. 1.8; D_{LCO} 94% vs. 109%	No data	Dyspnea: 27%; deficits related to level of exposure	Chlorine; severe vs. minimal	46% smoking, effect not controlled for	(138)
13/20	Construction workers at a pulp mill	12 yrs	Not reported	RV < 80% in 67% (significant change over 12-yr period); FEV_1/FVC < 80% in 62% (loss in FEV_1 not greater than the expected 25 mL/yr	NSBH 38% (5/13) related to initial airway obstruction ($p < 0.05$) and airway trapping ($p < 0.05$)	No initial nonspecific bronchial challenge test	Chlorine	70% smoking	(143)
51/56	Hospital employees	8 mo	No symptoms (70%) vs. transient symptoms (14%) vs. persistent symptoms for at least 3 mos (16%)	Not reported	NSBH 37% (9/24)	RADS in 4/51 (7.8%) approximately 1 yr after accident; relative risk in those w/high exposure: 9.8	Glacial acetic acid; graded by industrial hygienist	No confounding due to preexposure risk factors or smoking	(16)

(Continued)

Table 8 Workforce-Based Surveys of Reactive Airways Dysfunction Syndrome: Long-Term Effects of High-Level Irritant Exposure (*Continued*)

No. studied/ population	Type of population	Longest follow-up period	Outcome: Symptoms	Outcome: Functional tests	Outcome: Bronchial responsiveness	Persistence of effects (%)	Type of irritant exposure; estimated level	Host factors: smoking, personal, asthma	References
						(95% CI: 0.9–264.6)			
90/174	Pulp mill workers	7 yrs	First-aid reports related to work-related chest symptoms (odds ratio = 4.4, significant)	FEV_1/FVC less in workers with first-aid reports ($p < 0.05$)	No data	Greater decline in FEV_1/FVC in gassed group ($p < 0.05$)	Chlorine/ClO_2, SO_2, welding fumes; first-aid reports/ self-reports of gassing/ nonexposed	Control for age and smoking	(139)
64/71 at risk of developing RADS	Bleach plant workers (survey II)	18–24 mo	Respiratory symptoms: 91%	$FEV_1 < 80\%$ of predicted: 31% (16/51)	NSBH 57% (29/51)	RADS: 57%, related to severity of initial outcome	Chlorine, ClO_2; no. of accidents, severity of initial outcome	53% smokers, no effect of smoking	(20)
20/29 with RADS	Bleach plant workers (survey III)	2–3 yrs	Frequency of dyspnea: 80%	No change in FEV_1 after 1 yr	Significant decrease in 6/ 19 (32%) ($PC_{20} \geq 3.2$-fold)	NSBH 74% (14/19)	Chlorine, ClO_2; no such exposure during follow-up	No previous history of asthma	(132)

Abbreviations: VC, vital capacity; W_{el}, elastic work of breathing; D_{LCO}, diffusing capacity for carbon monoxide; RV, residual volume; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity: NSBH, nonspecific bronchial hyperresponsiveness; RADS, reactive airways dysfunction syndrome; PC_{20}, provocative concentration causing $\geq 20\%$ fall in FEV_1; CI, confidence intervals.
Source: From Refs. 87, 95.

long-term lung function abnormalities (132,138,139,143,144). By contrast, in the large population-based study, considered to be the most comprehensive follow-up study to date (205 subjects, 145 exposed, and assessed using spirometry initially and at follow-up), no changes were seen in pulmonary function testing over the six-year follow-up period (145). Airway responsiveness, however, was not assessed in this population (145). Comparisons between population- and occupation-based studies are limited owing to differences in exposure characteristics and prevalence of risk factors (143,144). In addition to a single and brief occupational exposure to high concentrations of an irritant, there may be chronic low-level exposure to the same or other agents in the workplace. Under these conditions, it has been hypothesized that the inflammatory reaction occurring in small airways after an accidental exposure to high concentrations of an irritant does not resolve completely because of continuous exposure to the offending stimulus (136).

OTHER FORMS OF IIA OR POSSIBLE VARIANTS OF RADS

Consequences of Low-Level Irritant Exposures

Before the entity of RADS was recognized, repetitive exposure to low concentrations of work-related irritant agents was not thought to give rise to OA. Early epidemiological studies of workers with low-level exposure and subsequent accidental high-level exposure to an irritant were conducted to compare the relative frequency of chest symptoms, increased airway obstruction, and nonspecific airway responsiveness between affected workers and those not exposed to the accidental spill. These studies did not demonstrate major differences between groups (146,147). Later, however, it was suggested that RADS may also include LICEDS, which is defined as a subtype of adult-onset asthma that develops after repeated low-dose exposure to one or more bronchial irritants (148). However, as discussed previously, individuals with this condition should more properly be considered to have a chronic exposure phenotype of IIA.

Variants of RADS

A clinical picture compatible with RADS has been described in several studies following accidental exposures in the community (133,134,149) and in the workplace (142). In a number of studies, the original diagnostic criteria of RADS have been modified to include asthma after repeated exposures to high and somewhat lower concentrations of the same irritant agent (2,20,82,139). When airway responsiveness could not be documented objectively but the other criteria were met, affected individuals were characterized as having symptoms similar to RADS (16) or at risk of developing the syndrome (20). However, the clinical criteria of RADS were not satisfied in such cases.

Activities in Workers Exposed to Chlorine Gas

Several more recent epidemiological surveys that were conducted in workers exposed to both low and high levels of chlorine in pulp mills and paper mills demonstrated adverse outcomes. The main findings are summarized in Table 9. A significantly greater prevalence of persistent wheezing was shown in workers who reported one or more episodes of accidental exposure to chlorine compared to other pulp mill workers with chronic low-level exposure to this irritant, regardless of smoking habits (140). Significantly lower

(Text continues on page 612)

Table 9 Workforce-Based Surveys of Reactive Airways Dysfunction Syndrome: Chronic Low-Level Irritant Exposures With or Without (Repeated) High-Level Irritant Exposure(s)

No. studied (exposed vs. nonexposed)	Type of population	Type of study	Outcome			Prevalence of a syndrome consistent with RADS (%)	Type of irritant exposure and duration	Host factors: smoking, personal asthma	References
			Symptoms	Functional tests	Airway responsiveness				
147 vs. 124	Pulp mill and papermill workers	Cross-sectional with control group	n.s. difference for chronic nonspecific respiratory disease	n.s. difference between groups for selected measures of lung function	Not assessed	No. of men with obstructive lung disease too small—no rates	Chlorine, ClO_2/SO_2; average Cl exposure duration 20 yrs	Current smokers (69%); control for smoking	(146)
58 with gassing vs. 81 with low exposure	Chlorine plant workers	Cross-sectional	Not related to exposure	Small decrease in MMF related to high exposure plus smoking[a]	Not assessed	Prevalence of ventilatory function impairment (3/139)	Chlorine—background $<$ ppm vs. background + accidental gassing	Ever smokers (73%)	(147)
392 vs. 310	Pulp mill and railyard workers	Cross-sectional with control group	Prevalence of wheezing greater in pulp mill work[a]	FEV_1/FVC and MMF less in young, nonsmoking bleach plant workers[a]	Not assessed	Incidence of asthma in pulp mill workers (2.7/1000) greater than in railyard workers (0.8/1000) n.s.	Chlorine, SO_2, H_2S, CH_3SH; average exposure duration 8.9 yrs	Current smokers (47%), atopy (17%)	(141)

316 vs. 237	Pulp mill and railyard workers	Cross-sectional with control group	Increased prevalence of wheezing in pulp mill with gassing incidents[a]	MMF and FEV_1/FVC less in nonsmoking and ex-smoking pulp mill workers with gassing incidents	Not assessed	Not reported	Chlorine/ClO_2, H_2S, SO_2 and other; average exposure duration 13 yrs	Control for smoking and childhood asthma	(140)
230	Pulp mill and papermill workers	Cross-sectional	Not reported	Changes in FEV_1 and FEV_1/FVC related to gassing[a]	Not assessed	Not reported	Chlorine or SO_2; duration: up to 54 yrs; cumulative exposure index, never vs. accidentally gassed (21%)	Control for smoking and assessment of interaction with cumulative exposure and gassing	(150)
273	Bleach plant workers (survey 1)	Cross-sectional	Irritation of the throat (78%), eyes (77%), cough (67%) shortness of breath (54%), headache (63%)	Not performed	Not assessed	Symptoms predictive of irritant-induced chronic lung disease: dyspnea (54%)	Chlorine, ClO_2; most significant exposure episode	Current smokers (53%): asthma or chronic bronchitis (7%), dyspnea not related to smoking or personal asthma	(142)

(*Continued*)

Table 9 Workforce-Based Surveys of Reactive Airways Dysfunction Syndrome: Chronic Low-Level Irritant Exposures With or Without (Repeated) High-Level Irritant Exposure(s) (*Continued*)

No. studied (exposed vs. nonexposed)	Type of population	Type of study	Outcome: Symptoms	Outcome: Functional tests	Outcome: Airway responsiveness	Prevalence of a syndrome consistent with RADS (%)	Type of irritant exposure and duration	Host factors: smoking, personal asthma	References
239/255 grouped according to exposure	Metal processing-plant workers	Cross-sectional	Low prevalence, not related to exposure	FVC less in subjects with mild vs. no symptomatic gassing; FEV_1, FVC, FEV_1/FVC less in workers with frequent gassing with mild symptoms[a]	In 239 workers; proportion with $PC_{20} \leq 32$ mg/mL and dose–response slope related to exposure[a]	No new cases of RADS	Chlorine, HCl; duration ≤3 yrs; accidental gassing plus self-evaluation of exposure	Ever smokers (55%), preexistent asthma (3%); control for both	(151)

211/239 from above described study (150)	Metal processing-plant workers	Longitudinal (2 yrs)	Persistent symptoms in 8.9%; related to chlorine puffs	In smokers: fall in FEV_1 associated with gassing during follow-up, fall in FEV_1/FVC predicted by number of puffs during follow-up	Increase in BHR (PC_{20} decrease by 1.5-fold) present in 19/211 workers, associated with gassing in the last 2 yrs	No new cases of RADS	Chlorine, HCl; duration ≤5 yrs; accidental gassing plus self-evaluation of exposure	Current smokers (22.7%); an interaction was found between gassing and pack-years smoking on lung function changes	(152)

[a]Significant difference, $p < 0.05$.

Abbreviations: RADS, reactive airways dysfunction syndrome; n.s., nonsignificant; MMF, midmaximal flow; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; PC_{20}, provocative concentration of methacholine inducing a 20% fall in FEV_1; BHR, bronchial hyperresponsiveness.

Source: From Ref. 87.

values for maximal mid-expiratory flows and FEV_1/FVC were found among nonsmokers and ex-smokers who reported at least one accidental gassing episode. These findings were confirmed in a longitudinal study in which first-aid reports of symptomatic inhalation accidents were used as estimates of exposure (139). Henneberger et al. (150) found significant changes in FEV_1 and FEV_1/FVC to be associated with high-level irritant gas accidental exposures and cumulative pulp mill exposure and smoking. The changes in lung function appeared to have persisted beyond cessation of exposure to irritant gases. A further study among younger and current workers at the same plant showed that airway obstruction was related to gassing in those with high and moderate pack-year histories of cigarette smoking (153).

Gautrin et al. assessed 239 workers who had experienced repeated exposure to chlorine in a metal-processing plant (151). Data from first-aid records and a detailed occupational history focusing on the occurrence of accidental chlorine puffs made it possible to estimate the degree of exposure. A mild reduction in expiratory flow rates and an increase in airway responsiveness, as assessed through the methacholine dose–response slope, were documented. The changes were significantly greater in workers who experienced mild symptoms than in those who were asymptomatic after exposure to chlorine puffs. In a two-year follow-up study of these workers, a fall in lung function was associated with the number of gassing incidents and the number of chlorine puffs causing mild symptoms among cigarette smokers of 20 pack-years or more. Also, a detectable increase in NSBH (PC_{20} decrease >1.5-fold) was associated with gassing events (152). A surveillance program for workers experiencing gassing incidents was initiated after the first survey to describe the time course of lung function changes. After four years, 13 workers out of the 278 workers at risk had reported a gassing incident at the first-aid unit. Three of those workers whose spirometry and NSBH were within normal range prior to the inhalation accident showed transient but significant changes in lung function (154). Although repetitive exposures to varying concentrations of chlorine gas exhibited irritative effects, it is noteworthy that the appearance of RADS was not uniformly observed.

Asthma Among Cleaners

Professional cleaners have emerged as one of the high-risk groups for WRA in industrialized nations. Based on cases reported by physicians in California during 1993–1996, janitors and cleaners had the highest average annual rate of 625 cases of WRA per 10^6 workers (43). From an analysis of National Health and Nutrition Examination Survey (NHANES) III data collected in the United States, cleaners had the fourth highest odds ratio (OR = 5.44, 95% CI: 2.43–12.18) for work-related wheeze among 28 occupational categories (155). The European Community Respiratory Health Survey (ECRHS) is a population-based study that was conducted in 26 areas in 12 industrialized nations and had over 15,000 participants in the 20 to 44 years age group. Cleaners had the fourth highest odds ratio for asthma (OR = 1.97, 95% CI: 1.33–2.92) among 29 occupational groups, and cleaners and farmers had the most consistent results among the different countries (156). Additional evidence about the association of professional cleaning with asthma comes from Finland (157,158), France (159), Singapore (160), South Africa (161), Spain (162,163), and the United States (164).

Some investigators have implicated the role of sensitizing agents associated with cleaning activities in the development of asthma. For example, a case report from the early 1900s described a pharmacist who developed asthma and was determined to be sensitized to lauryl dimethyl benzyl ammonium chloride, which was a component of the floor cleaner used in his office (165). However, in one study, none of the 334 indoor cleaners tested had IgE specific to detergent enzymes (i.e., protease and amylase) (162). Many studies have implicated irritant agents to be the exposures responsible for WRA among cleaners. Among the 123 cases of work-related RADS that were identified by the SENSOR program during 1993–1995, the most common class of agents was cleaning materials, which were associated with 18 (15%) of the RADS cases (36). Studies conducted in Spain revealed that the risk of asthma was especially elevated among female domestic cleaners (162,163). When the researchers in Spain looked more closely at the work practices among domestic cleaners, which were associated with asthma, they found elevated odds ratios for daily use of bleach (OR = 7.9, 95% CI: 1.6–38) and for use of degreasing sprays at least three times a week (OR = 6.5, 95% CI: 1.1–39) (166). They concluded that asthma among female domestic cleaners was associated with the use of bleach and other irritant cleaning products.

Meat Wrappers' Asthma

This was the term coined for three meat wrappers who were treated in an emergency room for asthma (167). Initial epidemiological investigations recounted a 10% to 57% prevalence of respiratory symptomatology among meat wrappers. The etiological agent was believed to be present in the emissions from the polyvinylchloride meat-wrapping film when it was cut with a hot wire; a fine particulate fume containing di-2-ethylhexyladipate combined with an aerosol or vapor of hydrogen chloride was vaporized (168). Subsequently, a clinical investigation concluded that a component of the emitted fumes from thermally activated price labels was the principal cause of meat wrappers' asthma (169). The major ingredient of the incriminated price label adhesive is dicylohexylphthalate. When heated, it emits irritants, mainly cyclohexyl ether (dicyclohexyl ether) and cyclohexylbenzoate (a cyclohexyl salt of benzoic acid) (144). A potential sensitizer was postulated to be phthalic anhydride, a minor emission product from the heated label (170,171).

Later investigations failed to demonstrate objective evidence of any major airways disease or chronic respiratory hazard among meat wrappers (168,172–174). For instance, in one study, while lower respiratory symptoms were observed in one-third of the meat wrappers, no cross-shift change in FEV_1 was detected, even in the most symptomatic workers (172). Phthalic anhydride was not measurable in the vicinity of the heated price label emissions (168). Thus, it seems unlikely that this emission product is actually present in significant concentrations or that it is present in the air for any reasonable period or even remains stable during heating. Another independent investigation failed to find any evidence of phthalic anhydride–specific IgE and IgG antibodies in exposed workers (172). The paucity of clinical occurrences in the last 25 years relegates this entity to a minor form of IIA.

Formaldehyde

This chemical has myriad applications including use in the chemical and plastics industries, textile processing, disinfectants, the tanning industry, the vulcanization process in the rubber industry, and as a preservative of anatomical and pathological material. A major application was in the production of urea–formaldehyde foam for mobile home insulation and phenol formaldehyde resin for particleboard production. Formaldehyde monomer as well as the degassing of formaldehyde from urea–formaldehyde foam insulation has been reported to cause a variety of symptoms, including asthma (175–178). Asthma caused by low-level exposure is uncommon, but it has been reported in workers with high risk of exposures such as pathologists and nurses working in a dialysis unit (178). There have been very few reported cases of formaldehyde-induced asthma proven by bronchial challenge tests. For example, among 230 exposed workers, positive challenges were obtained in only 12 workers (114). Formaldehyde-specific IgE antibodies have been reported in a case of anaphylactic shock occurring after long-term hemodialysis and in two nurses working in dialysis units (178–180). However, exposure to low levels of indoor formaldehyde does not result in significant levels of specific IgE antibody (181). Low titers of specific IgG antibodies and autoantibodies have been reported in subjects exposed to formaldehyde in various settings (182). The clinical significance of these findings is unclear because no definite correlations can be made between symptoms or other objective findings (180,182). Thus, the current evidence indicates that occupational asthma due to formaldehyde is rare and that most respiratory complaints are the result of the irritant effects of formaldehyde (175,183). The possibility of mixed mechanisms (immunologic and nonimmunologic) excludes this entity from RADS but not entirely from LICEDS.

Potroom Asthma

Although an asthmatic "irritation" syndrome was first observed over 50 years ago in the Norwegian literature, there is still disagreement about how this entity should be classified (184). Pot fume emissions contain particulate and gaseous fluorides, hydrofluoric acid, sulfur dioxide, and cold tar volatiles. Although each of these agents has been suspected as playing a role, there is no convincing evidence that a single agent induces symptoms. The duration of potroom exposure prior to the first attack ranges from one week to 10 years. Thus, those workers who develop symptoms soon after exposure to high peak levels of dust (as high as 54 mg/m^3) could possibly represent a small subset of RADS (185). However, because of the variability of prevalence and prognosis of potroom asthma, the possibility that some workers develop RADS or LICEDS after exposure to aluminum smelter emissions can only be addressed by future prospective epidemiological studies specifically designed to detect and characterize this entity. Potroom asthma is discussed in more detail in Chapter 23.

Machining Fluids

Machine lubricants may have irritant properties because of contamination with trace quantities of metals, additives (i.e., odorants, corrosion inhibitors, antifoam agents, emulsifiers, antioxidants, detergents, viscosity index improvers, antiwear agents, extreme pressure agents), and bactericidal substances. Occupational asthma has been documented in workers exposed to several varieties of machine oil. In one plant where clean suds oil was used, there was a latent period before the workers experienced symptoms (186). Some workers also exhibited asthma after controlled exposures to 1% nebulized aerosols of the clean suds oil. One worker showed a reaction to a pine odorant component in this oil. Other contaminating constituents of the oil were suspected but not proven to induce asthma in some of the other cases (186).

If bacterial substances are not present in sufficient concentrations, oil-in-water machine fluid emulsions will act as good growth media for bacteria and fungi. A study by Kennedy et al. reported significant FEV_1 cross-shift changes in 23.6% of heavily exposed machinists and 9.5% in minimally exposed assembly workers in the same plant (187). The exact etiological agent in machining fluids responsible for the FEV_1 cross-shift changes was not determined, but it was speculated that chemical irritants or endotoxin from contaminating gram-negative bacteria could be potential causes.

Similar to the above discussion of potroom asthma, it is not clear whether this entity should be considered a subtype of RADS, LICEDS, or simply an asthma-like disorder.

Other Workplace Irritants

Many airborne irritants may have the same irritant potential as cigarette smoking. Hypothetically, multiple exposures to such irritants could presumably lead to bronchial mucosal injury and increased permeability to sensitizing agents. Industrial operations utilizing irritant agents are therefore doubly dangerous because of the risk of heavy exposures, and occurrence of accidental spills may lead to nonimmunological and/or immunological asthmatic conditions. Irritant gases (e.g., chlorine and ammonia) are required in the platinum-refining process. Their presence may initiate bronchial epithelial injury.

Researchers in the Netherlands determined that pig farmers who experienced irritant exposures as a result of using disinfectants containing quaternary ammonium compounds (QACs) were at greater risk for sensitization to common allergens (188). Also, they observed an elevated risk for symptoms consistent with asthma among farmers who were both sensitized to common allergens (i.e., atopic) and exposed to QACs, but not among farmers who were only atopic or only exposed to QACs.

Biagini et al. (101) reported that platinum salt immunological sensitization in monkeys required concomitant exposure to ozone before sensitization to platinum salts could be induced. Other animal studies have documented that an antecedent exposure to an airborne irritant enhances the capacity for sensitization to an allergen. Exposure to low levels of SO_2 promotes sensitization in guinea pigs and rats and leads to increased epithelial permeability (189,190). Similar enhancement of allergic sensitization has also been reported to occur after ozone exposure (191). It has also been determined that exposure to low ozone concentrations increases bronchial hyperresponsiveness to allergens in people with atopic asthma (102,103). Other investigations employing prolonged low-level ozone exposure have documented a striking individual variability among normal subjects with a considerable range and response, suggesting that there are subpopulations that are very sensitive to low levels of ozone (192,193). These combined experimental and clinical experiences suggest that the designation of LICEDS in the induction of asthma among susceptible patients in the general population (i.e., atopic patients or "normal subjects" with preexisting but asymptomatic NSBH) is justified.

In a study of young adults with mild atopic asthma, ozone exposure after a late response to an allergen potentiated the eosinophilic inflammatory response that was itself induced by the allergen (194). The severity of allergic responsivity may be a risk factor after mixed allergen/irritant exposures. In a recent study, subjects allergic to ragweed who had rhinitis and/or mild asthma were compared to nonallergic subjects who did not smoke and did not have asthma (195). Both allergic and nonallergic subjects were exposed to ragweed, and then bronchial epithelial cells were harvested and exposed to an acid. The adverse impact of the acid on ciliary activity was less for allergic subjects who had a mild response to the ragweed than for both nonallergic and allergic subjects who had a severe response to the ragweed (195). In a study with rats, coexposure to ozone and endotoxin resulted in greater epithelial and inflammatory responses than observed with exposure to either agent alone (196). The synergistic response was mediated, in part, by neutrophils. It should be emphasized that this possible effect of multiple exposures to low-level irritants has no relationship to the multiple chemical sensitivity syndrome, which involves a variety of nonspecific and nonpulmonary symptoms.

IIA has occurred in several workers who would not be expected to develop this problem. Metal fume fever was initially observed in a worker exposed to heavy metals. This worker experienced symptoms of cough, fever, chills, malaise, and myalgia that were self-limited and of short duration. He also developed wheezing and impaired pulmonary function tests. Contrary to the expected rapid recovery of abnormal respiratory function, he developed prolonged wheezing and pulmonary function abnormalities which was consistent with the RADS syndrome (197). Several workers exposed to the thermal degradation products of chlorofluorocarbons developed acute IIA which persisted. Several other workers exposed to the freon decomposition products developed bronchitis without increase in NSBH. These observations emphasized the variability of exposure outcomes in that workers exposed to the same thermal decomposition accident developed entirely different syndromes (198).

PROGNOSIS

Many individuals with RADS generally continue to report bronchial irritability symptoms and demonstrate evidence of NSBH for years after the inciting incident. These persistent symptoms are analogous to those in TDI, snow-crab processors, or western red cedar workers who have persistent asthma after their exposures have been terminated (199–202). In contrast to immunological asthma in which a more favorable prognostic outcome is associated with a shorter duration of symptoms prior to diagnosis, it is not yet possible to predict which RADS workers will have persistent symptoms and permanent NSBH on the basis of the agent itself or the duration of exposure (203).

The functional sequelae of subjects with RADS or with a suspected syndrome of RADS are due not only to NSBH, but also to persisting airway obstruction (87). Airway obstruction has been documented after inhalation of high levels of irritant agents (17,144). This alteration can persist for several years (1,7,20). Of the ten subjects investigated by Brooks et al. (1), four had a decreased FEV_1 and FVC 4 months to 11 years after the offending exposure. Among three subjects suffering from RADS studied by Boulet, one presented with airway obstruction 6 years after the inhalation accident (7). Bherer et al. demonstrated airway obstruction in 16 of 51 bleach plant workers in a survey that took place 18 to 24 months after these workers had been repeatedly exposed to high concentrations of chlorine and had experienced nasal, conjunctival, and respiratory symptoms within minutes of exposure (20). In these 16 workers, no improvement was found in spirometry 30 to 36 months after the first survey (132).

A restrictive syndrome in association with airway obstruction after exposure to an irritant agent has been described (3,8). Gilbert and Auchincloss hypothesized that the onset of a restrictive pattern could be related to the site of bronchial obstruction (8). Large airway obstruction is more likely to result in an obstructive pattern with a restrictive component if the site of constriction also involves smaller airways. Associated decreases of FEV_1 and FVC have frequently been observed after exposure to high levels of irritant agents (12,86). The concurrent decrease of FVC suggesting a restrictive pattern could be due to hyperinflation with an increased residual volume and therefore not truly restrictive. Thus, it has been demonstrated that 10% of patients with pure obstruction may have a restrictive type of spirogram (204).

Airway responsiveness can either persist for several years after the exposure (1,78) or be reversible within months to years after an inhalation accident (154,205). Bherer et al. studied the time course of clinical and functional behavior of a group of 71 bleach plant workers with suspected RADS, on the basis of the clinical history (20). At 18 to 24 months after these workers were identified and withdrawn from exposure, 22 of 51 (43%) subjects showed normal NSBH. Of the 29 workers with NSBH at the time of the first follow-up, 19 were investigated 30 to 36 months after removal from work; six men had a significantly improved PC_{20} including five for whom the PC_{20} value had returned to a normal range. The six men had normal FEV_1 values on both assessments (132). These subjects had not received either oral or inhaled corticosteroids.

It is still unknown whether treatment with oral or inhaled corticosteroids affects the prognosis of the condition. Randomized studies on RADS are needed to evaluate the efficacy of inhaled corticosteroids. There have been few reports of improvement in pulmonary function with corticosteroid therapy in patients suffering from RADS. Chester et al. reported on two subjects exposed to toxic concentrations of chlorine (206). One was treated with corticosteroids and oxygen therapy while the other received only oxygen therapy. The FEV_1 showed an initial marked improvement in both patients. The first subject continued to improve progressively until her values reached the normal range at the end of the first year while the second subject (although improved at the end of one year) reached a plateau and stabilized at less than 80% of predicted. There is recent evidence that parenteral and/or inhaled steroids may modify the outcome of the condition. In a subject with RADS, treatment with inhaled corticosteroids normalized the heightened NSBH with exacerbation when the treatment was stopped (19).

MANAGEMENT

Because RADS is usually precipitated by an unforeseen industrial accident, removal of the worker is automatic. Emergency treatment of the acute obstructive symptoms might require inhaled or parenteral $beta_2$ agonists, intravenous aminophylline, and/or steroids and oxygen. The specific requirements of each of these agents depends upon the severity of the worker's symptoms.

The use of systemic or inhaled corticosteroids is suggested for managing acute episodes. Similarly, once the acute episode has been managed appropriately, appropriate treatment of the ongoing asthmatic situation is mandatory, using a combination of anti-inflammatory preparations and bronchodilators. Long-term inhaled corticosteroids may be appropriate in reducing the severity of NSBH (19,207,208). It should be stressed that medical therapy is not a substitute for environmental control. This is particularly important for RADS patients who may wish to return to work, because they are particularly susceptible to other, nonspecific irritants in the workplace as a result of the original RADS-induced bronchial hyperresponsiveness (209). In some cases, good protection against the effects of nonspecific irritants may be provided by an airstream helmet (210).

The important long term goals in the management of the worker with IIA asthma are: (*i*) confirm the diagnosis of irritant-induced occupational asthma; (*ii*) gauge the severity of disease; (*iii*) identify aggravants and trigger factors; (*iv*) provide appropriate treatment to curb and reverse the airway inflammation; (*v*) put a high priority on returning the worker back to work, in any capacity, as soon as possible; (*vi*) decide on the best disposition for the worker which may include complete removal from exposure and change to a new job or site; (*vii*) monitor the disease course and ensure patient guidance; and (*viii*) educate patients to develop a partnership in asthma management.

Attempts to return subjects rapidly and efficiently to the workplace are preferable to discontinuation of work. For IIA, removal from exposure may not be required if the risk for recurrent exposure to high levels is not present. However, if the risk for recurrent high levels of exposure is high, removal is the treatment of choice.

RADS is associated with persistent NSBH. Consequently, triggers of NSBH may include workplace irritants, indoor and outdoor air pollutants, changes in environmental temperature or humidity, and physical changes such as exercise, cold air, and high levels of emotional stress. Thus, a strategy of evaluating several exposure environments (including the workplace) at once is preferable. The practitioner should stress efforts to reduce workplace irritant exposures, avoid passive smoking, and limit contacts with vehicle emission and outdoor air pollution. Strategies such as the continued use of respiratory protective devices are not medically ethical for an already sensitized individual.

Education of the workers, their supervisors and coworkers on methods of controlling exposures and on dealing with emergency situations, such as a spill, can be accomplished. Effective control of asthma can be better achieved by educating patients to develop a partnership in asthma management, undergoing regular assessments and monitoring of asthma severity (symptom reports and measurements of lung function), avoiding or controling asthma trigger factors, and establishing an individual medication plan for long-term management.

CONCLUSIONS

IIA represents a spectrum of clinical presentations. In the most extreme case, a single massive exposure leads to the sudden onset of asthma as epitomized by the RADS. The massive exposure causes severe airway injury resulting in persistent airway inflammation and NSBH. Many of these cases resolve or improve over time and especially after treatment with inhaled steroids.

In some cases, the onset of asthma is not so sudden and follows a low level, intense, chronic (LICEDS) exposure to irritants. It is likely that in these individuals, there is a preexisting susceptibility or abnormality responsible for initiation of asthmatic symptoms. Some of these persons suffer from preexisting asthma in remission and the irritant stimulus reactivates (e.g., exacerbates) clinical symptoms. When diagnosing and treating patients with this type of presentation, it is imperative that preexisting history of asthmatic symptoms is carefully identified. The presence of preexisting asthma categorically excludes a diagnosis of RADS. An underlying atopic susceptibility is important because these individuals appear to be primed by showing an exaggerated release of cytokines and other biomediators following certain inhalant stimuli. In this clinical scenario, the irritant exposure causes an exaggerated response and sets up a cascade of biochemical and pathological changes leading to an acute asthma attack.

Even in asthmatic patients controlled by medication, prolonged irritant exposures may aggravate current symptoms and such situations must be clearly distinguished from RADS and LICEDS. Some workplace irritant exposures will pose serious problems for asthmatics and potentially susceptible populations; reducing or eliminating such exposures seems prudent. It is clear that future investigations will better define predisposing risk factors and perhaps uncover new host susceptibilities. Prevention measures for IIA should include the improved recognition of dangerous work, ongoing worker education, and employer commitment to environmental control strategies.

DIRECTIONS OF FUTURE RESEARCH

Major research efforts should encompass many of the following:

- Clinical and or physiologic determinants of RADS compared to LICEDS.
- How can RADS/LICEDS phenotypes of IIA be differentiated from bronchitis, vocal cord dysfunction, postnasal drip, or gastroesophageal reflux?
- Does concurrent exposure to multiple irritants (e.g., ozone, diesel fumes, chlorine, etc.) increase the probability of RADS or LICEDS?
- Can increased cough occurring after irritant exposure be caused by stimulation of unmyelinated C-fibers? How can this be clinically assessed?
- Can the presenting symptom of cough with or without sputum (such as occurred after the WTC disaster) be considered equivalent to RADS or LICEDS?
- Can the diagnosis of RADS ever be made retrospectively when the patient is seen for the first time after a period of time away from the exposure?
- The role of preexistent NSBH in RADS/LICEDS (susceptibility or otherwise) even if the patient is completely unaware of this condition.
- Why does the atopic risk factor differentiate LICEDS from RADS?
- Does RADS/LICEDS increase the severity of allergic symptoms (long or short term or both) in atopic workers who develop these problems?
- Identification of biomarkers for RADS and LICEDS.
- Genetic susceptibility or protective factors for RADS compared to LICEDS.
- What are the basic pathological differences between RADS/LICEDS and diseases of the terminal bronchioles?
- Do diagnostic adjuncts such as exhaled NO and induced sputum for eosinophils/neutrophils aid in the diagnosis either immediately or after a delayed time interval from the original exposure?
- Prospective epidemiologic studies of newly hired workers in industries where both high- and low-intensity exposure to irritants can be expected (e.g., potroom workers, hog farmers).

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And Related Conditions

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