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Irritants, Irritancy and Irritant Induced Asthma

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Abstract

An irritant represents a non-corrosive chemical that causes a reversible non-immunologic inflammatory reaction after direct contact with the skin, eyes, nose and/or respiratory system. There are numerous reactions to irritants including change in spirometry, elevated exhaled breath levels of nitric oxide, enhancement of the response to allergen provocation and alteration of antioxidant defenses. Irritancy prompts an "inflammatory soup" of signaling molecules leading to tissue changes characterized by infiltration of mononuclear inflammatory cells, vascular congestion, augmented blood flow, contiguous edema with leaking of plasma, glandular hyper secretion and nervous hyperresponsiveness. Acute irritant-induced asthma, also referred to as Reactive Airways Dysfunction Syndrome (RADS), is a non-allergic type of asthma presenting without a prior time-period of latency. The manifestations of RADS begin within 24 h following a single massive exposure to an irritating gas, vapor or fume resulting in continuing airway inflammation, changed airway remodeling, persistent structural changes, neural disturbances and unrelenting airway hyperresponsiveness. Recommendation is that RADS or any serious inhalation exposure be handled in a hospital setting. Serial bronchoscopic assessments assist management decisions. Management requires astute judgment and skill for a rapidly changing clinical scenario. The influence of odors and emotion in the pathogenesis irritant-induced inhalational responses is significant.

Keywords: RADS; Irritants; Irritancy; Inhalation injury; Asthma, Irritant-induced asthma; Reactive Airways Dysfunction Syndrome (RADS); Airway hyper responsiveness; Odors; Odorants

Introduction

Accidental irritant exposures may cause workplace and public health consequences as well as producing devastating population impacts [1,2]. In 1989, the Occupational Safety and Health Administration (OSHA), with a consensus by the American Conference of Governmental Industrial Hygienists (ACGIH), promulgate a workplace exposure limit for irritants based on objective signs of irritation [1]. The role of odors, as an indicator of a serious irritant exposure, may complicate cases of inhalational grievances [3-8]. Because of their pervasiveness, a better understanding of and preventive strategies for irritant exposures are indispensable [9,10].

Irritant

A practical definition of an irritant is a non-corrosive agent that causes a reversible non-immunologic inflammatory reaction after direct contact with the skin, eyes, nose, throat and/or lower respiratory system [11]. There is the consideration that irritants are chemicals; but, mechanical, thermal and radiation stimuli (i.e., ionizing radiations) are also irritants. Irritant releases follow a high-level irritant delivery, after repeated low-level discharges or by a mixture of both [12]. Radiation-induced tissue damage leads to the generation of short-lived free radicals, changes in cellular DNA, and incitement of an inflammatory response involving proinflammatory cytokines, chemokines, receptor tyrosine kinase, and adhesions molecules [13]. Initially, there is rapid proliferation and maturation of basal keratinocytes, hair follicle stem cells and melanocytes. Additional exposure to radiation results in further direct tissue injury, inflammation, and impaired epithelial regeneration. Table 1 lists a range of irritants and their origins [14]. Sometimes an allergen and irritant interact to create an incomplete antigen (i.e., hapten) with similar properties as the original allergen. In this circumstance, there is instigation of an immune-mediated reaction [15,16].

Instigated irritant exposures activate Transient Receptor Potential (TRP) ion channels that open cationic pores permitting intracellular influx of calcium and sodium ions to initiate the nerve impulse [17-21]. In particular, TRP subfamily A, member 1 (TRPA1) cationic channels located on the plasma membrane of many cells provides the final transduction cog through which irritant agents elicit inflammatory and other changes [22].

There is poor understanding of the induction of a greater irritant response among some individuals. Genetic factors may impose greater host susceptibility for acute lung injury [23-27]. Glutathione S-transferase P, encoded by the GSTP1 gene, causes more of a burden due to reactive oxygen species [28,29]. Feasibly, there is derangement of airway smooth muscle with faster proliferation of smooth muscle cells and heighten smooth muscle mass among subjects with irritant-induced asthma [30,31].

Exposure	Agent or process
Acids	Glacial acetic, sulfuric acid, sulfurous acid, hydrochloric acid, hydrofluoric acid, hydrofluoric acid, acetic acid, sulfur trioxide
Alkali	Bleach, lye, lime, calcium oxide, ammonia compounds, sodium hydroxide, World Trade Center dust, air bag emissions
Gases	Chlorine, sulfur dioxide, ammonia, mustard, ozone, hydrogen sulfide, phosgene, nitrogen dioxide
Spraying	Spraying of bleach, paints and coatings

Explosion	Irritant gases, vapors and fume releases under pressure
Fire/pyrolysis	Combustion and pyrolysis products of fires, burning paint fumes, pyrolysis products of polyvinylchloride (PVC) meat wrapping film; smoke inhalation
Confined spaces	Epichlorhydrin, acrolein, floor sealant, metal coating remover, biocides, fumigating aerosol, cleaning aerosol sprays, mixture of drain cleaning agents
Workplace	Glass bottle making workers; popcorn flavoring makers; second hand tobacco smoke; chlorine gas puffs; pyrite dust explosion; ozone used a disinfectant; locomotive and diesel exhaust; aerosols of metalworking (machining) fluids including aldehyde and formaldehyde; aluminum smelter workers exposed to pot-room fumes; metal processing plant workers; pulp mill workers; shoe and leather workers exposed to the organic solvents; workers exposed to SO2 from apricot sulfurization; airborne mineral spirits; SO3 release; cement dust in manufacturing; aldehydes including formaldehyde and glutaraldehyde; biologic dusts and endotoxins; tunnel construction workers; coke oven emissions; cleaning and disinfecting workers in the food industry; welding fumes; chili pepper pickers; cyanoacrylates glues used in large amounts; methyl isocyanate environmental release; airborne fiberglass insulation; dust exposure in Norwegian smelters; spray foam insulation; 2-hydroxyethyl methacrylate and methyl methacrylate in dentists; synthetic leather workers exposed to organic solvents toluene, xylene and methyl ethyl ketone; eucalyptus; fragranced aerosol products; bleach products used by cleaners; metal fumes; irritant gas containing chromate at a chrome pellet manufacturing plant; diesel exhaust exposure; nickel sulfate in electroplating; arsenic trichloride in pharmaceutical & pesticide manufacturing; phosgene; ammonium and NH3 agents; potassium solutions and sodium persulfate inorganic salts used as oxidizing agents in hair bleaches and hair-coloring preparation; gases from liquid manure; additive 2-diethylaminoethanolamine; cleaners using cleaning products in a spray form.

Table 1: Common causes of irritation.

Irritancy

Irritancy evolves within minutes to hours after an irritant exposure [1]. An irritant provokes reacting tissue to release an array of signaling molecules from an "inflammatory soup" [32-34]. The signaling molecules trigger infiltration of inflammatory cells, vascular congestion and augmented blood flow; there is adjoining edema from leaking plasma as well as glandular hyper secretion and nerve sensitivity [35]. Radiation-induced tissue damage leads to the generation of short-lived free radicals, changes in cellular DNA, and incitement of an inflammatory response containing proinflammatory cytokines, chemokines, receptor tyrosine kinase, and adhesions molecules [13]. Initially, there is rapid proliferation and maturation of basal keratinocytes, hair follicle stem cells and melanocytes. Additional exposure to radiation results in further direct tissue injury, inflammation, and impaired epithelial regeneration.

A rejoinder or response to irritancy may be unpleasant; but, perhaps it is just a warning signal evolved millions of generations ago [36]. Nociception is the sensory nervous system's response to harmful or potentially harmful stimuli propagated by a subpopulation of nerve fibers. Chemesthesis involves burning, stinging or definite pain; it is typically a response by the skin, eyes, nose and throat. The degree of irritancy is modified, enhanced or diminished by prior exposures or by pre-existing disease. It is not yet determined whether atopic individuals are more likely to note irritancy [37,38]. In a Guinea pig model, irritants bind to ion channels provoking neurogenic inflammation with release of neuropeptides; the small neuronal signaling molecules on cell surfaces liberate inflammatory moieties that signal between populations of neurons [39-41]. Possibly, neuropeptides act as a priming substance to increase vascular permeability related to skin irritancy [42]. A similar response in humans has not yet been definitively established [43,44].

Reactivity

Irritants form complex biological connections through chemical cross-linking reactions, interaction with sulfur or cysteine molecules and creation of double bonds with human proteins [45,46]. Reactive halogenated compounds display varying degrees of carbon atoms-halogen substitution. An irritant's vapor pressure, at normal air temperature, influences the likelihood of a higher air level after an accidental irritant release. Solubility governs irritant's airway localization, upper vs. lower airway involvement. A more soluble irritant will more likely dissolve in the upper airways' fluid milieu. The physical interaction between an irritant and a receptor protein embedded in a lipid layer is predictive of a chemical's potential for sensory irritation [47]. Various determinants of irritancy are available. RD50 refers to the concentration of an irritant causing a 50% decrease in the breathing rate (RD50) of an exposed mouse (48). Another irritancy predictor is the Quantitative Structure Relationship (QSAR) [49,50].

Manifestations

The most common of the irritant's effect is sensory annoyance involving different target sites. Prevention of chemical damage to the eye requires wearing tight-fitting protective goggles. Eye irritation manifests as a burning/stinging/pain sensation (chemesthesis), tearing and conjunctival redness. There may be accompanying eyelid swelling and blurred vision. Eye involvement is considered a medical emergency especially after a highly alkaline or extremely acidic chemical agent exposure; the grave risk is for corrosive eye damage that worsens by the minute [51]. In such an emergency, immediately flush the eye with water; continue to rinse for at least 10 minutes [52]. Remove contact lenses. Do not let the patient rub their eyes, even after flushing with water. Therapeutically, antibiotic ointment into the eye may prevent infection while a topical corticosteroid may reduce inflammation. In most cases, chemicals will merely cause eyes' surface damage and not permanent loss of vision. Subsequent follow-up eye examinations require slit-lamp assessment and, perhaps, a battery of ophthalmologic tests, such as measurement of the time for tear film break-up, adequacy of foam formation in the eye canthus and evidence of conjunctival epithelial damage; there may be additional eye testing parameters [52,53].

The nose, as an irritant target manifests nasal inflammation and mucosal erythema [54,55]. There is rhinorrhea along with swelling and congestion of the nasal mucosa. Excessive nasal fluid can drip down the back of the throat (i.e., post-nasal drip) or escape out from the nostrils. Sneezing happens whenever foreign particles irritate the nasal mucosa [53]. A massive irritant exposure leads to a worse nasal outcome [56-58]. Hyposmia refers to the reduced ability to smell and to detect odors while anosmia is the absolute incapability of detecting odors. Parosmia or troposmia misidentifies a pleasant or neutral odor for an unpleasant odor.

Throat irritation leads to a sore throat often with painful swallowing. There may be a scratchy feeling at the back of the throat or

a sensation of a lumpy feeling or something stuck at the back of the throat [59]. Usually, there is an ongoing dry cough. Hoarseness shadows laryngitis [60]. Pharyngeal edema, redness and posterior pharynx drainage are observed on physical examination. Most cases of throat irritation resolve without special treatment. Home remedies for throat irritation include gargling with warm water twice a day, sipping honey with lemon mixture or sucking on medicated lozenges (containing menthol). Additional therapy for difficulty in swallowing includes drinking more fluids and chewing on ice chips.

Skin irritation happens after there are disruptions of the protective skin barrier with subsequent water loss, suppressed epidermal lipid production, pH-dependent susceptibility to infection, inflammation and altered calcium gradients [61,62]. Skin keratinocytes release both inflammatory chemotactic and growth promoting cytokines; also, oxidative stress causes tissue damage [33,42,61].

Lung irritation may influence dendritic lung cells to release cytokines causing inflammation [63,64].

Irritation Effects

Spirometric Reductions in FEV1 follow exposures to phenol-formaldehyde resins and repeated chlorine gassings [65-71]. Aluminum pot room workers and individual exercising at room and cold temperatures show changes in FEV1 [72,73]. Boilermaker construction working at gas coal and oil-fired plants, exposure of emergency responders to a variety of fumes, gases, and particulates during the course of their job and machinists' exposures to machining fluids incite FEV1 alterations [74-76]. It is important to stress that performance of performing spirometry necessitates accurate methodology and use of an acceptable spirometer that displays a flow-volume curve [66,77].

Balance between Matrix Metalloproteinase (MMPS) and the Tissue Inhibitors of Metalloproteinase (TIMPS) may represent an inflammatory marker of irritancy [70,78,79].

Chronic Coughing is a common clinical response to a sustained irritant exposure [20, 80-84].

Enhanced Airway Response to an Allergen, to which an individual is before hand sensitized, follows inhaling a low level of an environmental irritant air pollutant [85-88]. In atopic subjects, an enhanced response occurs when particulates rather than clean air precedes the allergen challenge [89]. "Enhancement" refers to a greater-than-additive response after the delivery of an irritating agent to an allergen, compared with the responses when the irritant and allergen delivery occurs by itself.

Elevated Levels of Exhaled Breath Nitric Oxide (FENO) are reported for pulp-mill and bleachery workers sustaining episodes of ozone gassing [90]. Workers with different irritant exposures (i.e., underground workers exposed to particulates and nitrogen dioxide; shoe and leather workers exposed to toluene, xylene and methyl ethyl ketone; and, swine confinement workers) exhibit higher FENO [35,91-93]. Using FENO as a monitoring tool needs careful application [94].

Induced Sputum examination discerns different cell types, such as epithelial and squamous cell, cancer or atypical cells, neutrophils, macrophages and eosinophils [95]. Irritant-exposures influence neutrophilia rather than eosinophilia [22,96-101]. Higher induced sputum neutrophilia is seen after a diesel exhaust particulate exposure [102]. Testing New York City Firefighters 10 months after the collapse of the World Trade Center, shows more induced sputum neutrophilia in association with a more intense exposure to World Trade Center dust [103,104]. Asthmatic subjects and endurance athletes develop sputum neutrophilia after an ozone challenge [105,106]. Fast food grill kitchen workers exhibit high numbers of alveolar macrophages in induced sputum samples [107]. Bronchoalveolar lavage (BAL) fluid cells in rats following chlorine exposure display an increase in the numbers of neutrophils [108]. Pre-treatment of a one-week course of parenteral steroids dampens neutrophilic inflammation in rats after irritant instillation [108].

Glutathione conversion to an oxidized form (GSSG) provides less antioxidant protection [109]. An increase in the ratio of the oxidized disulfide form of glutathione (GSSG) in relations to the reduced glutathione configuration (GSH) is indicative of oxidative stress (i.e., GSSG/GSH) [109]. Numerous investigations address glutathione kinetics and oxidative stress after an irritant exposure.

Irritant-induced Asthma-the Beginning

For more than half of the 20th century, there is a primary belief that occupational asthma is an allergy-related disorder, preceded by latency (of months or years), whereby repeat inhalational exposures to one of more than 250 allergenic workplace agents initiate immunologic sensitization, which ultimately leads to workplace-associated asthmatic manifestations [110]. Yet concealed, is a seeming lack of appreciation for the relevancy of irritancy. Cases incriminating irritants seem overlooked perhaps because of limited reporting or a paucity subjects studied [111-114].

History warns about the potential for irritant consequences. In the 1920s, at the start of World War I, German forces fire more than 150 tons of chlorine gas against two French colonial divisions at Ypres, causing serious consequences [115]. By the time World War II ended in 1945, at least 4,000 Service Men participate in experimental exposures using mustard or Lewisite agents in gas chambers or in contaminated field experiments [116]. Surviving veterans report anatomic changes with symptomatic respiratory manifestations [117-120]. Use of mustard gas during the 1980s' Iran/Iraq War exposes Iranians soldiers who subsequently display persistent Spiro metric reductions [119]. More cases of asthma are noted among Iranian military veterans experiencing heavy mustard gas exposure 10 years before [121].

Gandevia et al. describe workers with new-onset asthma following exposures to high concentrations of hydrogen sulfide smoke and fumes from overheated plastics. There is reference to "acute inflammatory bronchoconstriction" [122]. Firemen fighting a fire at a polyurethane foam manufacturing factory are exposed to the high concentrations of toluene diisocyanate (TDI) vapors emanating from two large storage tanks damaged during the fire [123]. A majority of firefighters describes acute irritation of their eyes, nose, and throat and some firefighters develop acute tightness of the chest, breathlessness and cough at the scene of the fire. Some firefighters disclose temporary spirometric decline during the first 6 months after the fire. Because TDI is a very common cause of allergic occupational asthma, its irritancy (non-allergy) may not have been fully appreciated. Perhaps, the delay in the recognition of Reactive Airways Dysfunction Syndrome (RADS) and an acute irritant-induced airways disorder is because of RADS's low prevalence, somewhere less than 20% of workers with the diagnosis of "occupational asthma" [124,125].

Reactive Airways Dysfunction Syndrome (RADS)

In 1985, Brooks and associates coin the acronym "Reactive Airways Dysfunction Syndrome" (RADS) to depict cases of acute, non-allergic, irritant-induced asthma without latency following a high-level inhalation exposure to an irritating gas, vapor or fume. On occasion, RADS is consequential of an airborne aerosol or mist exposure [126]. Rarely if ever, does RADS follow an exposure to massive levels of dust particles.

Typically, the onset of RADS appears within 24-hours, especially when the afflicted person is in close proximity to the irritant's source of origin [127,128]. When first observing the patient with evolving RADS, he/she is in acute distress with a faster breathing rate (tachypnea) of more than 20 breaths per minute. There may be an accompanying tachycardia with the heart rate greater than 90 beats per minute. Blood pressure and temperature readings vary. Pulse oximetry level is often low or at a low-normal level. It is the health professional's obligation to determine whether there are physical examination findings depicting eye, nose, throat, and/or skin irritancy. Table 2 provides diagnostic criteria for RADS diagnosis.

Diagnostic criteria for RADS
A documented absence of preceding respiratory complaints manifesting asthma symptomatology, account of past childhood asthma or a history of asthma in remission
The onset of symptoms occurred after a single and specific exposure, which was present in very high concentrations and had irritant qualities to its nature
Onset of asthma complaints occurred within minutes to hours and always within 24 hours after the exposure.
The exposure was to a gas, smoke, fume, or vapor. Rarely, if ever was the exposure to a dust
Finding of a positive meth choline challenge test (≤ 8 mg/ml) following the exposure, indicative of non-specific bronchial hyper responsiveness.
Pulmonary function tests may show airflow obstruction.
Another pulmonary disorder to explain the symptoms and findings was excluded especially conditions that simulated asthma (such as vocal cord dysfunction)

Table 2: Diagnostic criteria for RADS.

As soon as clinically feasible, procure specific details about the exposure, especially the precise nature of the exposure (i.e., chemical name, physical state, vapor pressure, etc.); and, ask how long it lasted. A critical bit of information is to ascertain whether the exposure is massive in nature. Is the exposure the result of an accidental explosion with the irritant agent release under pressure? How close is the afflicted individual (s) to the exposure source? Does the exposure take place in an open or an enclosed space? Valuable information is contained in the Material Safety Data Sheets (MSDSs) uncovering the precise constituents of the exposure. Typically, the MSDS information discloses the percentage concentration of chemical ingredients and physical properties. Scrutinize whether the chemical exposure comprises a dilute concentration. Is there a fire with the emissions of combustion products (smoke, fumes, and/or gases)?

Various etiologic irritants are presumed for RADS development [127,129-137]. Transiently obstructive airways are unveiled in some of the workers four years after an industrial accident involving a pyrite dust explosion estimated to release between 300 and 1,600 ppm of sulfurous gases [138]. Respiratory symptoms follow a high-level hydrogen sulfide gas exposure from agitation of liquid manure [133]. An individual develops severe airway obstruction after inhaling fumes from a mixture of several drain cleaning agents [139].

Typically when investigating RADS cases, spirometry shows airflow obstruction [71]. A reduced Tiffeneau-Pinelli index (FEV1/FVC ratio) is an indicator of airflow limitation [140]. Some subjects show 'normal' or mild airflow limitation with insignificant bronchodilator response (≤ 12% improvement in FEV1). Infrequently, affected persons exhibit a restrictive lung defect suggestive of a mixed pattern [111]. The latter finding brings suspects for extra thoracic upper airways obstruction, such as with vocal cord dysfunction (VCD) [141].

Airway Hyperresponsiveness is the hallmark of RADS, usually by documenting a positive methacholine aerosol provocation with PC20 of ≤8 mg/ml. PC20 refers to the provocative conc entration of methacholine causing a 20% fall in FEV1 [142,143]. There may be employment of other methods for identifying hyperresponsive airways [143,144].

RADS's respiratory symptoms may be transient and resolve within 12 weeks or less [124]. One review of RADS reports a median duration of symptoms lasting 13 months (interquartile range, 6.5 to 43.5 months) [136]. Mostly, individuals with RADS demonstrate continuation of nonspecific airway hyperresponsiveness and chronic asthma-type symptoms [145].

Lung pathology recognizes denuded bronchial epithelium, polynuclear and mononuclear cellular inflammation (eosinophilia tends to be absent), edematous mucosa, squamous cell metaplasia, basement membrane thickening, collagen proliferation and bronchial wall fibrosis [69,129,146]. There is continuing airway mononuclear inflammation as well as perpetual structural changes, transformed airway remodeling, induced neural plasticity and incessant airway hyperresponsiveness [147]. An investigation involving accidental chlorine gas exposure reports pathological changes of repeat bronchial biopsies taken over a 5-month time-period [148]. Initial denudation of the bronchial epithelial cells accompanies exudative sub mucosal fibrinous hemorrhage. Later, there is epithelial layer proliferation with regeneration of basal and Para basal cells. The latest pathological change divulges collagen deposition. Bronchoepithelial cell injury and lymphocytic inflammation persist when bronchial biopsies are obtained 3 years after an exposure causing RADS [149,150].

Astute clinical scrutiny is a prerequisite for successful management of any serious inhalation injury since the clinical course may change from minute to minute. At the latest, the patient needs examination by

a physician within the first 1-2 h after the exposure. Preferably, there is prompt transport of the patient to a hospital's Emergency Department since it permits accessibility to necessary medical consultative services, the availability of observation and/or hospital treatment in an intensive care unit [151]. Several hours may ensue between the time an exposure occurs and when manifestations that are more critical evolve. It is best to insure an observation period lasting 24-48 h before discharge. With very serious acute lung inhalational injuries, the chest x-ray shows alveolar and/or mixed infiltrates or segmental consolidation [152]. Challenging clinical scenarios include diffuse alveolar envelopment, as with the Adult Respiratory Distress Syndrome (ARDS), disseminated pneumonia with sepsis and shock or massive non-cardiac pulmonary edema. Chest computed tomography will best define lung changes [153]. ARDS, localized pneumonia or non-cardiac heart failure that may accompany RADS requires appropriate management. Aerosolized bronchodilators may be the administration for bronchoconstriction (as measured by spirometry) or for bronchospasm (as determined by auscultation finding of wheezing). The use of inhaled bronchodilator is especially relevant when there is reversibility of airway obstruction. However, reversibility of airway obstruction tends to be less marked in RADS than in asthma [145,154].

Differential diagnosis may be challenging in RADS since the routine chest roentgenogram may appear relatively 'normal' in the immediate post-exposure period. As time passes, there may evolve a more hyper-inflated X-ray appearance with lower diaphragms. Fiber optic bronchoscopic inspection is considered helpful as a visual gauge of the severity of the airway injury for most, if not all, inhalation injuries, [151,155]. Serial fiber optic examinations objectively assess the extent of the airway injury and the therapeutic benefits; discoveries may necessitate alterations in management [152]. RADS cases show tracheobronchial mucosal erythema and edema. In more severe cases, there is bronchial lining ulceration and/or hemorrhage [156].

Systemic corticosteroid, in high doses, may provide limited benefit since inflammation is mononuclear rather than eosinophilic. A beneficial effect of parental steroids in a rat model of RADS is of note when dexamethasone administration is immediately before chlorine inhalation [157]. A short course of high dose corticosteroid therapy does not improve the outcomes of patients with ARDS [158]. There is not definitive data on corticosteroid use in RADS involving humans. An antidotal report claims inhaled steroids are beneficial in RADS [145,148].

Irritant-Assumed Conditions

Meat Wrapper's Asthma is the result of the meat wrapping procedure (used commonly in the 1970s) involving wrapping packages of meat with polyvinyl chloride (PVC) plastic wrapping film. After meat wrapping, the plastic film is cut from the main PVC roll using a thin wire heated to between 150-200°C; wrap edges are sealed using a hot plate. The labels are also heated. The heating process emits irritating PVC pyrolysis byproducts; an airborne pyrolytic byproduct includes di-2-ethyl-hexyl phthalate (DEHP) [159]. The condition is referred to as meat-wrapper's asthma [159]. Complaints include eye irritation, chest tightness, cough and sometimes wheezing.

Military Deployment, as a military-related exposure leading to new-onset asthma, is a mischaracterization [160]. There is reference to "Iraq/Afghanistan War-Lung Injury". There is rejection for labeling deployment as an exposure since it simply is a time spent in a specific military locale [161]. Yearly, nearly 3,000 US military applicants are disqualified from military service because of asthma [162]. A history of prior childhood asthma becomes important because military recruitment concentrates on the age group at which prior childhood asthmatics achieve "remission;" and, these individuals potentially are poised to relapse from a remission. Microscopic and biochemical changes continue into adulthood [163-173]. There is reporting, by countries other than the USA, of asthma recurrence after childhood asthma among military recruits including New Zealand [174-178]. Asthma among cleaners is the claim for new-onset asthma among domestic cleaning women and janitors from frequent use of bleach and other irritant cleaning agent. Supportive investigations for the asthma relationship among cleaners emanates from: 179-185]. New-onset asthma is linked to job tasks of waxing, wax stripping of floor, spot cleaning of carpets, cleaning tiles and cleaning grout [184,186-189].

Potroom asthma is the occurrence of work-related airway symptoms in association with airflow limitation, airway inflammation and persistent nonspecific airway hyperresponsiveness among workers engaged in the primary smelting of aluminum, and less commonly among smelters and casters of refined aluminum. The entity is referred to as "Potroom asthma" [73,190-194]. Suspicious etiologic factors are particulates of aluminum sodium fluoride along with hydrogen fluoride and other gases [194-199].

Swimming pool use and asthma occur among individuals frequenting public swimming pools that use chlorine as a disinfectant [200-209]. Swimming pool lifeguards with frequent exposure to total chloramine levels report acute eyes and upper airway symptoms but do not show bronchial hyperresponsiveness [204]. The process of disinfection of swimming pools requires generation of 'free chlorine' through addition of sodium hypochlorite (liquid bleach), calcium hypochlorite or chlorine gas [205,210]. Public swimming pool water is comprised of organic precursors of the tap water used to fill the pools. Additional swimming pool contaminants are sweat, urine, skin particles, hair, microorganisms, cosmetics, and personal care products [210].

Athletes Exposed to unconditioned cold air develop exercise-induced bronchospasm beginning 5-10 minutes of exercise; there is bronchospasm resolution within 30 to 60 minutes after stopping exercise or following a β2-agonist treatment [211,212]. A high prevalence of exercise-induced bronchospasm is of note for collegiate cross-country runners and elite athletes exercising in cold mountain environs [213]. Exercising speed and power athletes may increase their ventilation rate as much as 200 liters per minute for short periods of time [213]. The mechanism to explain exercise-induced bronchospasm suggests that hyperventilation leads either to airway cooling with airway water loss and/or, in some manner, changes the osmolality of periciliary fluid lining evoking mucosal release of endogenous mediators causing airway smooth muscle contraction [214,215]. Being in a cold (and relatively dry) mountain environment produces more rapid respiratory water vapor loss as the exercise ventilatory rate increases. There is also the possibility that strenuous exercise triggers injury to the airway epithelium rather than affecting airway smooth muscle. The ensuing airway epithelial injury-repair process contributes to subsequent bronchial hyperresponsiveness.

Exacerbation of mild or preexisting asthma in remission may be etiologic for some cases of acute irritant-induced asthma. Cases of asthma can achieve a "remission" and/or display a reduction in asthma complaints. However, there remains a risk for future exacerbations of asthma [166-173,216]. Sometimes, an acute asthmatic exacerbation ensues when an individual with mild or controlled asthma experiences

an irritant environment trigger. This response is an acute exacerbation of a "preexisting" condition and not "new onset" asthma.

Vocal Cord Dysfunction (VCD)

Asthma is an intrathoracic reversible obstructive airway disorder. In contrast, VCD represents a spectrum of extrathoracic upper airway/laryngeal obstructive entities [217-220]. VCD mimics an acute asthmatic attack (Table 3) offers clinical clues differing between asthma and VCD. With VCD, there is fleeting obstruction of the upper airways due to inspiratory closure of vocal folds; sometimes closure is also during expiration [217]. Approximately 15% of US-American military recruits with suspected asthma exhibit VCD [221]. Eucalyptus exposure precipitates VCD in a 46-year-old woman [222]. VCD may be provoked by methacholine challenge testing [223]. A 15 year old teen develops VCD while working in a corn field [224]. VCD is of note among elite athletes during sporting competitions [225]; some competitive swimmers develop VCD [226]. A unique investigation connects VCD to occupancy in water damaged buildings [227]. Finally, VCD is discovered in about 10% of former World Trade Center rescue and recovery workers as well as volunteers involved in the rescue operation [228]. Spirometry shows flattening of the inspiratory loop of the flow-volume curve. Typically during an acute VCD attack, endoscopy reveals adduction of the anterior two-thirds of the vocal cords with posterior chinking creating a diamond shape configuration [229]. Successful therapy and management of VCD requires a speech therapy approach rather than a physician's prescribed medications [230,231]. Phonatory function tests, videostroboscopy and laryngeal image analysis are available tests for VCD [60,232]. With videostroboscopy, a steel scope containing a tiny camera and strobe light is place in the subject's mouth. The angle of the camera allows a clear and painless view of the patient's glottis and supraglottic regions. There is slow motion videotape assessing of vocal cord movement and vibration by projecting a moving image of the vocal cords, frame by frame, onto the television monitor. Ancillary therapeutic approaches for VCD may require psychological and psychiatric management applying behavioral, psychodynamic and/or pharmacological options [229]. Relaxation training and using biofeedback may be appropriate if marked anxiety and/or panic contribute to VCD symptomatology. Marital and/or family counseling may also be beneficial.

Feature	Asthma	VCD
Affected Site	Intrathoracic	Extra thoracic
Onset	Minutes, Hours	Seconds, Sudden
Triggers	Allergens, Cold Air, Strenuous Exercise, Mental Stress	Exertion, Cold Air, Irritants, Mental Stress
Response to Odorant	No or Occasional	Typical
Duration of Attack	Variable, Hours or Days	Short, Seconds to Minutes
Dyspnea	During Attacks	Attacks and at Most Times
Cough	Episodic, Productive	Persistent, Dry
Throat Complaints	No	Yes
Nasal Polyps	Sometimes	No
Status Between Attacks	Normal	Complaints
Nocturnal Attack	Yes	No
Voice	Normal	Hoarseness, Actual Loss
Auscultation	Expiratory & Inspiratory Wheezing	Inspiratory Wheezing and Stridor
Spirometry	Reduced FEV1/FVC% & Expiratory Airflow Obstruction	Flattening or Truncated Inspiratory Loop of Flow-Volume Curve
Endoscopy	Bronchial Mucosal Erythema, Edema and Secretion	Vocal Cord Anterior 2/3 Adduction with Posterior Chinking
Role of Eosinophil	Yes & Often	No
Bronchodilator Response	Yes	No
Corticosteroid Response	Yes	No
Aggressive Therapy	May be Effective	Not Effective

Table 3: Differentiating Asthma and VCD.

Irritant-Associated Vocal Cord Dysfunction is linked to an inhalational exposure declared as being RADS [233]. Eleven individuals who manifest voice change are initially considered to have RADS or asthma because there was a temporal association between onset of respiratory symptom and prior occupational or environmental exposure. All 11 individuals show negative methacholine challenges but laryngoscopic evidence of VCD. Workplace exposures of note are ammonia, flux fumes after inappropriate mixing of flux and solder, aerosolized cleaning chemicals, a specific odor (cooked spicy salmon), organic solvent, aerosolized machining fluid and smoke and ceiling tile dust falling through the ceiling above his workstation engulfing the worker below. The facts about the exposures do not indicate a massive or high-level irritant gas, vapor or fume exposure as necessary for RADS diagnosis. Dust is almost never a cause of RADS. A question regarding this entity is analogous to asking the question: what arose first, the chicken or the egg? A pivotal question is whether VCD is caused by the irritant exposure and was the initial RADS declaration a physician's failure to correctly gauge the magnitude and toxicological aspects of the suspected/claimed inhalation exposure. The author believes the latter.

Irritable Larynx Syndrome, develops when laryngeal neurons are held in a "spasm-ready" state leading to triggering of symptoms by different extraneous stimuli [234]. Key clinical features of the over-reactive laryngeal process comprise muscular tension dysphonia, episodic laryngospasm and cough [234]. Important diagnostic criteria are when there are symptoms attributable to laryngeal tension such as dysphonia, laryngospasm with or without throat complaints and/or chronic cough. There may be evidence of visible and palpable muscular tension in and around the neck and larynx with an abnormal laryngeal posture; there is laryngoscopic evidence of vocal cord contraction and/or palpable muscular tension in and around the larynx with abnormal laryngeal posture. Finally, sensory triggers including perfume, foods, emotion, voice use, esophageal irritants and distinctive odorants produce laryngeal muscle spasm with episodic coughing

[234,235]. There may be episodic dyspnea, dysphonia, cough and sensation of tension in the throat. Gastroesophageal reflux disorder (GERD) plays a role in more than 90% of cases with resolution of complaints after effective treatment for GERD [236]. About 1/3rd of cases are considered either psychological or viral illness in origin [234]. As for the latter, in some manner a viral illness will "reset" the sensitivity of the larynx to various stimuli. Additionally, occupational exposures may act as an etiologic trigger in some cases [237]. Of interest is that approximately 10% of work-associated respiratory symptoms are referred to a specialist occupational lung disease clinic in Canada [237].

VCD among Exercising Athletes is a relatively common findings among those athletes screened for asthma while taking part in the 2004 Olympics [238]. Approximately 8% of the screened athletes suffered from VCD [239]. Many cases of VCD occurred only during exercise, especially among elite or intense-training athletes [238,240,241]. Elite or intense-training athletes as well as swimmers, runners and cold-air athletes are at the greatest risk for VCD development [206,207,242]. Eucapneic voluntary hyperventilation testing can uncover some cases of VCD divided into three categories of supraglottic, glottic and mixed (glottic and supraglottic) upper airway obstruction [243].

Role of Odors and Inhalation Exposures

It is a wonder how influential smelling an odor can be [244]. Clinical studies suggest enhancement of irritant sensitivity by an odorant [245,246]. Odorant stimuli evoke emotion and stimulate an autonomic state via nervous pathways from the amygdala, prefrontal cortex and hippocampus [247, 248]. Olfaction encompasses the chemoreception process prompting the sense of smell [249]. Chemoreception is the unique olfactory way that allows a volatile odorant to institute sensory input to parts of the brain designated for smell identification but also for memory and emotion [247,250]. Categorically, a workplace "smell" does not equate with the presence of a dangerous chemical exposure. There are vast differences between the detection concentration of an airborne odorant perceived by smell and the much higher level of the airborne odorant (by magnitudes) capable of causing pungency, irritation or even significant toxicity [5,251,252].

Pavlovian Sensitization is a mechanistic conditioning process taking place among some individuals who develop panic attacks with dyspnea following smelling an odorant [253-255]. Some individuals mention exposure to organic solvents as causing panic attacks. Such individuals acquire panic attacks after intravenous sodium lactate challenge; other persons with panic manifestations follow CO_2 provocation [8,256].

Aerotoxic Syndrome is recognized by noting a "burning, "oily- type odor leading to both short- and long-term ill-health effects and, in some cases, respiratory complaints purportedly due to breathing atomized engine oils and/or other chemicals contaminated by recirculated "bleed air" entering airline cabins (Wikipedia, 2017 #6270;Burdon J, 2012 #6271). Most modern aircrafts target a recirculating air system composed of 45% "bleed air" and 55% recirculated air. There is the addition of "bleed air" during flight, after takeoff, shortly before landing and sometimes while on the ground. In actuality, "bleed air" is variable and depends upon the speed of the engine, aircraft design and aircraft types. There is a paucity of reliable and objective information on the subject. Presently, there is an ongoing debate, among different interested parties, as to the actuality of the aerotoxic syndrome. Still, some passengers, pilots and cabin crew believe the addition of contaminated "bleed air" causes headaches, visual difficulties, breathing problems, muscle aching, more tiredness, difficulties concentrating, reduced ability for word finding as well as an inability to adequately focus.

Vocal Cord Dysfunction after an Inhalation Exposure epitomizes acute VCD after smelling an odor or scent presumed to be a toxic exposure [3]. Perchance, VCD misconstrued after noting an actual or presumed odor occurs in a susceptible person who misdirects a stressful experience into a physical manifestation [257]. For the susceptible individual, the perception and attribution of smell is influenced by their less accurate elucidation of the odor [258]. Subjective symptoms occur in response to an odor; other individuals, under the same circumstances, do not [255]. The odor or scent causes acute vocal cord spasm; the individual wishes to "protect" his/her lungs from inhaling a perceived "toxic" constituent. For the susceptible person, odorant-alerting properties of nasal receptors heighten the sensitivity of laryngeal reflexes promulgating VCD [245,246, 259]. A greater number of neural signals pass between the olfactory receptors and the olfactory cortex [260]. Besides enhancement of odor perception to different odorants and innocuous stimuli, there is also voice change and marked resistance to aggressive asthma therapy [3].

Airway Sensory Hyper reactivity encompasses persons with upper and lower airway complaints and persistent cough with triggering by odorants such as perfumes, flowers, colored paints, cigarette smoke and automobile exhaust fumes [261]. The individuals displays poorer quality of life scores and shows enhanced responsiveness to inhaled aerosols of capsaicin (capsaicin challenge) despite negative methacholine challenge indicative of absent nonspecific airway hyperresponsiveness [262].

Final Words

Irritancy reflects a state of being irritated, a condition evolving within minutes to hours. There is impact of irritant exposures in the workplace, public health and community populations. RADS represent an outcome of a massive irritant exposure, manifesting as non-allergic, irritant-induced intrathoracic asthma without latency. The outcome of the very high irritant inhalational exposure causes persistent airway inflammation, perpetual airway structural changes, transformed airway remodeling, induced neural plasticity and incessant airway hyperresponsiveness.

Inexplicably an odor becomes misinterpreted as a more serious consequence, both by patient but enigmatically also by the treating health professional. Besides RADS and clinical associations of irritancy, this manuscript extends examples of presumed irritant exposure incorrectly referenced as an odorous indicator of toxicity. It is important to emphasize that enhanced odorant/scent sensitivity is not a diagnostic criteria for RADS.

Importantly, an irritant-induced condition requires better consideration besides mere focus on a patient's perception or complaints. Of course, accidents or serious events happen. For inhalational injuries, numerous and divergent parties provide influence and take part in decision-making issues regarding the exposure event and the affected patient. Of course, there is critical participation and input by the treating physician. But, there may also be meetings with family members, conclusions recounted by coworkers, communications by the employer, discussions with public health officials, contact with regulatory agencies, at times, integrating industrial hygiene and/or toxicology information, conceivably deliberating with union representatives, responding to requests made

by insurance companies or Workers ' Compensation officials and possibly hiring an attorney.

Imperatively, when there are health concerns from an inhalational exposure, there is always a physician's participation. The afflicted patient seeks care from a physician/health care professional for treatment and management of their actual or perceived health issue caused by an inhalational irritant exposure. The concerned patient communicates their account of events and their complaints to a responsive physician/health care professional. The latter is expected to infer a correct diagnosis and recommend proper treatment of an assumed inhalational injury under the circumstances of the described exposure. Regrettably, there may be limitation of training in the intricacies of inhalation injuries and chemical toxicology for some practicing physicians. Analytic features of an inhalation exposure with essentials of chemical reactions, appreciation of acknowledged toxicological doctrines and better grasp of what constitutes a massive exposure may be serious knowledge-gaps of busy practicing physicians. Sometimes, the physician/health care professional's diagnostic inference is incorrect. Making the correct diagnosis is imperative because of the adverse therapeutic and economic consequences of miss-diagnosing RADS as a serious event. Because the clinical picture simulates RADS or asthma after a reported irritant inhalation exposure, a consulted pulmonary specialist or emergency care provider usually institutes asthma therapy with aerosolized bronchodilators and corticosteroids. The error can lead to repeated Emergency Department visits, continued corticosteroid and bronchodilator administration, possibly multiple hospitalizations and the unwarranted ongoing physician office visits. When the "pieces" of the clinical puzzle do not fit correctly, there must be inclusion of more "pieces" of the clinical picture or rearrangement of "pieces" allowing better scrutiny of the information.

Certainly, because of the notable existence of irritants there is a need for better professional expertise on the subject matter. Because of irritants' pervasiveness and common consequential health concerns, a better understanding of and preventive strategies for irritant exposures are important. Accordingly, irritantology will be the distinctive knowledge of irritants while an irritantologist holds special expertise in assessing irritants and their health and environmental impacts.

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