Asthma

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Asthma is a major chronic inflammatory disorder of the airways that is characterized by sporadic attacks of breathlessness, coughing and wheezing. Both genetic and environmental factors appear to play a role in the disease which poses a serious public health problem throughout the world.

Introductory article

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Introduction and Definition

Asthma is a major chronic airway disorder that poses a serious public health problem in countries throughout the world. It affects about 10% of the world's population and is an important cause of respiratory morbidity and mortality. The term 'asthma' was first used by Hippocrates (460–357 BC) to describe 'episodic shortness of breath' of any cause. In 1556, Agricola defined asthma as episodic breathlessness due to bronchial disease, while Henry Hyde Salter in 1860 described narrowing of the airways due to smooth muscle contraction as the major underlying mechanism for symptoms of asthma. However, with the advent of new research tools and rapid advances in the fields of immunology and molecular biology, asthma is now recognized to involve chronic airway inflammation, which underlies disordered airway function and symptomatology. Despite substantial advances in our understanding of the pathogenesis, clinical characteristics and genetics of asthma, an all-encompassing definition remains difficult to construct. A recent international consensus document provides the following description:Asthma is a chronic inflammatory disorder of the airways in which many cells play a role, in particular mast cells, eosinophils and T lymphocytes. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough particularly at night and/or in the early morning. These symptoms are usually associated with widespread but variable airflow limitation that is at least partly reversible either spontaneously or with treatment. The inflammation also causes an associated increase in airway hyperresponsiveness to a variety of stimuli. [In: *Global Initiative for Asthma: Global Strategy for Asthma Management and Prevention*. NHLBI/WHO Workshop, NIH Publication 95-3659. Bethesda, MD: NIH.]

Incidence and Prevalence

There is growing evidence that the incidence of asthma is increasing worldwide. Asthma affects individuals of all ages, but predominates in early life among children from westernized countries, with about one-half of all cases developing before the age of 10 years and another third occurring before age 40 years. Childhood asthma is more frequent in boys than girls (2:1), while during adolescence and adulthood the prevalence in females tends to equal or exceed that in males. The incidence of asthma in children aged under 5 years is 8.1–14 per 1000 per year for boys and 4.3–9 per 1000 per year for girls, while for all age groups the incidence of asthma has been estimated to lie between 2.65 and 4 per 1000 per year.

There is wide variation in the prevalence of asthma between populations. Higher rates have been found among children from westernized countries than in developing countries and in those from warmer climates compared to temperate regions. According to the International Survey of Asthma and Allergy in Children, the prevalence of asthma varies worldwide between 4% and 48% in 13–14 year olds and between 4.1% and 28.8% in adults. The highest figures occurred in children from New Zealand, Australia, the UK and the Republic of Ireland, while countries in eastern Europe, Asia and Africa have low rates.

Compared with other chronic lung diseases, the mortality rate for asthma is small, in part because most asthma is in young people and because asthmatic airway obstruction is usually reversible. Most recent figures indicate fewer than 5000 deaths per year out of a population of approximately 10 million patients at risk. Death rates, however, appear to be rising in some countries, whereas in others, possibly due to more effective treatment, they have stabilized or declined.

Factors Influencing the Development of Asthma

Genetic factors and atopy

It is well established that asthma and allergies (atopy) have an important hereditary component, the heritability being estimated to be between 40% and 60%. Parental (especially maternal) history of asthma and atopy is thought to have a powerful influence on the development of childhood asthma. However, despite overwhelming evidence of an important genetic component, controversy still exists over the mode of inheritance of both atopy and asthma, probably because multiple genes with major and minor effects are involved. Several genes have been implicated in asthma pathophysiology (**Table 1**). Family studies suggest that genetic and environmental components are required before asthma becomes evident (**Figure 1**).

Table 1 Genes implicated in the pathophysiology of asthma

Chromosomal location	Candidate genes
5q31	IL-3, IL-4, IL-5, IL-9, IL-13, GM-CSF
5q32	β_2 adrenoreceptor
6p	HLA complex
6p21-23	TNFα
11q13	FcεRI
12q	Constitutive form of nitric oxide synthase
	Mast cell growth factor
13q	Esterase D protein
14q	T-cell receptor $\alpha\beta$ complex

Atopy, defined as an increased predisposition to develop immunoglobulin (Ig) E antibodies to various antigens and/or one or more positive skin-prick tests to common aeroallergens, rhinitis or conjunctivitis, is the most important risk factor yet identified for the development of asthma, increasing the risk by 10–20-fold compared with those who are nonatopic. The commonest allergens identified by skin-prick tests as significant triggers are house-dust mites, cats, fungal spores, pollen and cockroaches. Although the majority of asthma is associated with atopy, some 30% of asthmatics are nonatopic, particularly patients with adult-onset asthma. These include aspirin-sensitive patients whose chronic severe asthma is exacerbated by exposure to aspirin and other nonsteroidal antiinflammatory drugs (NSAIDs).

Early life environmental factors

Intrauterine environmental factors may in part account for the maternal influence over the immune response of the progeny in favour of atopy. The effects of gestational

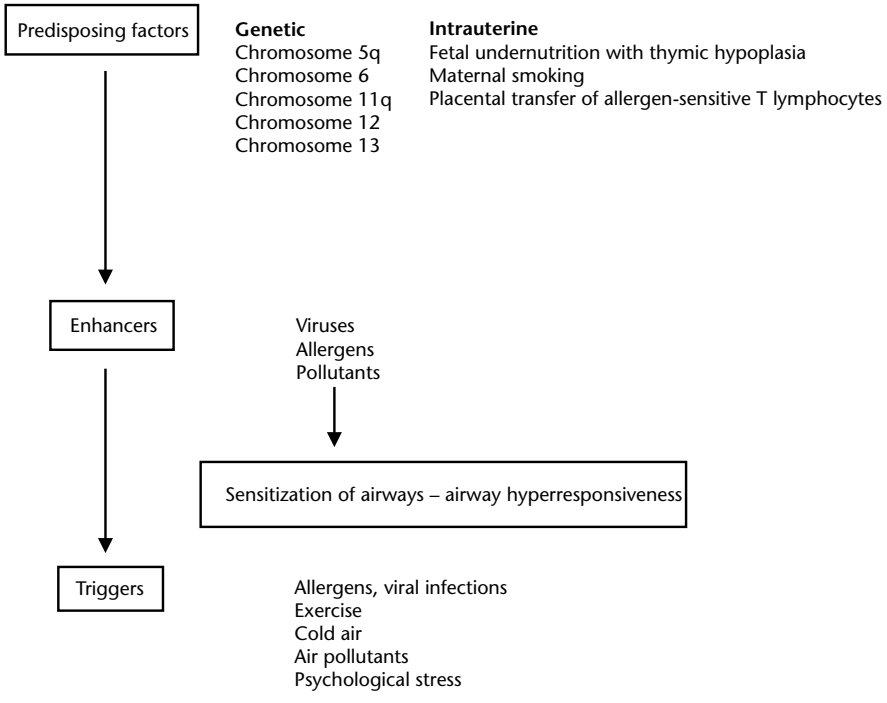

Figure 1 Factors influencing the development of asthma.

allergen exposure may be modulated by adjuvant factors including maternal smoking, which raises cord blood IgE levels and impairs lung function, and by fetal nutrition. Disproportionate fetal growth (large head and small trunk), which is often linked with a birthweight of less than 2.5 kg, has been shown to be associated with an increased risk of developing asthma during childhood or adolescence. Exposure to allergens *in utero* and during the first year of life appears to be important in many children who later develop allergic disorders. Exposure to viruses and air pollutants (especially environmental tobacco smoke) has also been identified as an important early life risk factor for the development of asthma, the level of exposure determining both the age of onset and severity of symptoms.

Other environmental factors

Indoor and outdoor allergens

The commonest allergens provoking asthma are proteins in the faecal particles of the house-dust mite *Dermatophagoides pteronyssinus* and protein components of wind-dispersed pollens from grasses (rye, couch, timothy), weeds (ragweed, mugwort) and trees (birch, alder). Mould spores (*Aspergillus*), bird feathers, and animal danders and urine (cat, dog, rodents) also contain common allergens. Allergens sensitize atopic subjects by stimulating the development of specific T-lymphocyte clones and the production of specific IgE antibodies. Once sensitized, re-exposure to the same allergen predisposes to the development of allergic inflammation and asthma exacerbations. Pollen allergen from trees, grasses and weeds, and fungal spores are the commonest outdoor allergens that cause asthma in susceptible people.

Occupational sensitizers

Occupational antigens include animal and plant proteins associated with farming, animal breeding, brewing and baking, bacterial enzymes used in detergents, and relatively small molecules that may sensitize only after haptenization, including oil paints, heavy metals and their salts.

Drugs and food additives

Drugs such as aspirin and other NSAIDs, antibiotics, food preservatives, monosodium glutamate and some food-colouring agents are recognized risk factors for the exacerbation of asthma symptoms.

Air pollution

Asthma is more frequent in industrialized countries. Air pollutants emitted from vehicular exhausts and industrial sources, such as ozone, nitrogen oxides, acidic aerosols and particulate matter, have been shown to be significant risk factors for the development of asthma exacerbations. There is, however, little evidence that air pollution is directly responsible for the increased prevalence of asthma in these countries.

Diet

The influence of diet on asthma has not been properly examined. Conflicting data have been reported about the protective role of breastfeeding for the development of asthma. Increased salt intake and reduced fish intake have been associated with an increased prevalence of asthma. There is some evidence that food allergy in infancy is followed by asthma.

Region of residence

Transfer from an urban to a rural environment appears substantially to increase the likelihood of developing childhood asthma. These increases are most likely due to environmental factors, in particular aeroallergens, which provoke expression of asthma symptoms in susceptible individuals in the new location.

Asthma triggers

Triggers are risk factors that cause asthma exacerbations by inducing inflammation or provoking acute bronchoconstriction or both. Allergens, exercise, cold air, irritant gases, air pollutants, weather changes, extreme emotional expression, viral respiratory infections, food additives, NSAIDs and other drugs, rhinitis, sinusitis and nasal polyposis are important triggers for asthma.

Pathophysiology

Histopathology of the asthmatic airway

Recent descriptions of asthma stress the chronic underlying airway inflammation that is linked to bronchial hyperresponsiveness to nonspecific triggers, including allergens, exercise/cold air, aspirin-like drugs, air pollutants and occupational chemicals. Major advances in understanding the inflammatory causes of episodic airway obstruction in asthma have come from investigation of pathological changes in bronchial mucosal biopsies and bronchoalveolar lavage fluid obtained at fibreoptic bronchoscopy. Even in relatively mild asthma, changes include mucus hypersecretion, airway oedema, epithelial desquamation, goblet cell hyperplasia, smooth muscle hypertrophy, infiltration of the bronchial wall with eosinophils and T lymphocytes, activation of mast cells, and deposition of collagen beneath the basement membrane (**Figure 2**).

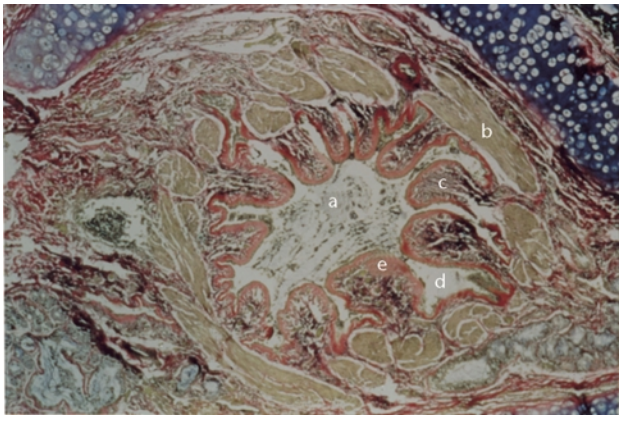

Figure 2 Pathology of the asthmatic airway. (a) mucous plugging; (b) smooth muscle hypertrophy; (c) thickening of basement membrane; (d) loss of epithelium; (e) mucus gland hypertrophy.

T lymphocytes

The T lymphocyte is a critical orchestrator of the response to allergen exposure as it is the T-cell receptor (TCR) that defines the specificity of the immune response by regulating the production of allergen-specific IgE by B lymphocytes. Allergic disease is associated with T-cell clones of the T helper cell 2 (T_H2) phenotype, most of which are allergen specific, and which express cytokines of the interleukin (IL)-4 gene cluster on chromosome 5q31–33, including granulocyte–macrophage colony-stimulating factor (GM-CSF), IL-4, IL-5, IL-9 and IL-13, but not IL-2 or interferon (IFN) γ. In contrast, delayed-type hypersensitivity reactions such as tuberculosis are associated with the T_H1 phenotype in which IFNγ, tumour necrosis factor (TNF) β and IL-2 are produced, but not IL-4 or IL-5. One hypothesis suggests that T_H1 responses are promoted by early life exposure to bacterial infections. The rising prevalence of allergic disease may be associated with reduced rates of bacterial infection in childhood, allowing T_H2-type responses to predominate in later life.

Epitopes on allergens are recognized by dendritic cells, and processed fragments are presented to T cells by an interaction involving major histocompatibility complex (MHC) class II molecules and the TCR (**Figure 3**). Costimulatory molecules are also required, including adhesion molecules. In the presence of IL-4, T cells are polarized to differentiate along the T_H2 pathway with further expression of cytokines of the IL-4 gene cluster. Continued expression by T_H2 cells of IL-4 and IL-13 and their action at specific receptors on B cells induces isotype switching from IgM and IgG to IgE and IgG4, involved in the process of allergen sensitization. In a positive feedback loop, IL-13 also promotes differentiation of dendritic cells, the antigen-presenting cells in the bronchial mucosa. Isotype switching to IgE by IL-4 is potently inhibited by IFNγ from T_H1 cells and macrophages.

Bronchoconstrictor mediators

In asthmatics who are atopic or whose asthma is linked to a specific sensitizing chemical, inhalation challenge results in an early bronchoconstrictor ('asthmatic') response (EAR) at 5–10 min lasting for up to 1 h and, in about half the subjects, a late bronchoconstrictor response (LAR) starting at 2–3 h and lasting for 3–12 h. The critical allergen interaction is the crosslinking of specific IgE molecules bound to high-affinity IgE receptors (FcεRI), expressed on mast cells, basophils, dendritic cells and eosinophils. Low-affinity IgE receptors (FcεRII) are expressed on macrophages, eosinophils and platelets. Crosslinkage of FcεRI on mast cells leads to the release of a range of inflammatory mediators, both preformed (histamine, heparin and tryptase) and newly synthesized (the cysteinyl leucotriene LTC_4 and prostaglandin (PG) D_2).

Histamine is a bronchoconstrictor and vasodilator acting at H_1 receptors on bronchial and vascular smooth muscle. Tryptase is a 130-kDa tetrameric protein that increases microvascular permeability, upregulates adhesion molecules, activates eosinophils, and promotes activation and proliferation of fibroblasts, epithelial cells and endothelial cells. PGD_2 is a bronchoconstrictor and mucus secretagogue acting at the thromboxane receptor. The cysteinyl leucotrienes LTC_4, LTD_4 and LTE_4 comprise the slow-reacting substance of anaphylaxis (SRS-A) and act at specific $CysLT_1$ receptors to produce long-lived bronchoconstriction, microvascular leakage and mucus secretion. They may also induce bronchial hyperresponsiveness and chemoattract eosinophils. Drugs that block the synthesis or activity of leucotrienes block most of the EAR following allergen challenge, whereas NSAIDs, which block prostanoid synthesis, and histamine receptor antagonists have little effect. Cysteinyl leucotrienes and histamine also contribute to bronchoconstriction in the LAR.

Leucocyte recruitment

Increases in bronchial responsiveness during the LAR are associated with selective recruitment of eosinophils into the lung from the vasculature, and these are eventually replenished by proliferation and release of eosinophil precursors from the bone marrow. Monocytes, lymphocytes, basophils and neutrophils may also be recruited. Eosinophil recruitment, activation in the vasculature, proliferation and enhanced survival are regulated by eosinophilopoietic cytokines including GM-CSF, IL-3 and IL-5. These are released by activated mast cells and T lymphocytes in the lung and act as paracrine and endocrine factors. The initial barrier to eosinophil recruitment in the lung is the vascular endothelium. Adhesion and migration of eosinophils are regulated by cell adhesion molecules (CAMs) expressed on the leucocyte and endothelial cell. Carbohydrate ligands (e.g. sialyl-Lewis

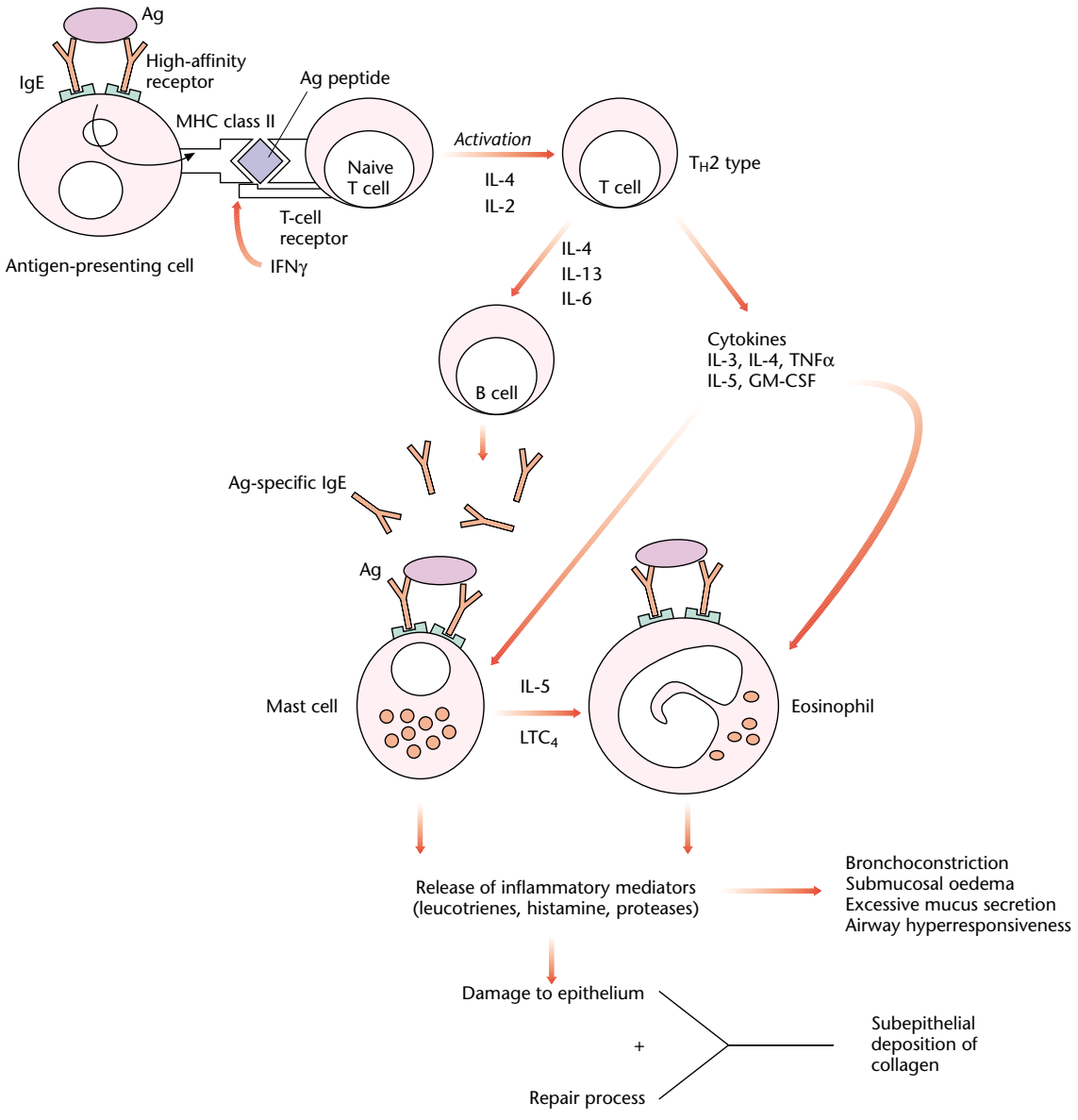

Figure 3 Allergen sensitization and the role of cytokines in asthma pathogenesis. Ag, antigen; GM-CSF, granulocyte–macrophage colony-stimulating factor; IFN, interferon; Ig, immunoglobulin; IL, interleukin; LTC_4, leucotriene C_4; T_H2, type 2 T helper cell; TNF, tumour necrosis factor.

X) on eosinophils initially interact loosely with lectin-binding regions of P-, L- and E-selectins, causing the leucocyte to roll along the endothelial wall. Selectin expression on endothelium is upregulated rapidly by histamine, leucotrienes and platelet-activating factor (PAF), and more slowly by proinflammatory cytokines including IL-1, TNFα and IFNγ. Eosinophil rolling is arrested by the interaction of leucocyte integrins including leucocyte functional antigen 1 (CD11a–CD18) with intercellular adhesion molecule 1 found on the endothelium. Flattening of the eosinophil on the endothelial wall is the first stage in its transendothelial migration. Selective recruitment of eosinophils may depend on interactions between the leucocyte integrin 'very late antigen' (VLA) 4, which is found on eosinophils but not neutrophils, and vascular cell adhesion molecule 1 (VCAM-1) on endothelium. VCAM-1 is upregulated by IL-1 or TNFα, but its expression persists only in combination with IL-4 or IL-13 released by mast cells, basophils and Tcells.

The eosinophil is a terminally differentiated cell with an important armoury of inflammatory mediators, toxic oxygen radicals and basic proteins. These include cysteinyl

leucotrienes and PAF, and proinflammatory cytokines such as GM-CSF, IL-3, IL-5, IL-8, TNFα, RANTES (regulated on activation normal T cell expressed and secreted) and eotaxin. These factors may act in an autocrine or paracrine fashion to prime and chemoattract eosinophils for enhanced mediator release and survival.

The eosinophil is the cell most closely implicated in bronchial epithelial damage in asthma. Clumps of shed epithelial cells (Creola bodies) are found in the sputum of symptomatic asthmatics, and stripping of the pseudostratified ciliated epithelium down to the basal cell layer occurs over large areas in the post-mortem lung of patients with status asthmaticus. In mild to moderate asthma, the epithelial cleavage occurs along the line of desmosomes in the plane between the columnar and basal cells. Damage to the desmosomes may occur by the release of tryptase from mast cells, or metalloproteases (e.g. matrix metalloproteinase 9) from eosinophils, or by the action of the arginine-rich basic proteins eosinophil cationic protein (ECP), major basic protein (MBP) or eosinophil peroxidase. MBP in particular is highly cytotoxic to bronchial epithelium and is found in high quantities in asthmatic sputum. Deposits of MBP and ECP are found specifically in areas of epithelial loss in post-mortem asthmatic lung.

Airway remodelling

The loss of bronchial epithelium and its ciliary layer impairs mucus clearance and allows greater access of allergens and noxious stimuli to the bronchial smooth muscle and to sensory nerve receptors, and also initiates a heightened epithelial repair response, altering its phenotype to one able to support both inflammation and airway remodelling. The latter response is mediated by the release of platelet-derived growth factor, endothelin-1 and basic fibroblast growth factor, and leads to the proliferation of subepithelial myofibroblasts. In the presence of transforming growth factor β, these myofibroblasts lay down types III and V collagen and other matrix proteins such as tenascin, β-laminin and versican, giving rise to the appearance of a 'thickened basement membrane'. Thus chronic inflammation in the asthmatic lung is associated with proliferative and repair processes which may extend through the mucosa to involve nerves, blood vessels and smooth muscle, and the deposition of new matrix in the submucosa and adventitia. Understanding the way in which this progression is regulated by cytokines released by epithelium, macrophages and fibroblasts may be of fundamental importance in understanding the dynamic relationship between inflammatory and repair processes in asthma and how these lead to disease chronicity.

Clinical Features and Diagnosis

Asthma is recognized by a characteristic pattern of symptoms including wheeze, cough, chest tightness and dyspnoea, and is best confirmed by evidence of variable or reversible airflow obstruction accompanying symptoms. In children, asthma usually presents only as nocturnal or postexercise cough. Wheeze, a polyphonic sound, may be present on inspiration as well as expiration and is generally thought to be the cardinal symptom of asthma. It is produced by vibrations set up in the narrowed airways, and is often detectable only on exercise and forced expiration. Some asthmatics do not experience wheeze and only report other airway symptoms.

Although these symptoms are also found in other respiratory conditions, a diagnosis of asthma is suggested by their episodic nature and by diurnal variability, with symptoms waking sufferers in the early hours of the morning (3–5 a.m.) or on waking at the normal time. A nocturnal influx of activated T cells and eosinophils into the lung periphery has been shown to be closely linked to nocturnal asthma but the mechanisms for this have yet to be defined.

Airway hyperresponsiveness is the cardinal pathophysiological feature of the asthmatic airway and often correlates with disease severity. It is defined as decreased threshold of airway narrowing in response to a variety of nonspecific stimuli that under healthy conditions do not evoke an airway obstruction. These nonspecific stimuli include pharmacological agents (histamine, methacholine, adenosine), exercise, cold air, fog, tobacco smoke, viral infections, inorganic dusts, perfumes, volatile organic compounds and chemical irritants. Airway hyperresponsiveness is absent in some patients with other clear evidence of asthma and may variably be present in some people without significant respiratory symptoms. Evidence of variable or reversible airflow obstruction, such as a 15% increase in forced expiratory volume in 1 s (FEV_1) or peak expiratory flow (PEF) occurring spontaneously or with treatment, is helpful if present. However, asthmatic patients who smoke or work in highly polluted atmospheres may develop less reversible disease, whereas some patients develop irreversible disease despite being life-long nonsmokers.

Differential Diagnosis

Upper airway obstruction by tumour, laryngeal oedema or glottic dysfunction can occasionally be confused with asthma. Persistent wheezing localized to one area of the chest in association with paroxysms of cough indicates endobronchial disease such as foreign-body aspiration, neoplasm or bronchial stenosis. The signs and symptoms of acute left ventricular failure may also mimic asthma.

Recurrent episodes of bronchospasm occur with carcinoid tumours, recurrent pulmonary emboli and chronic bronchitis. In chronic obstructive pulmonary disease there are no true symptom-free periods and a history of chronic cough and sputum production can usually be obtained as a background upon which acute attacks of wheezing are superimposed. Eosinophilic and chemical pneumonias are also often associated with symptoms of asthma.

Management

Asthma is a chronic disorder which often remits spontaneously in some individuals. With the recognition that asthma is a chronic inflammatory disorder of the airways, and that the accompanying inflammation causes recurrent episodes of symptoms, variable airflow limitation and increased airway responsiveness, treatment of the underlying inflammation and elimination of the causative agent(s) from the environment are the most successful means available for treating this condition. Numerous clinical studies have shown that persistent asthma is more effectively controlled by intervening to suppress and reverse the inflammation than by treating only the bronchoconstriction and related symptoms. Guidelines for asthma management stress a stepwise approach to the treatment of persistent asthma of varying severity (**Figure 4**).

Pharmacological control of asthma can be achieved with antiinflammatory 'controller' medications, of which the most effective at present are the inhaled corticosteroids. Corticosteroids interact with cytosolic receptors and with nuclear transcription factors, themselves interacting with gene promoter regions, to modulate the expression of inflammatory genes, including those for cytokines, adhesion molecules and mediator-synthesizing enzymes. In the airways, inhaled corticosteroid therapy reduces the numbers and activation status of mast cells, eosinophils and T cells, and reduces the number and severity of acute asthma exacerbations. Corticosteroids have to be used daily on a long-term basis to achieve and maintain control of persistent asthma. Systemic adverse effects are rare with inhaled corticosteroids even at high doses, and oral thrush and dysphonia can be reduced by the use of spacer devices. A burst or cycle of oral corticosteroids is often used when initiating long-term therapy for a patient with uncontrolled asthma or during a period when the patient experiences a gradual decline in their condition. Although longer-term oral corticosteroid therapy is sometimes required to control severe persistent asthma, its use is limited by the risk of systemic adverse effects, which include osteoporosis, arterial hypertension, diabetes, cataracts, obesity, muscle weakness, skin thinning and easy bruisability, suppression of the hypothalamic–pituitary–adrenal axis and peptic ulceration.

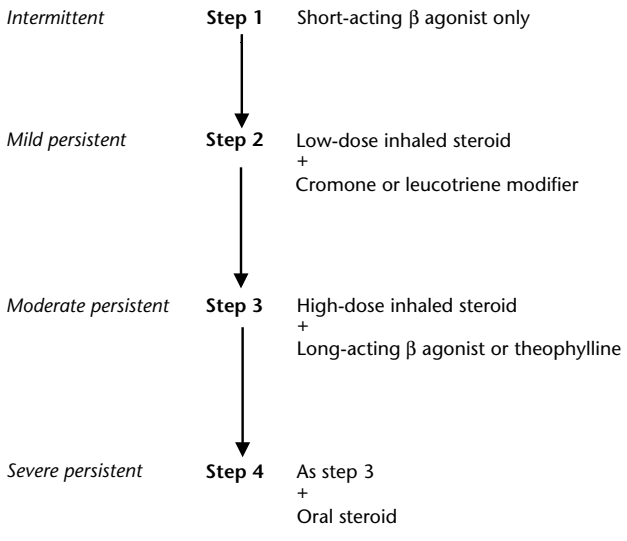

Figure 4 Stepwise management of chronic asthma.

Cysteinyl leucotrienes play an important role in bronchoconstriction and chronic airway inflammation in asthma. Inhibitors of leucotriene synthesis such as zileuton and cysteinyl leucotriene receptor antagonists such as montelukast and zafirlukast are significant new antiasthma drugs that have become available for oral maintenance therapy within the past 2 years. Antiallergic compounds such as ketotifen and antihistamines may be helpful in some asthmatics. Other controller medications include sustained release theophylline, long-acting β_2-adrenergic agonists (inhaled salmeterol, formoterol, oral bambuterol and slow-release terbutaline), and the 'mast cell stabilizing drugs' sodium cromoglycate and nedocromil sodium. Although these drugs improve baseline lung function and reduce the severity of asthma exacerbations, their capacity to suppress airway inflammation is unclear.

Short-acting bronchodilators (inhaled salbutamol, terbutaline) are used as rapid-onset 'reliever' medications to reverse acute manifestations of asthma such as respiratory symptoms and airflow limitation. They act selectively at β_2-adrenergic receptors to raise intracellular levels of cyclic adenosine, causing relaxation of bronchial smooth muscle and reduced release of mediators from mast cells, but they do not reverse airway inflammation. Severe exacerbations of asthma are managed by close monitoring of the patient's condition and response to treatment with serial measurements of lung function. Quite often patients need to be admitted to hospital and therapy started with oral corticosteroids, oxygen and subcutaneous adrenaline (epinephrine) along with nebulized β_2 agonists.

Identification and control of triggers is an important step in the management of asthma, preventing exacerbations, reducing symptoms and the requirement for medication, and in the long term decreasing airway inflammation and hyperresponsiveness. Some triggers

may be easier for susceptible patients to avoid than others. Prompt measures to avoid further exposure to chemical sensitizers as soon as occupational asthma has been recognized help to prevent the development of irreversible airflow obstruction. Desensitization or immunotherapy with extracts of the suspected allergens has enjoyed widespread favour, but controlled studies are limited and have not shown unequivocal efficacy.

A combination of increased awareness, enabling early recognition of the disorder, sensible application of effective prophylactic therapies, and education to ensure that management is optimal has succeeded in reducing much of the fear inspired by asthma and made it controllable in most sufferers. However, asthma cannot be cured. Although remissions occur, relapse is also frequent and continuous treatment over many years is a fact of life for most asthmatics.

Prognosis and Clinical Course

Evidence suggests a good prognosis for 50–80% of all patients with asthma, particularly those in whom disease is mild and develops in childhood. Spontaneous remissions occur in approximately 50% of patients who develop asthma during childhood and in 20% of those who develop asthma as adults. Even when untreated, asthmatics do not progress inexorably from mild to severe disease over time, the clinical course being characterized instead by exacerbations and remissions. Although some patients with asthma develop irreversible changes in lung function, these individuals frequently have comorbid stimuli such as cigarette smoking that could account for the findings.

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