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Host susceptibility to indoor air pollution

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FEV₁ Forced expiratory volume in 1 second

RADS Reactive airways dysfunction syndrome

VOCs Volatile organic compounds

Construction and architectural modifications were introduced in the 1970s as a result of the worldwide energy crisis. The response by the industrialized nations to the energy crisis was provoked because approximately one third of the energy consumed was used in the heating and cooling of indoor air. The approach was to add insulation and reduce building ventilation to

conserve fuel. Older buildings became better insulated, and newer buildings became tighter thermal envelopes, with less fresh air infiltrating into the structure. Windows were eliminated and replaced by mechanical, controlled ventilation in most of the new office buildings. Other types of building changes incorporated were prefabricated exterior sections mounted on steel frames, inoperable windows, heating, ventilation and air-conditioning systems (HVAC) with combined intake and exhaust located on the roofs, greater use of organic-emitting building materials and furnishings, tight construction of homes, less maintenance of buildings because of the complexity, and changes in formulation of cleaning agents used to clean the building's interior. Possibly as a result of all of these changes, many buildings became associated with building-related health complaints.

The precise health significance resulting from a prolonged exposure in a "tight building" or "sick building" is controversial. An important issue is, whether prolonged exposure to poor indoor air quality can lead to a permanent condition, or are the complaints simply an inconvenience with no identifiable illness produced at any time? In 1992 an internationally known allergist's opinion on the "sick building syndrome" was reported as "there is no scientific evidence whatsoever that this syndrome even exists. The majority of these people, we think, have other kinds of problems."¹

The following discussion will deal with host factors and susceptibility to adverse indoor air pollution. An important question is whether the persons affected derive their response because of some preexisting "sensitivity" or "susceptibility" that puts them at an increased risk for evolving symptoms from low levels of indoor air pollutants.

Nonhuman Factors Influencing Responses to Indoor Air Pollutants

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Exposure characteristics of indoor air pollution may be influenced by the location of the source including outdoor sources, building sources, interior furnishings sources, and/or human activities sources.² The sources of indoor air pollution differ considerably. An exposure may be classified by the way it is generated (e.g., combustion), by the type of pollutant group present (e.g., volatile organic compounds [VOCs], fibers), or by location, rate, and pattern of emissions. Some specific examples of sources are combustion of wood and coal, kerosene, and tobacco, building materials and furnishings, products for household cleaning and repair, central heating, cooling, humidifying, and air-conditioning systems, domestic flora and fauna, and outside sources. The chemical attributes of any indoor chemical exposure is important and includes chemical type and reactivity, irritant capacity, chemical bioactivity, concentration or dose, and potential synergism with other accompanying chemicals. Some building materials, furnishings, and household products release pollutants continually, whereas other sources are related to activities carried out in the home or office and release pollutants intermittently. These latter activities include cigarette smoking, house cleaning, and maintenance activities.

Building factors include proceedings essential to building operations and processes, unique working conditions of the persons employed in the building, building maintenance practices, and engineering characteristics such as lighting, temperature, humidity, and fresh air ventilation. Concrete, stone, plywood, particle board, insulation, fire retardants, adhesives, and paints can emit pollutants to the indoor air. There may be off-gassing from building materials, which is greater in newly constructed buildings, and may continue for several months. Radon may be emitted from building materials such as cinder block, aggregate, and building stone. Particle board and plywood (made from formaldehyde-containing resin-bonding agents) can release formaldehyde vapors. Deteriorating or

displaced asbestos and asbestos-containing products (e.g., ceiling and vinyl floor tile, pipe insulation, ceiling plaster, spackling compounds, concrete, and acoustic and thermal insulating materials), which were formerly used extensively in homes, office buildings, and schools, can release asbestos fibers into the air. Wall-to-wall carpeting glued to the floor with adhesives, draperies, of synthetic materials, and furniture constructed with particle board can release various types of VOC chemicals. Other emissions include organic dusts and fibrous glass particles from deteriorating foam cushions and curtains and VOCs from plastic and fabric-covered room dividers. In offices, photocopying machines may emit ozone and VOCs; small refrigerators may leak Freon, blueprint machines may release ammonia, and photographic equipment may release acetic acid. These topics have been discussed elsewhere in these proceedings.

Human activity can influence symptoms. Cooking, heating, smoking, and hobbies can lead to indoor air pollution. Other human activities that potentially contribute to the pollution burden include the use of home office equipment, room deodorizers, furniture polish, disinfectants, carpet shampoos, aerosol sprays, cosmetics, moth crystals, fabric care products, pesticides, cleaning products, personal, and other household products. The indoor use of fuel for heating and cooking can result in a buildup of indoor air carbon monoxide, carbon dioxide, sulfur dioxide, nitrogen oxides, and a variety of VOCs, especially in homes with unvented appliances. One of the most important types of indoor pollution is from tobacco smoke, which contributes to levels of respirable particles, nicotine, polycyclic aromatic hydrocarbons, carbon monoxide, acrolein, nitrogen dioxide, *N*-nitrosodimethylamine, acetone, and benzene.²

Outdoor sources may contribute indoor symptoms. Concentrations of outdoor air pollutants such as ozone, sulfate, aerosols, sulfur dioxide, and metals (e.g., lead, vanadium) are lower indoors than outdoors; levels range between 20% and 80% of the outdoor concentrations²; respirable-sized particles (i.e., “outdoor aerosols”) can also penetrate the indoor environment. Radon in the home, which is also considered an indoor pollutant, originates from the earth and rocks beneath the home, from well water, and from some building materials. Radon enters the home through cracks in concrete walls and floors and floor drains and becomes a problem when it becomes trapped within buildings. The location of a building near a factory emitting toxic smokes and vapors, which enter the fresh air ventilation, may be accountable for causing symptoms among the building's occupants. Accidental spills of irritant chemicals in the vicinity of the building involved may affect buildings downwind from the spill.

Economic factors could conceivably influence the prevalence of symptoms by increasing the use of a product that causes an exposure. There may be a “rush job” requiring increased office personnel activity with many reports produced and duplicated on copying machines and laser printers. There may be increased psychological stress because of employee discontent. Finally, economic factors may preclude an employer from properly maintaining or modifying a building.

Human Factors Influencing Responses to Indoor Air Pollutants

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A number of human factors will influence an individual's response to an indoor air pollutant. ■ Table I list these host factors. The following will discuss some of the factors listed in ■ Table I.

TABLE I. Some host factors affecting susceptibility

Genetic background Species differences	
Age	Nutrition
Gender	Preexisting disease
Tobacco smoking	Physical exertion
Atopy	Preexisting asthma
Airway hyperreactivity	Psychosocial

Genetic factors may be influential in increasing the risk for developing an irritant response, although there is minimal knowledge about this issue. Genetic factors such as individual differences in clearance rates, bronchial and nasal anatomy, and other factors may be important. The site at which antigen or environmental particles come into contact with responding tissue may be an important determinant of the nature and severity of the conjunctival, nasal, or bronchial responses. The number of mast cells are greatest in the terminal bronchioles, and more peripheral distribution of an inhaled pollutant may have more serious consequences. The site of deposition of inhaled particles depends on the anatomic and physiologic status of the airways. In the presence of increased bronchial tone and narrowing, airway radius decreases and deposition occurs more by impaction. The net effect is a more central deposition of inhaled material. As bronchial constriction subsides, the particles can reach more peripheral airways. The normal pulmonary defenses may be impaired by environmental pollutants indigenous to the building, including cigarette smoke, biologic agents, chemicals, and dust. This situation may in turn impair particle clearance, possibly leading to longer persistence of a particulate within the lung.

Tobacco smoking may increase the risk of atopic individuals developing allergic sensitization.^{3 5} A potential mechanism to explain the connection between cigarette smoking and allergic sensitization is that the inhalation of cigarette smoke produces an injury to the bronchial epithelium. Possibly as a result of widening of the tight junctions between epithelial cells, the epithelial injury could enhance bronchial epithelial permeability and lead to increased penetration of antigen through the epithelial layer. Presumably this would increase the possibility of an immunologic response. Passive tobacco smoke is one of the most important types of exposure related to indoor air pollution. Investigations dealing with passive cigarette smoking and adverse health effects have focused on various health outcomes, ranging from heart disease to respiratory diseases in children. Passive smoking is associated with clinically significant childhood asthma. Smoking by the mother or maternal caregiver is the exposure variable most strongly associated with the asthmatic state in children, and maternal smoking increases the risk and severity of asthma or wheezing in children. Because maternal smoking in the households of asthmatic children is common, reduction of this potentially important risk factor should be the target of practitioners and health educators working with the families of asthmatic children.^{6 8} Irritant exposures may provoke consequences similar to cigarette smoking. Environmental exposures to especially irritating agents leads to bronchial mucosal injury and increased deposition of allergens in the submucosa. Animal studies have documented that an antecedent exposure to an airborne irritant enhances allergic sensitization to an allergen. The manifestations of increased permeability from irritant agents may be related to the initiation of

bronchial inflammation.

Atopy and allergic disorders may be important in determining whether a building occupant will react to indoor pollutants. Normal subjects may show small and immediate changes in lung function testing after exposure to environmental tobacco smoke. In contrast, persons who are atopic or have an allergic illness (i.e., asthma or allergic rhinitis) often respond more acutely and vigorously to environmental tobacco smoke. Although a prolonged low-level irritant gas exposure produces some airway inflammation in normal persons, a similar exposure in asthmatic and atopic persons leads to an exaggerated response. Persons with nonspecific airway hyperresponsiveness have more bronchoconstriction and respiratory symptoms with irritant exposures than normal persons. The differences in response may be from the preexisting pathologic alteration in the subjects with airway hyperresponsiveness. For instance it is known that airway epithelial damage can be present in asthmatic subjects (and some atopic persons) who have minimal symptoms and require little or no medication. Bronchial mucosa–mast cell degranulation and mediator release occur continuously among atopic asthmatic subjects.

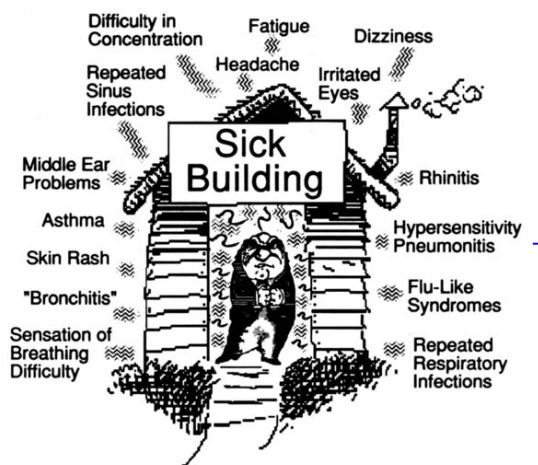
Nonspecific bronchial hyperresponsiveness may be a risk factor for symptoms with exposure to an indoor irritant gas, aerosol, or vapor. The prevalence of bronchial hyperreactivity in the general population is more common than previously suspected. One estimate is 10% to 50% of presumed normal persons, with higher prevalence in the young.^{9 11} In addition, the following have been reported to have demonstrable bronchial hyperreactivity: 47% of persons with cough and no other chest symptom, 40% of patients with rhinitis and vague chest symptoms without clinical asthma, and 22% of persons with rhinitis and no chest symptoms, 47% of cigarette smokers with normal lung function; and in 35% of cigarette smokers without symptoms.^{12 14}

Clinical descriptions

Building-related complaints are often nonspecific and include the ocular, dermatologic, and upper airway complaints as well as systemic symptoms of headache and fatigue. The symptoms are generally not related to a specific substance but are usually attributable to exposures to a combination of substances or to an individual's increased susceptibility (e.g., atopy, preexisting asthma) to lower concentrations of contaminants. In most cases the symptoms are reversible and disappear or ameliorate once the individual leaves the building. Symptoms have been causally linked to various environmental factors including VOC hydrocarbons, wall-to-wall carpets or fleecy material, newer buildings, selected ventilation systems, degree of crowding, passive smoking, molds, and building moisture. The magnitude of the sick building syndrome has not been defined, but an accumulating body of data suggests that it represents a very serious health problem.

The term “building-related illness” refers to specific medical conditions of known cause with objective physical signs and laboratory findings. Such illnesses include asthma, hypersensitivity pneumonia, and respiratory infections (e.g., Legionnaire's disease). ■ Fig. 1 graphically presents various building-related illnesses. In contrast to sick building syndrome, building-related illnesses are caused by a specific contaminant source such as microbial growth in cooling towers and air-handling systems or mold infestation of water-damaged furnishings.

FIG. 1. Various building-related complaints and illnesses; in contrast to sick building syndrome, building-related illnesses are often traceable to a specific contaminant source, such as mold infestation and microbial growth in cooling towers, air-handling systems, and water-damaged furnishings.



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New-onset asthma may be a building-related health issue.¹⁵ To examine the role of irritant exposure in persons with suspected occupational or environmentally induced asthma, clinical information on subjects with a diagnosis of work-related bronchial asthma was analyzed.¹⁶ The study population was identified through a retrospective analysis of the clinical information on all subjects who were referred to the University of South Florida Medical Center and underwent an evaluation during a 3½-year period (June 1989 to December 1992) with a final diagnosis of “asthma.” There were 136 subjects identified and the following data were verified: (1) completeness of the medical, occupational, and environmental history and documentation of whether there was a suspected causal exposure or event, with details concerning duration, quality, intensity, and characteristics; (2) performance of a complete physical examination; (3) performance of spirometry in all and other lung function tests in some; (4) sufficient information to determine if inhalant allergy was present; (5) sufficient information to diagnose or rule out “reactive airways”; (6) availability for review of previous medical records and capacity to document the presence or absence of a preexisting disease to provide the clinical details of an exposure event; (7) sufficient information on the toxicology and analysis of the environment related to the exposure event.

Clinical and environmental/occupational data were systematically extracted and analyzed according to specific definitions and/or diagnostic criteria for various clinical types of asthma. The patient's medical evaluation at the University of South Florida and the results of laboratory testing were analyzed to validate the diagnosis of “asthma” for each subject. The diagnosis of “asthma” required three major findings: (1) the presence of asthma symptoms, including at least three of the following: cough, chest tightness, wheezing, shortness of breath, and “bronchial irritability” symptoms (i.e., response to nonspecific irritants, physical factors, and odorants); (2) the documentation of a “reactive airways”; and (3) a previous diagnosis of asthma made by a physician. The medical

information was also reviewed to determine when the patient first sought medical care, when a diagnosis of “asthma” was first made by a physician, and a physician's written documentation of this diagnosis.

The documentation of “reactive airways” was accepted if one or more of the following were present: (1) an increase in forced expiratory volume in second (FEV₁) values of $\geq 15\%$ after inhalation of a β_2 bronchodilator; (2) a 20% or greater decrease in FEV₁ at a methacholine/histamine concentration of ≤ 16 mg/ml (provocation dose of methacholine/histamine, i.e., PC₂₀); and (3) a decrease in FEV₁ of $\geq 15\%$ after submaximal exercise on a treadmill. The asthma cases were examined to determine when asthma symptoms first manifested.

Allergy was also evaluated because of its importance in the pathogenesis of asthma. An “allergic diathesis” was defined by any one of the following: (1) family history of allergy or asthma; (2) personal history of allergies, hay fever, asthma, or allergic conjunctivitis; (3) at least one positive RAST; (4) at least two positive skin tests; and (5) total IgE of ≥ 250 units/ml.

Of the initially identified 136 patients, 50 were excluded because nine were investigated for alleged asbestos-related disorders but subsequently had nonoccupationally related asthma, 17 did not have asthma, and 24 had insufficient clinical information available. The final study population consisted of 86 subjects (10 men and 46 women) whose ages ranged between 17 and 71 years; 46 (53%) were current or ex-smokers. Four clinical types of asthma were identified: (1) new-onset asthma caused by an irritant exposure, that is, irritant-induced asthma; (2) asthma reactivated by an irritant exposure in a person with preexisting asthma, that is, preexistent asthma; (3) new-onset asthma not related to a workplace irritant or sensitizer exposure, that is, adult-onset asthma, and (4) new-onset asthma exposure to a known sensitizer in the workplace, that is, occupational asthma.

Among the 86 study subjects with asthma, 38 (44%) persons were classified as having irritant-induced asthma, whereas 16 persons (19%) had reactivation of preexisting quiescent asthma after an exposure. Occupational asthma caused by a sensitizer (bakers, toluene diisocyanate, and acrylates) was noted in 11 persons (12%). Twenty-one (24%) subjects were determined to have adult-onset asthma believed not to be of occupational origin. Patients with adult-onset asthma were slightly older (p , not significant) than patients in the other three groups. Review of the available data from the three excluded groups (i.e., asthma/asbestos, not asthma, and insufficient information) did not reveal any obvious differences in age, gender, or other demographic characteristics compared with the study population.

A designation of a “reactive airways” was noted in all 86 subjects; 68 (79%) had methacholine or histamine challenge testing performed. One patient had a normal methacholine challenge but demonstrated profound exercise-induced bronchospasm. Seventeen individuals demonstrated a bronchodilator response of $\geq 15\%$ FEV₁. Of the 68 subjects with a positive methacholine/histamine challenge, the test was positive at a methacholine/histamine concentration (PC₂₀) of ≤ 8 mg/ml in 62 (91%) persons and ≤ 16 mg/ml in six persons. In most, lung function tests reflected mild airflow limitation, whereas six persons showed severe obstructive airways. An “allergic diathesis” was reported in 49 of 86 (57%) subjects, with 25 (66%) occurring in patients with irritant-induced asthma. Thirteen (81%) had preexisting asthma exacerbated by the indoor air problem. Eight (38%) individuals had adult-onset asthma. Only one (9%) patient with occupational asthma had an allergic diathesis.

For 23 of 38 (61%) patients with irritant-induced asthma, the onset of asthma was “sudden” (≤ 24 hours) and considered reactive airways dysfunction syndrome (RADS). In each patient the exposure was massive and related to an accident. The remaining patients with irritant-induced asthma consisted of 15 (39%) persons who did not fit the RADS criteria, and their asthma onset was designated as “not so sudden.” For this latter group, their exposures were more prolonged, and the initiation of their asthma took longer. For the “not so sudden” asthma group, the duration of exposure before initiation of asthma was considered acute (1 to 7 days) in four (10%) persons and subacute (7 to 30 days) in six (16%) individuals. It was designated as prolonged (1 to 3 months) in two (5%) persons and considered chronic (3 to 8 months) in three (8%) patients. Four subjects in the prolonged and chronic groups were part of a “sick building” situation. Careful investigation of these cases documented a sustained low-level irritant exposure. Among the patients with “not so sudden” irritant-induced asthma, 13 of 15 (87%) showed an “allergic diathesis.” This finding suggests that for these asthmatic patients, an “allergic diathesis” appeared important in the initiation of their new-onset asthma. All patients with new-onset asthma associated with building-related pollution had an allergic diathesis.

Discussion

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Irritant exposures have been reported to cause new-onset asthma in exposed individuals.¹⁶⁻¹⁸ High-level irritant exposure can lead to “sudden” onset asthma, designated as RADS.¹⁷ In this scenario, asthma symptoms develop abruptly, usually within minutes or hours, and by definition, within at least 24 hours of the exposure. Any irritant-induced asthma syndrome developing after 24 hours with a “not so sudden onset” is not considered RADS. Variations of this latter clinical response have been reported.¹⁶⁻¹⁸

The hypothesis that there are groups of susceptible persons present in the general population who may be at an increased risk to develop asthma after a rather moderate-level or low-level, prolonged exposure to irritant gases or vapors is provocative. From the new data presented here, asthma initiation that occurs days or weeks after an intermittent and repeated irritant exposure is more likely to occur in the atopic person.¹⁶ This contention assumes that this “susceptible” person most likely had preexisting but asymptomatic nonspecific airway hyperresponsiveness. The irritant exposure in these susceptible persons initiates the onset of asthma, perhaps comparable with a viral respiratory infection or a large allergen load. The hypothesis that a “sensitive” or susceptible subpopulation exists in the general population has been considered by others.¹⁹ Human exposure studies that use low levels of ozone provide evidence, suggesting a subpopulation that is sensitive to irritants.²⁰⁻²¹ In addition, irritant gas induces airway inflammation in normal volunteers, but a similar exposure in asthmatic and atopic persons produces an exaggerated inflammatory response.²²⁻²⁴ Atopic persons may have “leaky” airways with enhanced permeability and a capacity for increase allergen penetration. In such a situation, an irritant exposure may aggravate this occurrence and further increase bronchial permeability and enhance allergen penetration.²⁴

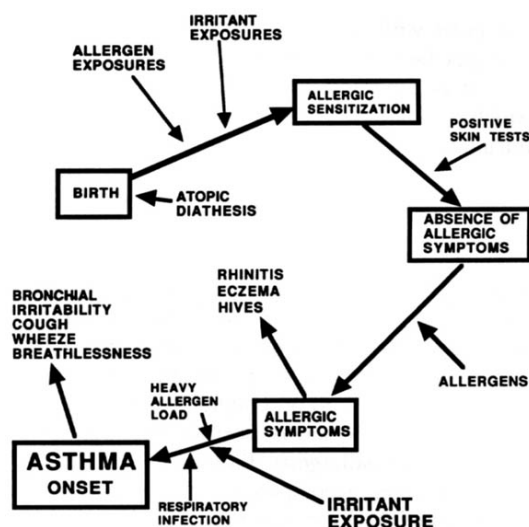
Persons with nonspecific airway hyperresponsiveness respond more adversely to irritant exposures than those persons with normal airways.²⁵⁻²⁶ However, the existence of a hyperresponsive airways

state can be present with very few if any symptoms.⁹⁻¹¹ 30 The prevalence of nonspecific bronchial hyperreactivity in the general population is not uncommon.⁹⁻¹¹ Airway epithelial damage may be preexistent in susceptible persons (i.e., atopic individuals and persons with preexisting airway hyperresponsiveness) who have minimal symptoms and require no medication.²⁷⁻²⁹ Bronchial mucosal–mast cell degranulation and mediator release, which proceeds continuously in atopic and asthmatic subjects, may be an important stimulus in an inflamed bronchial mucosa that is worsened by an irritant exposure.³¹⁻³² An irritant exposure in this group of persons can lead to a cascade of biochemical events that culminates in clinical asthma symptoms.

■ Fig. 2 depicts a proposed scheme in the pathogenesis of new-onset asthma. Certain individuals are born with a tendency to develop IgE-type allergies because of genetic predisposition. The person is exposed to a variety of aeroallergens, which eventually leads to allergic sensitization during the first few years of life. It is possible that concomitant irritant exposures (e.g., tobacco smoke, home aerosol, or cleaning products, etc.) may have an effect on airway permeability and enhance the bronchial mucosal absorption of aeroallergens. Initially, the patient reports few if any allergic symptoms. With further passage of time and continued exposures, the person may continue to have no symptoms or may develop allergic rhinitis and/or conjunctivitis symptoms. Skin testing now shows positive skin tests to a variety of aeroallergens. Pathologic examination of the airways, accomplished by taking a biopsy specimen of the bronchial mucosa, will document changes in bronchial epithelial disruption and mucosal inflammation. Results of a methacholine challenge test are likely to be positive. Thus because of allergic predisposition, this person is at increased risk for developing asthma in the future. Subsequently there is the initiation of a clinical asthma syndrome with cough, wheezing, and dyspnea. In some persons, the initiation of bronchial asthma is caused by a viral respiratory infection (i.e., “adult-onset asthma”); in others it may be related to an exposure to a very heavy concentration of aeroallergens (i.e., “extrinsic asthma”). It is hypothesized that in some susceptible persons, a prolonged irritant exposure can also lead to the initiation of new-onset asthma (i.e., “irritant-induced asthma”). In some patients the irritant exposure is part of an indoor air pollution problem.

FIG. 2. Proposed scheme in pathogenesis of new-onset asthma. Individuals who are born with a genetic predisposition to develop IgE-type allergies have atopic predisposition. Initially the person has few if any allergic symptoms but with passage and continued exposures may continue to have no symptoms or develop allergic rhinitis and/or conjunctivitis symptoms. Results of prick skin tests to various aeroallergens at this point in time are positive; a biopsy of the airways documents bronchial epithelial disruption and mucosal inflammation, and results of methacholine challenge tests are likely to be positive. At some future point, there is initiation of clinical asthma. Initiation of bronchial asthma may be the result of a viral respiratory infection (i.e., “adult-onset asthma”); in others it may be related to an exposure to aeroallergens (i.e., “extrinsic asthma”).

A prolonged irritant exposure in some persons leads to new-onset asthma (i.e., "irritant-induced asthma").



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The role of allergic rhinitis in nasal responses to sudden temperature changes

Journal of Allergy and Clinical Immunology, The

November 2006 • Volume 118 • Number 5

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