William J. Meggs *Editor*

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Chapter 1
Introduction: Irritant Asthma, Irritant Rhinitis, and Related Conditions

William J. Meggs

Abstract Inhaled substances produce airway inflammation by two well-defined and distinct mechanisms. Aeroallergens are proteins on airborne particles that induce IgE antibodies with a high affinity for mast cells and basophils. Exposure causes degranulation and the release of inflammatory mediators. Respiratory irritants are chemicals that bind to chemoreceptors on sensory nerve fibers, leading to the release of mediators of neurogenic inflammation. Clinical manifestations are independent of the mechanism, have intra- and interindividual variability, and range from rhinorrhea and congestion in the upper airway to bronchospasm and bronchorrhea in the lower airway. Acute exposures to respiratory irritants are known to induce persistent upper and lower airway inflammation that have been termed reactive airways dysfunction syndrome and reactive upper-airway dysfunction syndrome, respectively. The mechanism is a remodeling of the structure of the airway mucosa, leading to pathological changes that lower the threshold for irritant sensitivity, so that chronic inflammation is induced by ongoing previously tolerated exposures.

Keywords Asthma • Rhinitis • Reactive airways dysfunction syndrome • Reactive upper-airways dysfunction syndrome • Respiratory irritants

Introduction

Several decades ago asthma was classified as extrinsic or intrinsic. Rhinitis was likewise classified as allergic or non-allergic. Extrinsic asthma was allergic asthma. Both allergic asthma and rhinitis are well understood as a characteristic lower

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airway inflammation induced by inhaled allergens in the environment. The mechanism is production of antibodies of the IgE class directed against proteins found on pollen grains and mold spores and arising from animals such as dust mites and cat. The IgE antibodies are found on the surfaces of mast cells and basophils. When environment proteins interact with these antibodies, a number of substances are released that lead to inflammation of the airway. Clinical manifestations include varying degrees of rhinorrhea, congestion, sinus headaches, dyspnea, bronchospasm, bronchorrhea, and cough. Allergy skin tests, in vitro measurements of specific IgE antibodies, inhalational challenges, and correlation of symptoms with exposures can be used to diagnose allergy asthma. Allergy immunotherapy is efficacious and cost effective to prevent exacerbations of allergic asthma, rhinitis, and conjunctivitis resulting from exposures (Simoens 2012).

Those with asthma but negative evaluations for allergy were classified as having intrinsic asthma. Their asthma was thought to be internal with no external triggers. Over time, it was realized that environmental exposures other than allergens can trigger asthma attacks in individuals with susceptibility to a particular exposure. These range from exposure to cold dry air, exercise, and emotional stress. It has also been established that there is another mechanism through which airborne exposures trigger exacerbations of asthma, rhinitis, and conjunctivitis. A class of chemical inhalants termed *respiratory irritants* can induce an exacerbation of asthma and rhinitis in susceptible individuals. Examples of respiratory irritants that can exacerbate asthma, rhinosinusitis, or conjunctivitis are given in Table 1.1.

There has been an increasing recognition of the role of irritants in exacerbating the airway inflammation of asthma (Brooks et al. 1990, Nordin et al. 2004) and rhinitis (Bernstein 2012; Millqvist et al. 2005). It is generally true that more attention is given to asthma than to rhinitis, even though rhinitis is more prevalent than asthma. Deaths from rhinitis are virtually unknown, while asthma can be devastating and fatal. Rhinitis would be more deadly than asthma except for anatomical redundancy with an alternative path for the upper airway; that is, the alimentary canal provides an alternative airway to the nasal passages. Significant blockage of the nasal passages by congestion is common and would be a major emergency except an afflicted person can bypass nasal airway obstruction by opening the mouth.

Rhinitis is sometimes regarded as a trivial disease, but this is not the case. Quality of life studies document the devastating impact rhinitis can have on the quality of life (Rudmik and Smith 2011). To quote from the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma & Immunology; the American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy, Asthma and Immunology (Wallace et al. 2008): "Although sometimes mistakenly viewed as a trivial disease, symptoms of allergic and non-allergic rhinitis may significantly affect a patient's quality of life and can be associated with conditions such as *fatigue, headache, cognitive impairment, and sleep disturbance*." (Italics added). Asthma, rhinitis, and sinusitis are terms denoting airway inflammation in different parts of the airway, with overlapping pathophysiology, exacerbating causes, and treatments. Rhinitis and sinusitis are so similar that the American

Table 1.1 Examples of irritants associated with exacerbations of asthma, rhinosinusitis, or conjunctivitis

Substance	Selected references
Products of combustion	
Environmental tobacco smoke	Al-Sayed and Abrahim 2012, Bascom 1991, Bascom et al. 1991, Willes et al. 1998
Diesel exhaust	Hussain et al. 2012
Wood smoke	Van Miert et al. 2012, Henderson and Johnston 2012
Vehicle exhaust	Gasana et al. 2012
Dusts	
Cement dust	Baur et al. 2012
Grain dust	Baur et al. 2012
Cotton dust	Yerpude and Jogdand 2010
Fragrances and perfumes	Elberling et al. 2005, 2007, Heydorn et al. 2003, Kumar et al. 1995, Millqvist and Lowhagen 1998, Millqvist et al. 1999, Opiekun et al. 2003, Steinemann 2009, Steinemann et al. 2011
Pesticides	Senthilselvan et al. 1992, Hernandez et al. 2011
Noxious gases	
Sulfur dioxide	Deger et al. 2012, Kim et al. 2012
Ozone	Youssefagha et al. 2012
Chlorine	Bougault and Boulet 2012, Bougault et al. 2012
Oxides of nitrogen	Youssefagha et al. 2012
Chlorine dioxide	Meggs 1995
Ammonia	Baur et al. 2012
Chloramine	D'Alò et al. 2012
Bleach (sodium hypochlorite)	Arif and Delclos 2012
Complex mixtures	Banauch et al. 2003

Academy of Otolaryngology has proposed using the diagnosis rhinosinusitis rather than the separate terms.

Accompanying our increasing knowledge of the role irritants play in human disease has been the recognition that irritant exposures can induce permanent and lifelong asthma and/or rhinitis. Soldiers who survived the irritant gas exposures such as chlorine and mustard gas in the trenches of World War I developed chronic asthma (Ghanei and Harandi 2007). The classic description of asthma induced by irritant exposures as described by Brooks and his collaborators has been termed reactive airways dysfunction syndrome (RADS) (Brooks, Brooks). This syndrome is discussed in detail in Chap. 3. Persistent rhinitis can also occur after an irritant exposure (Meggs and Cleveland 1993; Meggs et al. 1996b; Leroyer et al. 1999; Moscato et al. 2008; Hellgren et al. 2003; Gautrin et al. 2006; Castano and Malo 2010). Extension to rhinitis induced by an acute exposure to irritants has been termed reactive upper-airway dysfunction syndrome (RUDS) (Meggs and Cleveland 1993; Meggs et al. 1996b).

Mechanism of Irritant Asthma and Irritant Rhinitis

In a classic set of experiments a century ago, the German physiologist A. N. Bruce demonstrated that the inflammatory response to an irritant was dependent upon sensory innovation. Mustard oil was instilled into the conjunctiva in experimental models. Bruce proved that the inflammatory response was blocked by cutting the sensory nerves to the conjunctiva (Bruce 1910, 1913). Since that time, literally thousands of studies have established the role of sensory nerve stimulation in inflammatory processes in the skin, airway, conjunctiva, gastrointestinal tract, synovial lining of joints, and genitourinary tract. There have been many reviews that summarize our knowledge in this area (Jansco 2008; Veronesi and Oortgiesen 2001; Nielsen 1991; Barnes 2001; Meggs 1995; Stahl 1999; Spampinato and Ferri 1991; Groneberg et al. 2004). The subject is so vast that we will not be able to reference and credit the many investigators who have made contributions to this important area of research, from identification and synthesis of neuropeptides and their receptors, mechanisms of action, and interactions with other systems. The mechanism will be summarized here. Receptors on nerve cells that identify external stimuli and initiate a reaction are termed nociceptors. Nociceptors can be stimulated by chemical irritants, mechanical stimulation such as stretch, and thermal stimuli. Nociceptors that respond to chemical irritants are sometimes termed chemoreceptors or irritant receptors. Respiratory irritants are chemicals that bind to nociceptors on sensory nerve fibers in the airway and initiate an inflammatory response. The nerve cells release inflammatory mediators termed neurokinins. These include substance P, vasopressin, and calcitonin gene-related peptide.

Many mast cells have receptors for substance P on their surface, so mast cells can be stimulated to add to the inflammatory process, with the release of histamine and chemotactic factors. Immune cells are recruited to the site. Blood vessels dilate and can leak fluid into the tissues, producing congestion. Mucus glands are stimulated, leading to bronchorrhea and rhinorrhea. There can be burning of the nasal passages and secondarily itching from histamine release. Coughing and bronchospasm can occur. The end result is an exacerbation of asthma and/or rhinosinusitis. A schematic of this process is given in Fig. 1.1.

Induction of Irritant Asthma and Rhinitis

A distinction must be made between exacerbation of asthma and/or rhinosinusitis in an individual with preexisting airway inflammation and the induction of chronic airway inflammation from irritant exposures. RADS describes a chronic asthma-like syndrome following irritant exposures (Brooks et al. 1985). RADS is discussed in detail in Chap. 3. Chronic rhinitis following irritant exposures (Meggs et al. 1996b) has been termed RUDS. Exacerbations from exposures represent hyperreactivity, occur at low doses generally tolerated by healthy individuals, and are not

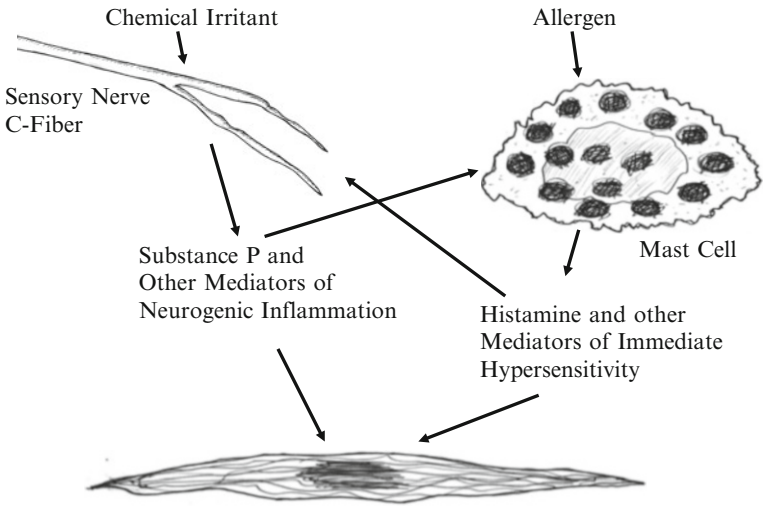

Fig. 1.1 Schematic showing the mechanisms by which allergens and chemical irritants act on effector cells. Allergens bind to immunoglobulins (IgE) on mast cells, triggering the release of allergic mediators. Chemical irritants bind to chemoreceptors on sensory nerve fibers, triggering the release of neurokinins. The crossover network between allergic and irritant reactions is depicted, with histamine binding to receptors on nerve fibers and substance P binding to receptors on mast cells. The clinical manifestations can be similar, with rhinorrhea, bronchorrhea, bronchospasm, etc.

dose dependent, though there might be a threshold dose below which the inflammatory cascade is not activated. The induction of chronic airway inflammation from an irritant exposure is thought to be a toxic event that follows a dose–response curve. The higher the dose, the more likely the effect is to occur.

Historically, induction of chronic airway inflammation from irritant exposures was described in veterans who were exposed to irritant gases such as chlorine in the trenches of World War One (US Army). Asthma, rhinitis, emphysema, and chronic obstructive pulmonary disease are related conditions that can all result from irritant exposures.

Chronic airway inflammation results from an irritant exposure because irritants induce inflammation. The effects of the irritant and resulting inflammation lead to a remodeling of the airway. Remodeling refers to the pathological changes that occur in the airway that changes the anatomy and physiology. An important change is a proliferation of sensory nerves in the airway that respond to respiratory irritants, as demonstrated by increases in nerve growth factor in the airways of subjects with rhinitis (Sanico et al. 1999, 2000; Millqvist et al. 2005). These can be verified by light microscopy and electron microscopy of biopsy specimens (Meggs 1992) as well as changes in the composition of interstitial and bronchial fluids. Figure 1.2 depicts these changes graphically.

Electron micrographs of nasal biopsies from individuals who developed chronic airway inflammation after an irritant exposure are depicted in Figs. 1.3 and 1.4.

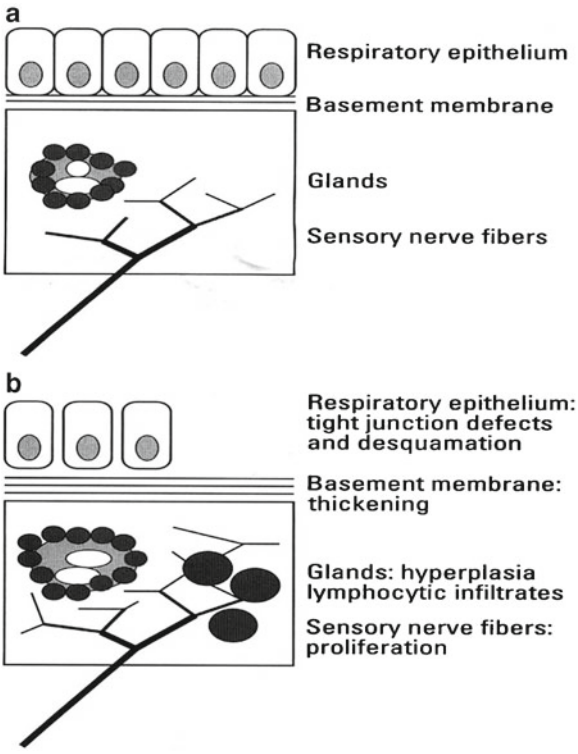

Fig. 1.2 Mechanism of chronic airway inflammation and hyper-reactivity to respiratory irritants resulting from an irritant exposure. (**a**) Schematic of normal airway epithelium. (**b**) Schematic of changes in airway epithelium in individuals with remodeling secondary to irritant exposures. Reprinted from Meggs (1997) with permission

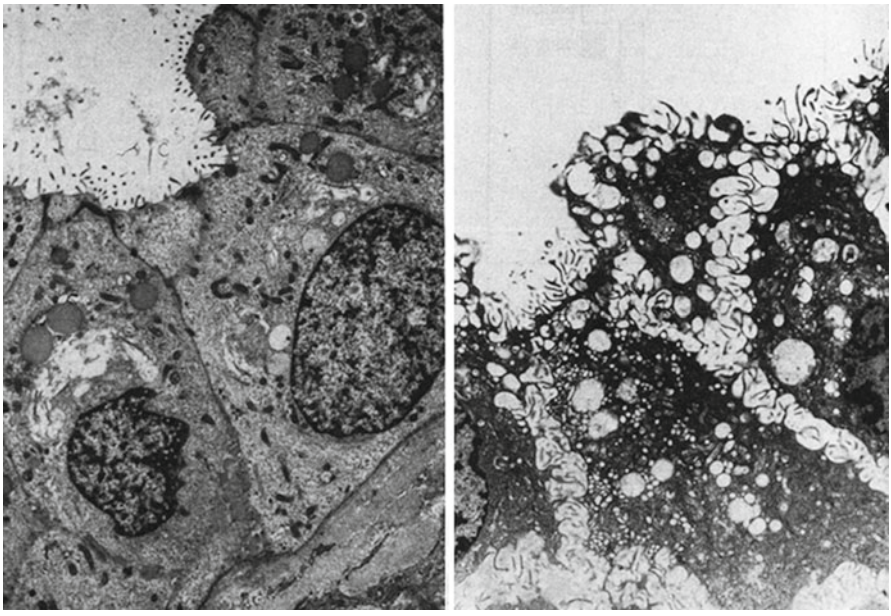

Fig. 1.3 Electron micrograph of nasal mucosa biopsy of an individual with irritant rhinitis (*right*), compared to a normal mucosa (*left*). Note the defects in tight junctions. Reprinted from Meggs (1996b) with permission

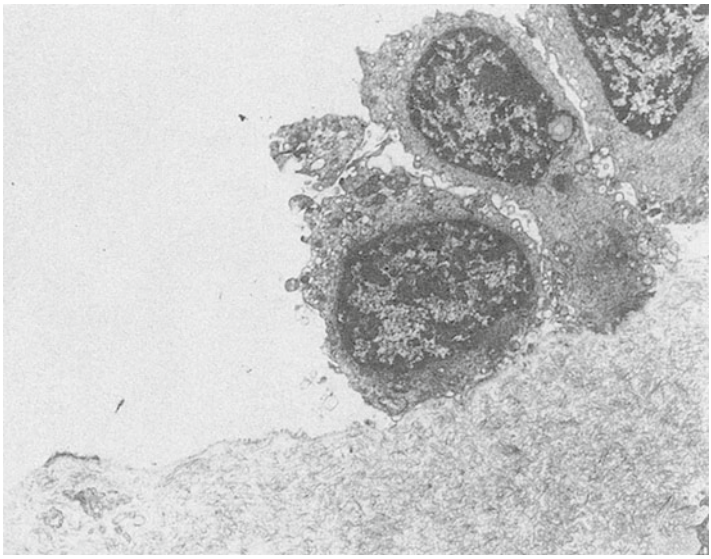

Fig. 1.4 Electron micrograph of an individual with irritant rhinitis. Note the defects in the tight junctions between epithelial cells, the defects in the junctions between respiratory epithelial cells and the basement membrane, and the loss of respiratory epithelial cells. Reprinted from Meggs (1996b) with permission

Figure 1.3 compares the findings in a normal biopsy, in which there are tight junctions between respiratory epithelial cells and those of an individual with RUDS, with defects in tight junctions between adjacent cells. Tumor necrosis factor has been shown to disrupt tight junctions (Shen 2012), and the abnormal lymphocytic infiltrates in the airway of affected individuals may be the source of tumor necrosis factor, though further work is needed to verify this hypothesis. In Fig. 1.4, one sees disruption of the tight junctions not only between adjacent respiratory epithelial cells but also between epithelial cells and the basement membrane, with loss of epithelial cells (desquamation).

Individuals with irritant rhinitis have characteristic findings on visualization of the upper airway that are best appreciated with rhinolaryngoscopy. Figure 1.5 is a photograph of the nasal passages of an individual who developed chronic irritant rhinitis after an acute high-dose exposure to respiratory irritants. There is a patchy loss of the normal uniform rose coloration of the upper airway, with pale-to-yellow coloration. In the areas of discoloration, blood vessels are clearly visible. These changes are often seen on the uvula and soft pallet. Biopsies of the discolored areas in comparison to the areas of normal coloration in individuals with irritant rhinitis revealed no difference in light microscopy, with chronic inflammation being seen at both sites (Meggs and Cleveland 1993).

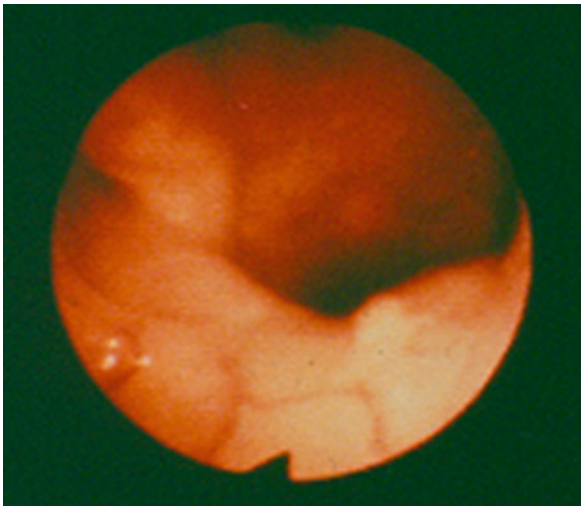

Fig. 1.5 Nasal airway of an individual with irritant rhinitis. Note the area of discoloration with loss of the uniform coloration seen in a normal airway. There are also prominent blood vessels in the areas of discoloration. This pattern can be seen in the nasal mucosa, soft pallet, and uvula

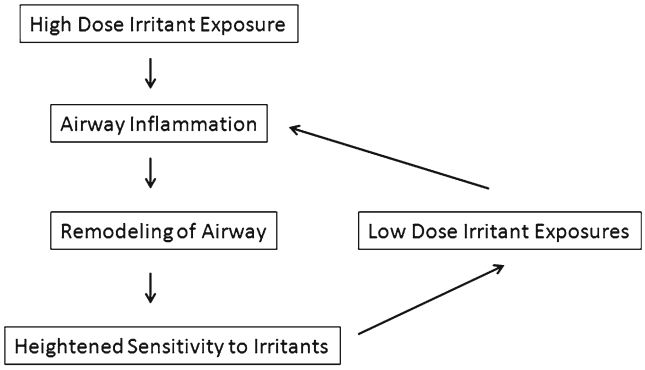

Fig. 1.6 A positive feedback loop is set up when a high-dose irritant exposure initiates airway inflammation which leads to remodeling of the airway. The remodeled airway has a heightened sensitivity to irritants so that exposures to lower levels that were previously tolerated produce inflammation, which in turn prevents normalization of the remodeled airway

One of the consequences of remodeling is a decreased threshold for irritants to trigger airway inflammation. An individual who develops RADS or RUDS will have susceptibility to irritant exposures at lower concentrations than that were tolerated before the onset of illness. In situations where exposures to respiratory irritants are unavoidable, inflammation becomes chronic and remodeling becomes permanent. In effect, a positive feedback loop is established, as depicted in Fig. 1.6.

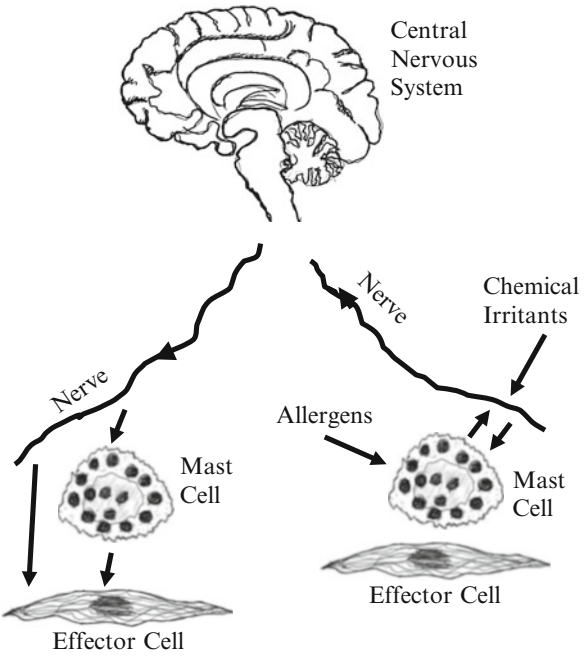

Fig. 1.7 Neurogenic switching in allergic and irritant reactions. Initiating event sends nerve pulse upward, with retrograde propagation of the nerve signal to another site

Relationship of Allergy and Irritant Sensitivity

Site Switching

Allergens and irritants generally induce inflammation at the site of inoculation. There are well-documented situations where inflammation can develop at other sites. This is best established for allergic reactions. Examples include urticaria and asthma attacks from food allergy, a condition known as gustatory rhinitis, and even systemic anaphylaxis. Site switching to the central nervous system may underlie cognitive dysfunction, mood disturbance, chronic fatigue, and sleep disturbances associated with allergic and irritant rhinitis (Wallace). A discussion of the brain as a target organ for both allergic and irritant reactions is given in Chap. 10.

There are several mechanisms for site switching. Polyclonal activation occurs when stimulation of a clone of immune cells to one antigen or irritant results in the activation of other unrelated clones. The release of cytokines from one site of infection may enhance inflammation at other sites of preexisting inflammation. This phenomenon may underlie the clinical observation that viral infections including influenza infections can lead to exacerbations of conditions such as asthma (Yamaya 2012). The critical role of the nervous system in site switching has been termed *neurogenic switching* (Meggs 1995). This process, in which a nerve signal is transmitted to the central nervous system from the site of inoculation, followed by retrograde propagation (Hinsey and Gasser 1930; Chahl 1988) to another site, is depicted in Fig. 1.7.

A positive allergy skin test consists of two components, wheal and flare. Wheal is a palpable swelling about the site of inoculation. Flare is a larger area of erythema about the site of inoculation. The flare is an example of neurogenic switching. Inoculation of the skin with antigen induces mast cell degranulation. Histamine induces capillary leak, with edema of the dermis (wheal) at the site of inoculation. Histamine binds to receptors on sensory nerve c-fibers so that an electrical pulse travels toward the central nervous system. The pulse flows in a retrograde fashion down the neighboring nerve fibers leading to substance P release at their terminal ends. Substance P in turn binds to vessels to increase blood flow to the area, resulting in hyperemia (flare).

Systemic anaphylaxis may be a manifestation of neurogenic switching. Cutaneous inoculation with an antigen, such as a bee sting, or gut inoculation, as in the ingestion of a food or a drug, can affect multiple organ systems immediately. Respiratory involvement with bronchospasm, bronchorrhea, and laryngeal edema; gastrointestinal symptoms; skin involvement away from the site of inoculation with diffuse flushing or urticaria; and cardiovascular symptoms with hypotension from diffuse vasodilation can all arise. A role for the nervous system in systemic anaphylaxis has been demonstrated in experimental models. It is known that vagotomy protects rats from lethal anaphylaxis without changing the production of antibody or histamine release (Levy et al. 1976). Experimental lesions of the anterior hypothalamus lessen the anaphylactic reaction in a guinea pig model (Leslie and Mathe 1989). Neurogenic switching may be the mechanism for this observed modulation of anaphylaxis by the nervous system.

Gustatory rhinitis is known to be an example of neurogenic switching based on pharmaceutical studies. In this syndrome, rhinorrhea, nasal congestion, and facial sweating develop after the ingestion of spicy foods. Ingested irritants such as capsaicin, the active ingredient in chili peppers, interact with branches of the trigeminal nerve innervating the oral cavity. The efferent signal is switched to the nose and face (Raphael et al. 1989). That atropine, an antagonist of the neurotransmitter acetylcholine at muscarinic receptors, blocks the effect is convincing evidence of the role of the nervous system in site switching.

Site switching has been rigorously demonstrated in experiments by Dr. Eva Millqvist and her collaborators in Sweden. Instilling fragrance in the lateral conjunctival sac, away from the lacrimal duct and without sensations of odor or taste, of subjects with sensitivity to irritants resulted in respiratory symptoms even though a mask was used to isolate the respiratory and conjunctival systems (Millqvist et al. 1999). Millqvist developed the capsaicin cough challenge that demonstrates that subjects with irritant sensitivity develop increased coughing relative to controls with inhalation of nebulized capsaicin (Ternesten-Hasséus et al. 2002). That remodeling of the airway in response to neuroinflammatory activation is a role in irritant sensitivity was further demonstrated by increased levels of nerve growth factor in this patient population relative to controls after inhalation of capsaicin (Millqvist et al. 2005).

Environmental Adjuvants

The concept of environmental adjuvants closes the loop relating allergic and irritant sensitivity. In immunology, an adjuvant is a substance that potentiates the immune response to other substances. Environmental adjuvants are substances in the environment that induce immune reactivity to other environmental substances. The prevalence of asthma, atopy, and rhinitis, both allergic and nonallergic, is increasing in many countries (Tang et al. 2008). One possible reason for this increase is that environmental exposures both initiate and exacerbate airway inflammation. It is reasonable to assume that inflamed tissue will process antigens so that an immune response develops to allergens that are present concurrently. It has been demonstrated that inhalation of irritant gases can induce production of IgE antibody to concomitant exposures. A notable example is diesel exhaust particles that can induce IgE responses to a co-administered aeroallergen (Nel et al. 1998). Other irritant exposures that can enhance immunity to other substances include ozone (Biagini et al. 1986; Matsumura et al. 1972), nitrogen dioxide (Matsumura et al. 1972), and sulfur dioxide (Reidel; Matsumura et al. 1972). Hence, air polluted with irritants is a possible explanation for increases in allergic diseases. The notable rise in allergy to Japanese cedar in Japan, from a rare condition to the most common immunological disease, after the introduction of motor vehicles, illustrates the remarkable effects irritants can have in a population (Matsumura et al. 1972).

Related Conditions

A number of conditions and/or terminologies are related to irritant airway inflammation. These include atherosclerosis, sick building syndrome, world trade center syndrome, chronic fatigue syndrome, office eye syndrome, irritable bowel syndrome, irritant contact dermatitis, airborne contact dermatitis, multiple chemical sensitivity syndrome, idiopathic environmental intolerances, and fibromyalgia.

Atherosclerosis is an inflammatory process of arterial walls that can lead to heart attacks and strokes. It has long been recognized that both active and passive exposures to cigarette smoke can accelerate atherosclerosis. There is increasing recognition that other forms of air pollution are associated with atherosclerosis and in particular traffic fumes (Berglind et al. 2009). It has been found that transient exposure to traffic fumes can increase the risk of myocardial infarction in susceptible individuals (Peters et al. 2004). Small particulates from fossil fuel combustion are associated with myocardial infarction (Murakami and Ono 2006). Particulate exposure and cardiovascular inflammation are discussed in detail in Chap. 5.

Sick building syndrome is a term introduced by a World Health Organization Committee to describe widespread complaints in poorly ventilated buildings. These occurred after the energy crisis of the 1970s, when ventilation in buildings was reduced to save heating and cooling costs. Symptoms were most commonly

respiratory. A comparison of a poorly ventilated building to a traditional building found a marked increase in respiratory complaints.

Irritant-associated vocal cord dysfunction syndrome: Vocal cord dysfunction syndrome, in which there is a paradoxical adduction of the vocal cords during inspiration, can be associated with irritant exposures, from both extrinsic chemical irritant exposures and intrinsic causes (acid reflux in gastroesophageal reflux disease, rhinitis and sinusitis, and laryngopharyngeal reflux) (Morris and Christopher 2010).

Chronic fatigue syndrome is defined by the Centers for Diseases Control as severe chronic fatigue for 6 or more consecutive months that is not due to ongoing exertion or other medical conditions associated with fatigue, significantly interferes with daily activities and work, and has four or more of the eight symptoms: post-exertion malaise lasting more than 24 h; unrefreshing sleep; significant impairment of short-term memory or concentration; muscle pain; pain in the joints without swelling or redness; headaches of a new type, pattern, or severity; tender lymph nodes in the neck or armpit; and a sore throat that is frequent or recurring (http://www.cdc.gov/cfs/case-definition/index.html). Fatigue is commonly seen in chronic rhinitis (Bhattacharyya 2003). Chronic rhinitis should be ruled out before a diagnosis of chronic fatigue syndrome is made, recognizing that individuals with chronic rhinitis may present with complaints of face pain, headache, fatigue, or other associated symptoms while minimizing or denying symptoms of rhinitis. Individuals with perennial allergic rhinitis or irritant rhinitis who are chronically exposed to allergens or irritants suffer from chronic fatigue.

Irritable bowel syndrome (IBS). This chronic condition characterized by crampy abdominal pain, nausea, emesis, and diarrhea alternating with constipation is reportedly induced after both chemical and infectious exposures. Post-infectious IBS is common, with the onset of IBS after an episode of acute gastroenteritis (Thabane and Marshall 2009). In analogy to RADS, the term reactive intestinal dysfunction syndrome (RIDS) has been introduced to describe individuals who develop IBS after irritant exposures (Lieberman and Craven 1998). IBS shares mechanistic aspects with irritant rhinitis and related conditions, including the roles of substance P, neurogenic inflammation, nociceptors, and central nervous system modulation and associated co-morbidities (Hunt and Tougas 2002; Stasi et al. 2012).

Multiple chemical sensitivity syndrome (MCS). This syndrome was defined as a condition of self-reported intolerance to environmental chemicals. In one description, it is an acquired condition in association with a chemical exposure, with symptoms involving multiple organ systems that are exacerbated by exposure to chemicals of diverse classes (Cullen 1987). This syndrome differs from RADS and RUDS with exacerbations when exposed to some of the irritants given in Table 1.1 in that reported symptoms involve more than one organ system. Hence, someone with airway inflammation exacerbated by irritant exposures who also experienced fatigue, headaches, rashes, and sleep disturbances—conditions known to be associated with rhinitis—would meet a case definition of MCS. Individuals with somatic disorders, odor aversion, chemophobia, anxiety attacks triggered by odors, and other psychological

conditions would likewise meet these case definitions. Idiopathic environmental intolerances (IEI) is a term introduced to describe patients with no diagnosable medical condition and reported chemical intolerances (Anonymous 1996). IEI should only be used as a diagnosis for individuals without diagnosable medical conditions that can be caused or exacerbated by environmental exposures. Subjects who develop RADS and/or RUDS after a chemical exposure meet case definitions for MCS (Meggs 1992).

As our knowledge of the brain as a target organ for irritant and allergic reactions advances, diagnostic methods for irritant sensitivity improve, and understanding of the neuroscience of conditions such as depression and anxiety matures, some individuals now classified as IEI may have better descriptors.

The concept of MCS is in a sense flawed because it confuses diagnosis with etiology. Further, there are many conditions known to be caused by or exacerbated by chemical exposures, including irritant asthma and rhinitis, dermatitis, and so forth. Physicians would better serve their patients by diagnosing the conditions such as rhinitis or asthma and headaches than labeling them as having MCS. Case definitions of MCS do not specify the symptoms that are exacerbated by chemical exposures. Despite these challenges, the burden in the population of individuals who meet case definitions is huge. A study conducted by the California Department of Health found that 15.9 % of the population meet the criteria for MCS and that 7 % of the population had been diagnosed with MCS by a physician (Kreutzer et al. 1999). A prevalence of 15 % was found in New Mexico (Voorhees 1998) and 12.6 % in Georgia (Caress and Steinemann 2004a).

A population-based study in the United States found the prevalence of hypersensitivity to common chemical products such as perfume, fresh paint, pesticides, and other petrochemical-based substances to be 11.2 % (Caress and Steinemann 2004b). Further, 2.5 % reported that they had been medically diagnosed with MCS. Additionally, 31.1 % of those sampled reported adverse reactions to fragranced products, and 17.6 % experienced breathing difficulties and other health problems when exposed to air fresheners. Although chemical hypersensitivity was more common in women, it affected individuals in all demographic groups studied.

A study in North Carolina of the prevalence of allergies and chemical sensitivity that was more general—the screening questions would capture individuals with conditions such as asthma and/or rhinitis exacerbated by irritants but did not meet more stringent criteria for MCS—found a prevalence of 33 % for chemical sensitivity, comparable to the 35 % reporting allergy, with a 50 % overlap between the two groups (Meggs 1996a). These studies indicate that the burden of chemical sensitivity in the population is significant.

The burden of airway inflammation is also significant. In the United States, 20 % of the population suffers from allergic rhinitis, but the burden of nonallergic rhinitis is even greater, with 25 % suffering from nonallergic rhinitis and 50 % with mixed rhinitis (Bernstein 2010, Molgaard et al. 2007, Settipane and Lieberman 2001; Settipane and Charnock 2007).