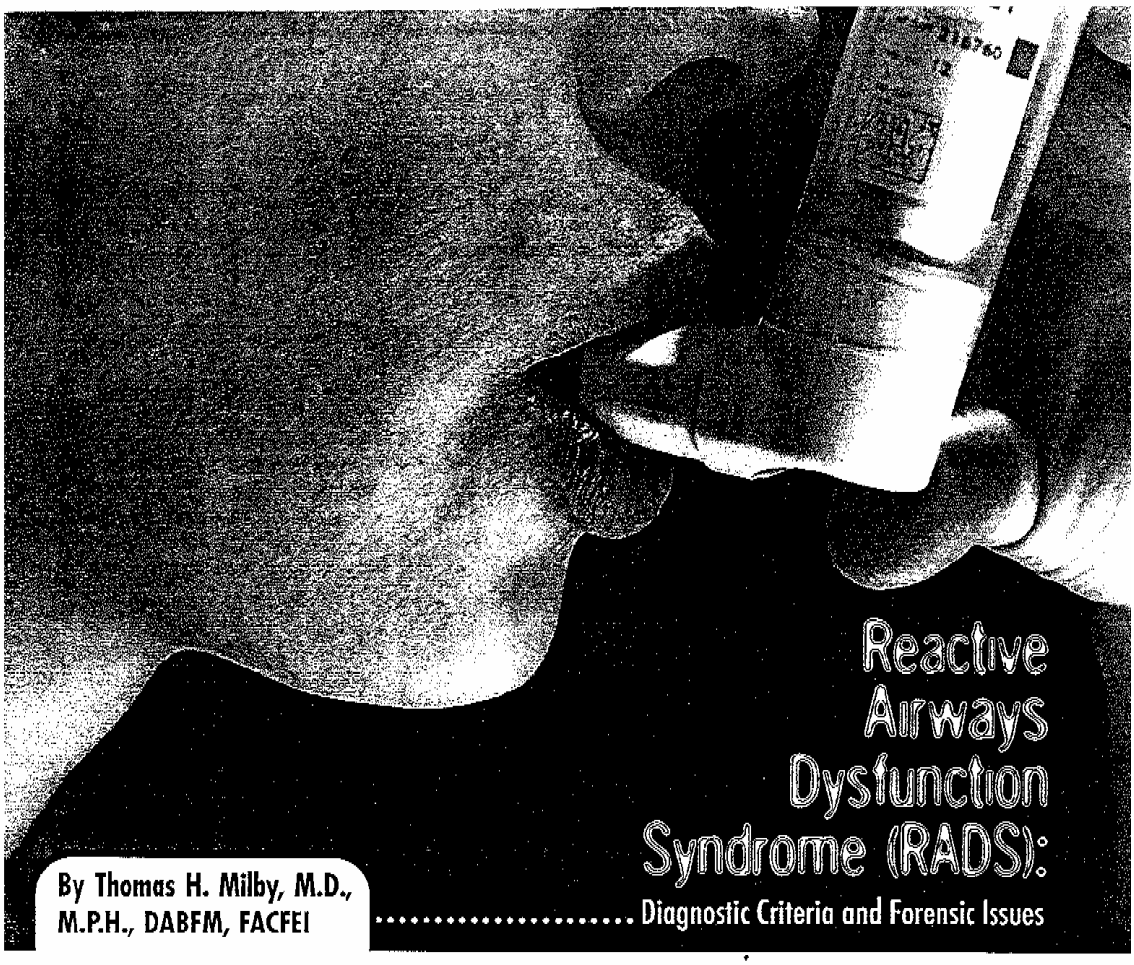


Reactive Airways Dysfunction Syndrome (RADS): Diagnostic Criteria and Forensic Issues

By Thomas H. Milby, M.D., M.P.H., DABFM, FACFEI

This article is approved by the following for continuing education credit:

ACFEI is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. Release date: 5/1/04; Expiration date: 4/31/05.

ACFEI provides this continuing education credit for Diplomates after June 2001 who are required to obtain 15 credits per year to maintain their status.

ACFEI provides this continuing education credit for Certified Medical Investigators who are required to obtain 15 credits per year to maintain their status.

ACFEI is California Board of Registered Nursing Provider 13133.

Key Words: Reactive Airways Dysfunction Syndrome (RADS), Irritant-Induced Asthma (IIA)

Abstract

Reactive Airways Dysfunction Syndrome (RADS) is a pulmonary disorder characterized by the sudden appearance of new-onset asthma – or in some cases, aggravation of preexisting asthma -- following exposure to a pulmonary tract irritant. When first described in the United States in 1985, RADS was defined as a new onset of asthmatic symptoms occurring within 24 hours following a single exposure to a very high concentration of a respiratory tract irritant, followed closely by demonstrable nonspecific bronchial hyper-responsiveness. Over the years, the diagnostic criteria for RADS have been modified by a number of investigators to include the not-so-sudden onset of symptoms following either single or multiple exposures to an airborne irritant. This not-so-sudden onset asthma is now referred to as Irritant Induced Asthma (IIA).

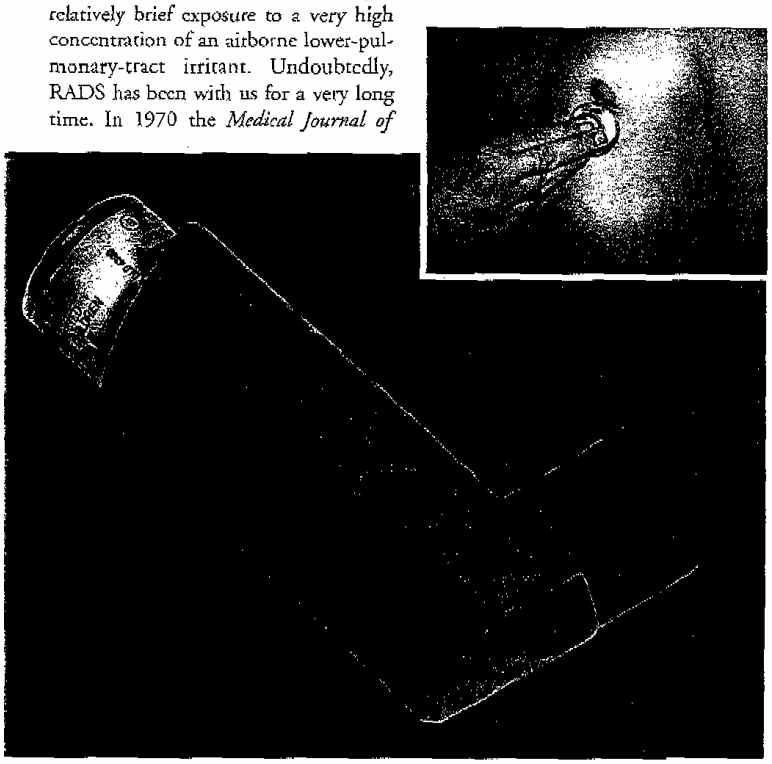
Introduction

Reactive Airways Dysfunction Syndrome (RADS) and Irritant-Induced Asthma (IIA) are both new-onset, irritant-induced asthma. Legal representatives of both defendants and clients have displayed an increased forensic interest in these pulmonary conditions.

RADS is new-onset asthma – or in some cases, reactivation of preexisting, albeit quiescent asthma – caused by a relatively brief exposure to a very high concentration of an airborne lower-pulmonary-tract irritant. Undoubtedly, RADS has been with us for a very long time. In 1970 the *Medical Journal of Australia* published what might have been the first description of this condition in medical literature as defined by Australian physician Brian Gandevia, who referred to the condition as Acute Inflammatory Bronchoconstriction. Stuart Brooks and his associates are generally credited with defining the criteria for irritant-induced asthma and designating the illness as RADS (Brooks, Weiss, & Bernstein, 1995). These investigators initially listed the following eight clinical criteria for the diagnosis of RADS:

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

"Reactive Airways Dysfunction Syndrome (RADS) and Irritant-Induced Asthma (IIA) are clinical pathological entities caused by exposure to a toxic or irritant agent and characterized by a negative history of asthma symptoms for at least 2 years prior to exposure, persistence of asthma symptoms for at least 3 months, objective evidence of obstructive airway disease and/or nonspecific bronchial hyper-responsiveness, and arguably, abnormal airway histopathology."



As additional observations have been reported over the ensuing years, the 1985 Brooks et al. criteria have been significantly modified. (Alberts & do Pico, 1996; Brooks, Hammad, Richards, Giovinco-Barbas, & Jenkins, 1998; Cone, et al., 1994; Kipen, Blume, & Hutt, 1994; Tarlo & Broder, 1989; Tarlo, 2000).

Tarlo and Broder (1989) described RADS patients whose exposure to workplace irritants was not limited to a single incident or accident. These included 3 subjects with irritant-induced asthma who had been exposed at work for over 6 months before the onset of their symptoms. They were still working when diagnosed, but were unable to link the initial onset of their respiratory symptoms to any given accident or unusual workplace event. These cases added the notion of non-dramatic, tolerable concentrations of workplace irritants as a potential cause of RADS and modified the 1985 Brooks et al. requirement for a very high concentration of an airborne irritant.

Cone et al. (1994) reported the occurrence of persistent irritant-induced asthma (RADS) in 20 individuals exposed to an environmental spill of the pesticide metam sodium. These investigators broadened the original 1985 Brooks, et al. criteria for the diagnosis of RADS to include persons who developed lower respiratory irritative symptoms within one week of exposure; the original Brooks, et al. criteria for diagnosis required no more than a 24-hour delay between exposure and onset of symptoms.

Kipen et al. (1994) reported 10 cases of low-dose RADS wherein symptoms developed following repetitive exposures to low doses of irritants. These investigators described the irritant exposure levels as noticeable but distinctly "tolerable." These cases modified the original Brooks et al. (1985) criteria that called for a single high-dose exposure.

Brooks et al. (1998) reported a series of cases they described as "not-so-sudden-onset" irritant-induced asthma. Characteristically, the irritant exposures of the not-so-sudden asthma cases were neither massive nor single, and ensuing asthma took longer to develop, sometimes days or weeks after repeated exposures occurred. These cases also modified the initial requirement for a single high-dose exposure. The authors differentiated between RADS and IIA as follows: If clinical symptoms appear within 24 hours of the causal irritant exposure, the consequent asthma is referred to as RADS. In other words, RADS is new-onset, irritant-induced asthma without latency. If more than 24 symptom-free hours pass after exposure to the causal irritant, the resulting asthma is referred to as IIA. Brooks et al. (1998) emphasized that for either condition, initiation of asthma symptoms must be temporally related to the irritant exposure; that is, asthma symptoms must develop during the period when the irritant exposure is taking place, although this exposure can be intermittent or continuous in nature. Of course, IIA must be differentiated from sensitizer-induced asthma, keeping in mind that both conditions have latencies. To complicate things further, allergy-atopy status and preexisting asthma are risk factors for IIA, but not for RADS (Brooks, et al., 1998).

Henceforth in this review, I will use the term IIA rather than RADS when referring to irritant-induced asthma wherein the clinical onset of asthma symptoms occurs more than 24 hours after exposure.

Below is a summary of criteria for the diagnosis of RADS defined in The American College of Chest Physicians (ACP) Consensus Statement (cited in Alberts & do Pico, 1996). I have also added several recently suggested modifications to these criteria, as well as some comments and clarifications drawn from the literature. A discussion of the mechanisms proposed to explain the persistent airway hyper-responsiveness in patients with RADS/IIA is beyond the scope of this article. The interested reader is referred to Alberts and do Pico (1996), Bardana (1999), and Tarlo (2000) for a more extensive discussion.

Criteria for the Diagnosis of RADS

1. A documented absence of preceding respiratory complaints. More recent authors (Henneberger, et al., 2003) have modified this criterion to include people who had asthma and then did not have asthma symptoms or treatment for asthma during the two years before entering a new work setting where they then developed work-related, irritant-induced asthma. These individuals are eligible for a diagnosis of RADS or IIA. As an example, irritant-induced asthma appearing in an adult with a medical history of childhood or adolescent asthma that had been quiescent for years could qualify for a diagnosis of RADS or IIA if other factors were consistent with the diagnosis.

The phrase "A documented absence of preceding respiratory complaints" is probably too vague to be of much use to the diagnostician. I will not attempt to clarify the word "documented" as used here. However, Alberts and do Pico (1996) have interpreted the remainder of the phrase– "absence of preceding respiratory complaints" as follows: a "negative history of obstructive [pulmonary] symptoms prior to exposure".

2. Onset of asthma symptoms after a single-exposure incident or accident. Of course, we now have a recognized condition called IIA that does not fit this criterion; this is discussed above.

3. Exposures to a gas, smoke, fume, or vapor with irritant properties present in very high concentrations. Asthma induced by repeated exposure to lower concentrations of irritants is now called IIA.

4. Onset of symptoms within 24 hours after exposure, with persistence of symptoms for at least 3 months. As discussed above, onset of symptoms more than 24 hours after exposure to the causative irritant is now referred to as IIA.

5. Symptoms of asthma with coughing, wheezing, and dyspnea.

6. Presence of airflow obstruction on pulmonary function tests and/or the presence of nonspecific bronchial hyper-responsiveness. Airflow obstruction may not be readily identifiable on pulmonary function tests if RADS/IIA is not active at the time of testing. Pulmonary function tests may be normal between active periods. This is a critical point because clinical manifestations wax and wane. In addition, it should be noted that a restrictive, rather than obstructive, pattern has been reported on several occasions (Gilbert & Auchincloss, 1989; Brooks, et al., 1998). Nonspecific bronchial hyper-responsiveness may be demonstrated by a significant spirometric response to an inhaled bronchodilator or a positive nonspecific bronchoprovocation challenge test (the Methacholine Challenge is such a test). A positive Methacholine Challenge Test is required by some to validate a diagnosis of RADS/IIA. I have seen several patients with RADS/IIA-related airway hyper-responsiveness too sensitive to res-

piratory inhalants to safely undergo this test.

7. Other pulmonary diseases ruled out. Diseases included in the differential diagnosis of RADS/IIA include acute tracheobronchitis, vocal cord dysfunction syndrome, gastroesophageal reflux disease (GERD), hypersensitivity pneumonitis, adult onset allergic asthma, and organic toxic dust syndrome (Bardana, 1995).

Forensic Issues

Diagnostic criteria. There is no "gold standard" for the diagnosis of RADS (Alberts & do Pico, 1996). An unambiguous exposure history and demonstration of persistent nonspecific bronchial hyper-responsiveness are required elements of the diagnosis. Above, I have presented the diagnostic criteria for RADS/IIA in some detail.

Differential diagnosis. Above, I have cited Bardana (1995) as a source of this information.

Agents demonstrated to be capable of causing RADS/IIA. These number in the hundreds, and others will undoubtedly be added as additional observations are reported. Here are two citations that list 165 cases: Rosenman, et al., 2003 (42 RADS cases); Henneberger, et al., 2003 (123 RADS cases). The largest agglomeration of occupational asthmagens of which I am aware can be found at: www.aoec.org/aoeccode.htm. On this site, asthmagens are not classified as to whether they induce RADS, IIA, or sensitizer-induced work-related asthma.

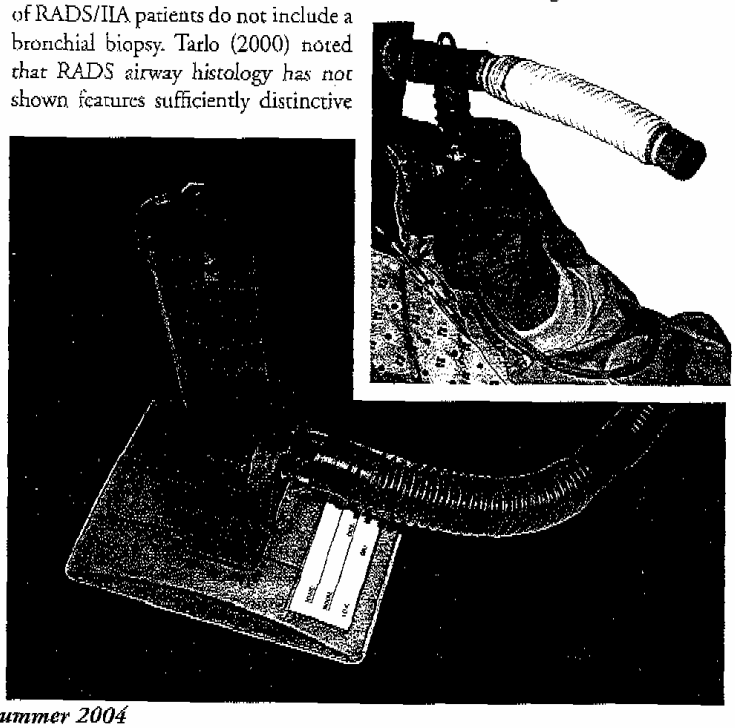
Exposure/dose. In my experience, it is rarely possible to ascertain the airborne concentration of the causative chemical agent through standard industrial hygiene procedures. In the case of RADS, air analysis instrumentation is rarely if ever available at the time of exposure; for IIA, the prolonged or intermittent nature of exposure does not lend itself to meaningful quantitative measurement. The medical literature reflects this problem; few, if any, reports on RADS/IIA include quantitative exposure data.

Chronicity. The medical literature is not clear on the issue of RADS/IIA chronicity (how long symptoms will persist). Some investigators have reported RADS lasting for months, some for years (Rosenman, et al., 2003). I have personally seen one case of RADS clinically active after more than 6 years; others have described even longer periods of chronicity (Demeter, Cordasco, & Guidotti, 2001).

Bronchial biopsy. It has been proposed that the diagnostic criteria for RADS include a requirement for a bronchial biopsy demonstrating minimal lymphocyte inflammation without eosinophilia (an abnormal increase in the number of eosinophils in the blood, characteristic of allergic states and various parasitic infections) (Bardana, 1999). However, to date, most studies of RADS/IIA patients do not include a bronchial biopsy. Tarlo (2000) noted that RADS airway histology has not shown features sufficiently distinctive to be helpful in diagnosis of the individual case. In my opinion, there is little justification for requiring a biopsy in order to validate a diagnosis of RADS/IIA. The biopsy procedure is invasive, uncomfortable, and not without risk; most importantly, the histopathology has been shown to be of little or no diagnostic help.

A real clinical entity? Current scientific evidence appears to support the conclusion that RADS is a distinct clinical entity. This view is held by the American Thoracic Society, the Canadian Thoracic Society, the American College of Chest Physicians (Alberts & do Pico, 1996), and the legal community (personal experience).

RADS/IIA and the World Trade Center disaster. Perhaps the most noteworthy outbreak of reactive airways dysfunction syndrome was reported in 2002 among firefighters exposed to irritants before and after the World Trade Center disaster. The "World Trade Center Cough" was defined as a



persistent cough that developed after exposure to the site (Prezant, et al., 2002). This cough was often accompanied by airway obstruction and/or nonspecific bronchial hyper-responsiveness, as well as the clinical signs and symptoms of asthma. By the time the authors of the World Trade Center article presented their data, they had examined nearly 100 firefighters who exhibited symptoms thought to be consistent with RADS/IIA.

Conclusions

Reactive Airways Dysfunction Syndrome (RADS) and Irritant-Induced Asthma (IIA) are clinical pathological entities caused by exposure to a toxic or irritant agent and characterized by a negative history of asthma symptoms for at least 2 years prior to exposure, persistence of asthma symptoms for at least 3 months, objective evidence of obstructive airway disease and/or nonspecific bronchial hyper-responsiveness, and arguably, abnormal airway histopathology.

References

Alberts, W.M., & do Pico, G.A. (1996). Reactive airways dysfunction syndrome. *Chest, 109,* 1618-1626.

Bardana, E.J. (1995). Occupational asthma and related respiratory disorders. *Disease-a-Month 41*(3). St. Louis, MO: Mosby-Year Book Inc.

Bardana, E.J. (1999). Reactive airways dysfunction syndrome (RADS). Guidelines for diagnosis and treatment and insight into likely prognosis. *Annals of Allergy, Asthma & Immunology, 83,* 583-586.

Brooks, S.M., Weiss, M.A., & Bernstein, I.L. (1995). Reactive airways dysfunction syndrome (RADS). *Chest, 88,* 376-384.

Brooks, S.M., Hammad,Y., Richards, I., Giovinco-Barbas, J., & Jenkins, K. (1998). The spectrum of irritant-induced asthma. Sudden and not-so-sudden onset and the role of allergy. *Chest, 113,* 42-49.

Cone, J.E., Wugofski, L., Balmes, J.R., Rupali, D., Bowler, R., Alexeeff, G., & Shusterman, D. (1994). Persistent respiratory health effects after a metam sodium pesticide spill. *Chest, 106,* 500-508.

Demeter, S.L., Cordasco, E.M., & Guidotti, T.L. (2001). Permanent respiratory impairment and upper airway symptoms despite clinical improvement in patients with reactive airways dysfunction syndrome. *Science & Total Environment, 270,* 49-55.

Gandevia, B. Occupational asthma. Part 1. (1970). *Medical Journal of Australia, 2,* 332-335.

Gilbert, R., & Auchincloss, J.H. (1989). Reactive airways dysfunction syndrome presenting as a reversible restrictive defect. *Lung: Journal of Acute & Critical Care, 167,* 55-61.

Henneberger, P.K., Derk, S.J., Davis, L., Tumpowsky, C., Reilly, M.J., Rosenman, K.D., et al. (2003). Work-related reactive airways dysfunction syndrome cases from surveillance in selected states. *Journal of Occupational Environmental Medicine, 45,* 360-368.

Kipen, H.N., Blume, R., & Hutt, D. (1994). Asthma experience in an occupational and environmental health clinic. Low-dose reactive airways dysfunction syndrome. *Journal of Occupational Medicine, 36,* 1133-1137.

Prezant, D.J., Weiden, M., Banauch, G.I., McGuinness, G., Rom, W.N., Aldrich, T.K., & Kelly, K.J. (2002). Cough and bronchial responsiveness in firefighters at the World Trade Center site. *New England Journal of Medicine, 347,* 806-815.

Rosenman, K.D., Reilly, M.J., Schill, D.P., Valiante, D., Flattery, J., Harrison, R., et al. (2003). Cleaning products and work-related asthma. *Journal of Occupational Environmental Medicine, 45,* 556-563.

Tarlo, S.M., & Broder, I. (1989). Irritant-induced asthma. *Chest, 96,* 297-300.

Tarlo, S.M. (2000). Workplace respiratory irritants and asthma. *Journal of Occupational Medicine, 15,* 471-483.

About the Author

Thomas H. Milby, M.D., M.P.H., DABFM, FACFEI, is a consulting toxicologist who has practiced for more than 20 years. He is board certified in occupational medicine, a Fellow of the American College of Epidemiology, a Diplomate of the American Board of Forensic Medicine, and a Fellow of the American College of Forensic Examiners International. His past experience includes serving as a medical professor at the University of California, Berkeley and a senior research physician at the Stanford Research Institute. He has consulted on toxicological problems with the World Health Organization in India and the U.S. Food and Drug Administration in Japan, and has consulted on several domestic problems for the U.S. Department of Justice. Milby has published more than 50 articles in medical and scientific journals. He has been particularly interested in RADS as a forensic issue and has served as a medical/toxicological consultant and expert on a number of cases for both defendants and plaintiffs.

"RADS is new-onset asthma – or in some cases, reactivation of preexisting, albeit quiescent asthma – caused by a relatively brief exposure to a very high concentration of an airborne lower-pulmonary-tract irritant. Undoubtedly, RADS has been with us for a very long time."

Required CME Disclosure Statement

The following author has indicated that he has no relationship(s) with industry to disclose relative to the content of this CME activity: Thomas H. Milby, M.D., M.P.H., DABFM, FACFEI

Earn CE Credit

To earn CE credit, complete the exam for this article on page 47 or complete the exam online at www.acfei.com (select "Online CE").