mechanical factors may contribute, it may also be linked to the pro-inflammatory adipokines and reduced anti-inflammatory adipokines that are released from fat stores.

Other Factors Several other factors have been implicated in the etiology of asthma, including lower maternal age, duration of breast-feeding, prematurity and low birthweight, and inactivity, but are unlikely to contribute to the recent global increase in asthma prevalence. There is also an association with acetaminophen (paracetamol) consumption in childhood, which may be linked to increased oxidative stress.

Intrinsic Asthma A minority of asthmatic patients (approximately 10%) have negative skin tests to common inhalant allergens and normal serum concentrations of IgE. These patients, with nonatopic or intrinsic asthma, usually show later onset of disease (adult-onset asthma), commonly have concomitant nasal polyps, and may be aspirin-sensitive. They usually have more severe, persistent asthma. Little is understood about mechanism, but the immunopathology in bronchial biopsies and sputum appears to be identical to that found in atopic asthma. There is recent evidence for increased local production of IgE in the airways, suggesting that there may be common IgE-mediated mechanisms; staphylococcal enterotoxins, which serve as "superantigens," have been implicated.

Asthma Triggers Several stimuli trigger airway narrowing, wheezing, and dyspnea in asthmatic patients. Although a previous view held that these stimuli should be avoided, the triggering of asthma by these stimuli is now seen as evidence for poor control and an indicator of the need to increase controller (preventive) therapy.

ALLERGENS Inhaled allergens activate mast cells with bound IgE directly leading to the immediate release of bronchoconstrictor mediators, resulting in the early response that is reversed by bronchodilators. Often, experimental allergen challenge is followed by a late response when there is airway edema and an acute inflammatory response with increased eosinophils and neutrophils that are not very reversible with bronchodilators. The most common allergens to trigger asthma are *Dermatophagoides* species, and environmental exposure leads to low-grade chronic symptoms that are perennial. Other perennial allergens are derived from cats and other domestic pets, as well as cockroaches. Other allergens, including grass pollen, ragweed, tree pollen, and fungal spores, are seasonal. Pollens usually cause allergic rhinitis rather than asthma, but in thunderstorms, the pollen grains are disrupted and the particles that may be released can trigger severe asthma exacerbations (thunderstorm asthma).

VIRUS INFECTIONS Upper respiratory tract virus infections such as rhinovirus, respiratory syncytial virus, and coronavirus are the most common triggers of acute severe exacerbations and may invade epithelial cells of the lower as well as the upper airways. The mechanism whereby these viruses cause exacerbations is poorly understood, but there is an increase in airway inflammation with increased numbers of eosinophils and neutrophils. There is evidence for reduced production of type I interferons by epithelial cells from asthmatic patients, resulting in increased susceptibility to these viral infections and a greater inflammatory response.

PHARMACOLOGIC AGENTS Several drugs may trigger asthma. Beta-adrenergic blockers commonly acutely worsen asthma, and their use may be fatal. The mechanisms are not clear, but are likely mediated through increased cholinergic bronchoconstriction. All β blockers need to be avoided, and even selective β_2 blockers or topical application (e.g., timolol eye drops) may be dangerous. Angiotensin-converting enzyme inhibitors are theoretically detrimental as they inhibit breakdown of kinins, which are bronchoconstrictors; however, they rarely worsen asthma, and the characteristic cough is no more frequent in asthmatics than in nonasthmatics. Aspirin may worsen asthma in some patients (aspirin-sensitive asthma is discussed below under "Special Considerations").

EXERCISE Exercise is a common trigger of asthma, particularly in children. The mechanism is linked to hyperventilation, which results in increased osmolality in airway lining fluid and triggers mast cell mediator release, resulting in bronchoconstriction. Exercise-induced asthma (EIA) typically begins after exercise has ended and resolves spontaneously within about 30 min. EIA is worse in cold, dry climates than in hot, humid conditions. It is, therefore, more common in sports activities such as cross-country running in cold weather, overland skiing, and ice hockey than in swimming. It may be prevented by prior administration of β_2-agonists and antileukotrienes, but is best prevented by regular treatment with ICSs, which reduce the population of surface mast cells required for this response.

PHYSICAL FACTORS Cold air and hyperventilation may trigger asthma through the same mechanisms as exercise. Laughter may also be a trigger. Many patients report worsening of asthma in hot weather and when the weather changes. Some asthmatics become worse when exposed to strong smells or perfumes, but the mechanism of this response is uncertain.

FOOD AND DIET There is little evidence that allergic reactions to food lead to increased asthma symptoms, despite the belief of many patients that their symptoms are triggered by particular food constituents. Exclusion diets are usually unsuccessful at reducing the frequency of episodes. Some foods such as shellfish and nuts may induce anaphylactic reactions that may include wheezing. Patients with aspirin-induced asthma may benefit from a salicylate-free diet, but these are difficult to maintain. Certain food additives may trigger asthma. Metabisulfite, which is used as a food preservative, may trigger asthma through the release of sulfur dioxide gas in the stomach. Tartrazine, a yellow food-coloring agent, was believed to be a trigger for asthma, but there is little convincing evidence for this.

AIR POLLUTION Increased ambient levels of sulfur dioxide, ozone, and nitrogen oxides are associated with increased asthma symptoms.

OCCUPATIONAL FACTORS Several substances found in the workplace may act as sensitizing agents, as discussed above, but may also act as triggers of asthma symptoms. Occupational asthma is characteristically associated with symptoms at work with relief on weekends and holidays. If removed from exposure within the first 6 months of symptoms, there is usually complete recovery. More persistent symptoms lead to irreversible airway changes, and thus, early detection and avoidance are important.

HORMONES Some women show premenstrual worsening of asthma, which can occasionally be very severe. The mechanisms are not completely understood, but are related to a fall in progesterone and in severe cases may be improved by treatment with high doses of progesterone or gonadotropin-releasing factors. Thyrotoxicosis and hypothyroidism can both worsen asthma, although the mechanisms are uncertain.

GASTROESOPHAGEAL REFLUX Gastroesophageal reflux is common in asthmatic patients because it is increased by bronchodilators. Although acid reflux might trigger reflex bronchoconstriction, it rarely causes asthma symptoms, and antireflux therapy usually fails to reduce asthma symptoms in most patients.

STRESS Many asthmatics report worsening of symptoms with stress. Psychological factors can induce bronchoconstriction through cholinergic reflex pathways. Paradoxically, very severe stress such as bereavement usually does not worsen, and may even improve, asthma symptoms.

PATHOPHYSIOLOGY

Asthma is associated with a specific chronic inflammation of the mucosa of the lower airways. One of the main aims of treatment is to reduce this inflammation.

Pathology The pathology of asthma has been revealed through examining the lungs of patients who have died of asthma and from bronchial biopsies. The airway mucosa is infiltrated with activated eosinophils and T lymphocytes, and there is activation of mucosal mast cells. The degree of inflammation is poorly related to disease