REACTIVE AIRWAY DISEASE

Repeated modest and even "tolerable" dose irritant exposures\(^1,2\) or higher dose single\(^3\) or repeated\(^4\) irritant exposure can induce permanent or long term reactive airway disease rendering the individual with long-standing heightened susceptibility to exacerbating symptoms from future irritant exposures.\(^1,3\) Irritants cause reactive airways (upper and/or lower airways) by release of the inflammatory substance P and neurogenic inflammation.\(^4\) Irritant exposure has been shown to cause loss of the protective nasal epithelial cells, increased permeability (which would allow future irritants to enter more readily), chronic inflammatory changes and an increase in nasal nerve fiber endings (which help heighten neurologic and bodily effects from future exposures) on biopsy.\(^5\)

Reactive upper airway disease following inhaled irritant exposure shows rhinitis on rhinolaryngoscopy and rhinolaryngeal microscopy, with thickening of the basement membrane, damage to the epithelium (desquamation) and infiltration with activated mast cells.\(^6\) Rhinolaryngoscopy in these patients showed excess mucous and cobblestone appearance.\(^6\)

The irritation of the eyes\(^7\) and respiratory system\(^8,9\) at even low levels of exposure to a mixture of irritants and/or volatile chemicals shows more than an additive effect in humans. The degree of hyperadditivity increases with the number of substances present and also with the fat solubility (lipophilicity) of the chemicals.\(^7\) Prior irritant exposure increased the irritant effect of subsequent irritant exposure.\(^8\) Longer duration of low level exposures and/or higher levels of chemical mixtures increased the adverse response and sensitization.\(^10\) Reactive airway dysfunction can involve upper and/or lower airways, according to the official publication of the National Institute of Environmental Health Sciences, part of the National Institutes of Health of the U.S. Government.\(^11\)

Reactive airway disease can be triggered by volatile organic compounds. Following the onset of reactive airway dysfunction, there is damage to the respiratory epithelium\(^2,7\) including loss of the protective barrier\(^7\), which can allow chemical irritants to reach and trigger irritant nerve receptors at lower levels of exposure.\(^7\) The key feature of reactive airway dysfunction is heightened respiratory\(^1,2,3,7\) and systemic\(^7\) symptoms in response to lower future exposures to irritants. Intolerance to chemical irritants has been reported in asthma\(^5,12\) and in rhinitis.\(^7\) Volatile organic compounds (commonly encountered in buildings) and most other petrochemicals are irritants\(^13,14\) as are nonpetrochemicals such as ammonia, chlorine\(^8,9\) and the latter in widespread use in cleaning agents and thus commonly encountered. Other chemical classes which exacerbatie reactive airways include solvents,\(^5\) pesticides,\(^5\) indoor air pollutants,\(^15\) and inorganic irritants.\(^5,16\) Lower respiratory reactive airway dysfunction can be evaluated by a medical history of respiratory symptoms following irritant levels tolerated by healthy individuals or reduction of peak flow using a peak flow meter.\(^3\)

A study of non-smoking persons with airway hyperactivity to irritants showed that methacholine challenge tests, chest x-rays, and lung function tests were not reliable predictors of reactivity, that symptoms typically involved upper and lower airways and often failed to respond to (Beta 2 agonist) bronchodilators or steroids, and were not uncommonly accompanied by fatigue, headache and/or musculoskeletal aching. In challenge testing of such patients, the authors found that the hyperactivity involved the eyes as well as upper and lower airways, and that perfume challenge below smell level exacerbated symptoms of eyes, upper and lower respiratory tract as well as headache and fatigue. The authors ruled out psychologic causation.\(^10,18\)

A community based epidemiologic study confirms that persons with a diagnosis of asthma also have a significantly higher degree of illness exacerbation from irritants such as new carpets, scented
products and cleaning agents compared to nonasthmatics. Persons with a diagnosis of hay fever experienced frequent illness exacerbation from irritants such as pesticides and vehicle exhaust. Both groups experienced significant exacerbation from irritants such as drying paint and passive smoke. The authors felt that these responses indicated significantly increased hyperresponsiveness to irritants (reactive airway disease) involving lower (asthmatics) and upper airways. Once occupational asthma has been induced, the majority of affected persons continue to demonstrate asthma symptoms and airway hyperreactivity/hyperresponsiveness years after the initial causal exposure has ceased. This leaves them with a long-standing medical condition involving symptoms triggered by a wide variety of irritants.

Epidemiologic study comparing healthy controls to patients who had upper and lower airway symptoms exacerbated by scented products and other chemical irritants showed that the latter group had neurochemical changes manifesting as sensory hyperreactivity. This was documented by increased levels of nerve growth factor in nasal lavage fluid after, compared to before capsaicin inhalation as well as a dose-dependent cough response. The significant increase of nerve growth factor response was considered by the authors to indicate abnormal pathophysiology in the airways of the hyperreactive patients. Increased nerve growth factor can also increase the number of nerve endings of the olfactory nerve, causing further potential for respiratory irritation at low level exposure. These changes were present in patients who had normal lung function, normal methacholine testing, and normal allergy tests (both groups).

14. R.E. Lenga, Editor, The Sigma-Aldrich Library of Chemical Safety Data, pp. 1-3636, Sigma Aldrich Corporation, Milwaukee, WI.
20. L. Perfetti et al., "Changes in IgE-mediated allergy to ubiquitous inhalants after removal from or diminution of exposure to the agent causing occupational asthma", Clinical and Experimental Allergy 28: 66-73, 1998.