Clinical phenotypes of asthma
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Purpose of review
Asthma is a phenotypically heterogeneous disorder and, over the years, many different clinical subtypes of asthma have been described. A precise definition of asthma phenotypes is now becoming more and more important, not only for a better understanding of pathophysiologic mechanisms, but in particular to ascertain the specific genes associated with these phenotypes.

Recent findings
In children, three asthma phenotypes are now well defined: transient infant wheezing, nonatopic wheezing of the toddler, and IgE-mediated wheezing/asthma. Recently, a fourth phenotype, late-onset childhood asthma has been added to this list. In adults, asthma persisting from childhood into adulthood should be distinguished from asthma starting in adulthood. The phenotypes of adult-onset asthma are still poorly defined. Until now, phenotypic classification has been based primarily on etiologic factors (eg, aspirin sensitivity, persistent respiratory infections, occupational factors, or toxic exposures) or clinical characteristics of the disease (eg, mild, severe, brittle, near fatal, with fixed airflow obstruction, steroid resistant). Novel noninvasive techniques to assess the type and severity of airway inflammation and dysfunction are increasingly used to identify better the different phenotypes.

Summary
The classic phenotype of IgE-mediated asthma starting in childhood is now clearly defined. However, many other phenotypes of asthma in childhood as well in adulthood are being recognized. In particular, asthma starting in adulthood and noneosinophilic asthma constitute an important part of the adult asthma population, and are still poorly defined. A precise definition of these asthma phenotypes is urgently needed because they are likely to be associated with different genotypes, responses to treatment, and prognoses.

Keywords
phenotypes, childhood asthma, adult-onset asthma, severe asthma

Introduction
Asthma is a phenotypically heterogeneous disorder that results from complex interactions between environmental and genetic factors. The expression of asthma may vary according to age and gender, association with atopy or specific provoking factors, type of airway inflammation, or severity of the disease. Over the years, many different clinical subtypes of asthma have been described in the literature. Until now, it is uncertain regarding whether all these different subtypes represent the variable expression of one single disease or whether some subtypes represent distinct diseases with similar symptomatology. This article highlights and discusses papers on specific asthma phenotypes published between July 1, 2002, and June 30, 2003, with special emphasis on risk factors, pathogenetic mechanisms, and treatment approaches.

Childhood asthma
Epidemiologic studies in children have suggested that there are several different asthma phenotypes. Three of these phenotypes have been described in detail and are based on the findings of the Tucson Children’s Respiratory Study [1,2•]. They include transient infant wheezing (wheezing up to 3 years but not after), nonatopic wheezing of the toddler and early school years, and IgE-mediated wheezing/asthma. Recently, a fourth phenotype, so called late-onset childhood asthma, was added [3•].

Transient infant wheezing
Most children who wheeze during infancy do not wheeze after the age of 3 years. These “transient wheezers” do not have a family history of asthma or any marker of atopic diathesis, but are characterized by impaired lung function at birth. The prognosis of these children is favorable. Children with transient wheezing were followed prospectively in the German Multicenter Allergy Study, and showed only a slight impairment in maximal expiratory flow at age 7 years [4•].

Abbreviations
AIA aspirin-induced asthma
Cys-LT cysteinyl–leukotriene
PG Prostaglandin

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1070-5287

Nonatopic wheezing of the toddler and early school years
A second group of children continues to wheeze beyond the third year of life. Approximately 40% of these children are nonatopic, and often these children have a history of viral lower respiratory tract infection early in life (in particular, respiratory syncytial virus) [5]. These nonatopic wheezers are more likely to develop airway obstruction in relation to viral infection, probably as a result of an alteration in the control of airway tone. An interesting observation in this respect is the beneficial effect of the leukotriene receptor antagonist montelukast on cough and wheeze during respiratory syncytial virus bronchiolitis [6].

Persistent IgE-mediated wheezing/asthma
A third group of children will go on to have persistent, nonatopic wheezing of the toddler and early school years [3•]. prospectively examined characteristics of childhood wheezing phenotypes during the first 10 years of life. Thirty-seven percent of early life wheezers still wheezed at age 10 years. This persistent wheezing phenotype was associated with high levels of atopy, bronchial responsiveness, and impaired lung function. Previous studies had already identified a variety of risk factors for persistent IgE-mediated wheezing, of which genetic factors (atopy, parental history of asthma, male gender) and early allergic sensitization (house dust mite, cockroach) are the most important [8].

Of interest, certain early exposures seem to decrease the risk for persistent wheezing [9]. Early exposure to farm animals has been shown to have a protective effect against both allergic sensitization and asthma. Recent evidence suggests that this effect might be mediated by exposure to bacterial endotoxins [10•]. Also, growing up in a house with pets or dogs appears to decrease the risk of allergic sensitization and wheeze [11••,12], independent of the effects of endotoxin [13•].

Systemic bacterial [14] or parasitic infections [15] in early life might protect against the development of atopy and asthma as well. Certain infections, mainly food-borne and orofecal, are associated with a lower risk of asthma and common allergies [16], and neonatal bacille calmette-guérin (BCG) vaccination is associated with a reduced prevalence of allergy and asthma in children with an inherited predisposition to allergic diseases [17].

The debate regarding whether certain exposures in early life such as specific allergens, viruses, bacteria, and helminths are inducing or protecting from the development of atopy and asthma is far from resolved, and will certainly continue to be a challenge of future asthma research [18].

Late-onset childhood asthma
Late-onset childhood asthma is the least well-described subtype of childhood asthma. De Marco et al. [3•] analyzed the data from a large multicenter cross-sectional survey aimed at assessing the incidence and remission of asthma. They described an asthma phenotype occurring during or after puberty, affecting mainly women and with a low remission rate. In a prospective study of Montreal school children, a higher prevalence of bronchial hyperresponsiveness among postpubertal compared with prepubertal girls was confirmed, and also in these children atopy was the major determinant of bronchial hyperresponsiveness [19].

Asthma persisting from childhood into adulthood
Most children with asthma have a favorable outcome as they grow toward adulthood [20]. Some have a remission of their symptoms during puberty but develop symptoms again in early adult years. These children have been shown to have ongoing airway inflammation. Others with more severe disease may continue to wheeze into adult life [21•]. Risk factors for asthma continuing into adulthood include early age of onset, female gender, atopy, eczema, impaired lung function, and bronchial hyperresponsiveness.

Adult-onset asthma
Asthma starting in adulthood appears to be different from childhood asthma. Rackemann, in 1947 [21a], already subdivided asthma into “extrinsic” or atopic asthma that started before the age of 30 years and “intrinsic” or nonatopic asthma, starting after the age of 40 years. In the literature, the terms adult-onset asthma, intrinsic asthma, and nonatopic asthma are being used interchangeably to describe a subtype of asthma characterized by later onset in life, female predominance, higher degree of severity, and more frequent association with nasal polyposis. Apart from smoking and chronic rhinosinusitis [22,23] risk factors of adult-onset asthma have not yet been elucidated. The role of genetic predisposition in adult-onset asthma is less clear than in atopic childhood-onset asthma. A family history of asthma is often lacking, and atopy is not more common than in the general population. Still, specific host genetic factors might be important in the development of adult-onset asthma, as follows, for example, from a recent study showing a functional polymorphism in the regulated upon activation, normal T-cell expressed and secreted (RANTES) gene promoter to be associated with adult-onset asthma in Japanese patients [24].

It has now become evident that adult-onset asthma may have distinct clinical patterns. Subtypes of adult-onset asthma are primarily based on the type of exogenous or endogenous trigger factors, and include asthma associated with aspirin sensitivity, asthma related to chronic infection with respiratory pathogens, asthma induced by
Asthma associated with aspirin sensitivity

Asthma that is exacerbated by aspirin, also referred to as aspirin-induced asthma (AIA), is a distinct clinical syndrome characterized by chronic hyperplastic rhinosinusitis, nasal polyps, and asthma attacks after ingestion of aspirin and other nonsteroidal antiinflammatory drugs. The prevalence of AIA in the adult asthma population is estimated to be approximately 10 to 20% [25], with a higher prevalence in women. The disease typically starts in the third or fourth decade of life with refractory rhinitis [26•], which then evolves into hyperplastic rhinosinusitis with nasal polyposis. In the meantime, persistent asthma develops, and aspirin sensitivity becomes manifest. AIA is usually severe and, in half the patients, adequate control of asthma can only be achieved with oral corticosteroids. Alternative treatment is provided by aspirin desensitization [27]. The mechanism by which aspirin desensitization may lead to symptomatic improvement has been partially elucidated. Sousa et al. [28••] found that local aspirin desensitization significantly reduced the high number of cells expressing the cysteinyl-leukotriene type 1 (Cys-LT1) receptor in nasal mucosa of AIA patients.

The pathophysiologic mechanisms of AIA are not fully understood [29]. Persistent eosinophilic inflammation is a prominent feature and is likely to result from a non-IgE-mediated mechanism. Human leukocyte antigen association with AIA suggests an immunologic response toward an as yet unknown antigen.

Clinical studies indicate that inhibition of cyclooxygenase-1 and not cyclooxygenase-2 by aspirin precipitates asthmatic attacks. This is confirmed by the finding that aspirin-sensitive patients can tolerate the cyclooxygenase-2 selective analgesic drug celecoxib [30•]. A crucial role for prostaglandin E2 (PGE2) in AIA has been proposed, acting as a brake on excessive synthesis of Cys-LTs and release of mediators from mast cells. This is supported by the observation that patients with AIA have continuous release of PGD2 and tryptase into the blood [31], and that bronchial fibroblasts from AIA patients have deficient PGE2 production under proinflammatory conditions [32]. This concept was challenged, however, by the lack of a significant difference in PGE2 in exhaled air from patients with or without aspirin sensitivity [33•]. An alternative hypothesis is that expression of cyclooxygenase-2 is reduced as a result of downregulation of nuclear factor-κB, as has been observed in nasal polyps of aspirin-sensitive patients [34].

Asthma related to chronic, persistent respiratory infection

A subgroup of patients with adult-onset asthma reports a typical onset of their disease subsequent to a severe respiratory infection. Two organisms have been implicated in this type of asthma: *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* [35]. The data on *Chlamydia* are most convincing [36]. Studies in adults with recently diagnosed asthma have demonstrated serologic evidence of persistent respiratory tract infection with *C. pneumoniae* in a high proportion of patients [37]. Alternatively, patients with evidence of persistent *C. pneumoniae* infection have more often asthma and upper respiratory infections compared with control subjects [38]. The mechanism whereby *Chlamydia* might induce asthma is unknown, but an antigenic response against heat shock proteins is suggested [39].

Asthma related to immunologic or nonimmunologic exposure in the workplace

Occupational asthma constitutes an important part of the population with adult-onset asthma, with a prevalence as high as 20% in some studies [40]. A number of state-of-the-art reviews on occupational asthma have been published during the last year [41•,42–45]. Two types of occupational asthma can be distinguished: immunologic (which can be IgE or non-IgE mediated) and nonimmunologic (ie, irritant-induced asthma or reactive airways syndrome).

There are more than 250 agents that have been adequately documented to cause immunologic occupational asthma. Atopic constitution and airway hyperresponsiveness to AMP [46•] appear to be contributing risk factors to the IgE-dependent subtype. Jeal et al. [47] have shown evidence that the human leukocyte antigen phenotype is an important determinant of individual susceptibility to sensitization and asthma among laboratory animal workers. Evidence for involvement of human leukocyte antigen class 2 molecules has also been reported for non-IgE-mediated sensitization to low-molecular weight chemicals [48]. Mapp et al. [49] investigated the role of the π class glutathione-S-transferase locus on chromosome 11q13 and found that polymorphic variants in glutathione-S-transferase locus were associated with increased susceptibility to asthma induced by exposure to toluene disocyanate. Also the N-acetyltransferase genotype has been shown to pose a significant risk of toluene disocyanate-induced asthma [50]. A comprehensive review of toluene disocyanate-induced asthma has been written recently [51].

Nonimmunologic occupational asthma, also referred to as irritant-induced asthma or reactive airways syndrome, is now generally accepted to be a separate clinical syndrome [52]. However, there is no clearcut definition of this condition, nor are there validated diagnostic criteria. Smoke inhalation [53•] and chlorine exposure [54•,55] are examples of irritants that can cause irritant-induced asthma.
Eosinophilic and noneosinophilic asthma

Since the introduction of noninvasive procedures to estimate airway inflammation in asthma, it has become fashionable to distinguish subtypes of asthma on the basis of inflammatory markers. Wenzel et al. [56] were the first to distinguish in patients with severe asthma different types of inflammation in mucosal biopsies. All these patients had higher percentages of neutrophils than patients with mild asthma, but some had persistent eosinophilia despite high-dose corticosteroid therapy. These patients had more severe disease and more near-fatal events than equally severe asthmatic control subjects [56]. For a long time it was assumed that infiltration of eosinophils into the airway wall was the hallmark of all asthma. By using induced sputum, several studies have shown that a substantial proportion of patients with severe asthma and occupational asthma have noneosinophilic inflammation [57]. Recently, noneosinophilic inflammation has also been confirmed in patients with milder disease [58••]. It is likely that further classification of asthma based on the type of inflammation will improve our insight into the pathogenesis of the disease.

Severe asthma

Severe asthma may occur in childhood as well as in adulthood, may be associated with different allergic or nonallergic provoking factors, and may exhibit an eosinophilic or noneosinophilic type of inflammation [59]. Clinically, different patterns of severe asthma may be observed, including near-fatal asthma, asthma with fixed airflow obstruction, and corticosteroid-resistant asthma.

Near-fatal asthma

Risk factors of (near-) fatal exacerbations have been extensively studied in the past. Major risk factors include recurrent severe exacerbations with hospitalization and emergency visits during the previous year, and psychosocial factors [60]. Patients with near-fatal asthma are more likely to have gradually deteriorated during the last weeks before the attack, and to have delayed seeking medical help during the final attack [61,62]. Among the genetic factors that have been implicated recently in severe asthma and life-threatening attacks are a polymorphism of the interleukin-12 promoter [63] and a RANTES –28C/G polymorphism [64].

Asthma with fixed airflow obstruction

Although asthma has been considered a condition of reversible airway obstruction, many children [65] and adults [66] gradually develop irreversible or fixed obstruction, probably related to airway inflammation and remodeling [67]. Population studies have shown that even never-smoking asthmatic patients have a faster decline in forced expiratory volume in 1 second compared with nonasthmatic subjects [68]. In particular, patients with adult-onset asthma rather than childhood asthma appear to have a faster decline in lung function compared with the general population [20,69].

The prevalence of irreversible airflow obstruction in adult asthmatic patients is estimated to be 35 to 50%. Risk factors for its development include male gender, absence of atopy, adult-onset asthma, and persistent eosinophilia despite intensive treatment. In contrast to previous studies, a retrospective follow-up study shows that asthmatic patients with a low level of airway hyperresponsiveness and reversibility are most likely to develop chronic airflow obstruction [66]. The pathology of chronic airflow obstruction in asthma differs from that seen in chronic obstructive pulmonary disease, and is characterized by higher numbers of eosinophils in peripheral blood and airway walls, lower numbers of neutrophils, a higher CD4+-to-CD8+ ratio of T cells, and a thicker reticular layer of the epithelial basement membrane [70••]. Fibroblast accumulation and airway smooth muscle (ASM) hypertrophy in proximal airways is another characteristic of chronic airflow obstruction in asthma [71••]. An understanding of the cellular and molecular mechanisms underlying remodeling is now evolving. Airway fibroblasts from severe asthmatics seem to be of the synthetic phenotype, with altered production capabilities [72], whereas ASM hypertrophy may be related to the action of Cys-LTs acting in synergy with interleukin-13 and interferon-γ [73•]. Davies et al. [74•] stress the importance of the epithelial mesenchymal trophic unit, and highlight the potential role of the ADAM33 gene, which is abundantly expressed in airway fibroblasts and smooth muscle cells in patients with asthma.

Steroid-resistant asthma

Glucocorticoids are the mainstay of asthma treatment, but a small subset of patients demonstrates persistent tissue inflammation despite treatment with high doses of inhaled and oral glucocorticoids. Recent studies have greatly improved the understanding of the molecular mechanism whereby glucocorticoids exert their effect. The cellular and molecular mechanisms of glucocorticoid action and resistance have been reviewed by Leung and Bloom [75•]. One of the main conclusions of their article is that steroid resistance in asthma is acquired in 95% of the patients, and in itself represents several subtypes, depending on the trigger or genetic background of the host. Leung and Bloom [75•] also provide a very useful algorithm for approaching glucocorticoid-resistant subjects in a stepwise approach.

Summary

In summary, many phenotypic classifications of asthma, based on age of onset, the type of inflammation, and pattern of severity, have been described in the literature. Currently we are far from a clear definition of the different subtypes, although, little by little, more insight into risk factors, pathophysiologic mechanisms, and prognosis
is gained. A precise definition of asthma phenotypes is urgently needed because different phenotypes may be associated with different genotypes, and different responses to treatment.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- Of special interest
- Of outstanding interest


30. Immunohistochemical analysis of nasal biopsies in 22 aspirin-sensitive and 12 non-aspirin-sensitive persons with rhinosinusitis showed increased expression of the OCS-L1 receptor on leukocytes infiltrating the nasal mucosa, and a downregulation of these receptors after aspirin desensitization.


This double-blind, placebo-controlled trial of 33 subjects with typical histories of AIA and confirmed intolerance to aspirin showed that all subjects tolerated acute exposure to celecoxib. This was documented with regard to pulmonary and extra-pulmonary symptoms as well as measurements of biochemical markers of AIA.

Clinical phenotypes of asthma

Bel 49

Severe cough occurred in 332 of 9914 firefighters after the collapse of the World Trade Center. Sixty-three percent had a response to a bronchodilator and 24% had bronchial hyperresponsiveness 6 months after the event. The development and perpetuation of hyperreactivity and reactive airways dysfunction were strongly and independently associated with exposure intensity.


In an A/J mouse model, a 5-minute exposure to chlorine caused oxidative injury to the airways with epithelial loss and an increase in airway responsiveness to methacholine 24 hours after exposure. Inducible nitric oxide synthase was involved in the induction of changes in responsiveness to methacholine.


Sputum specimens were obtained from 259 adults with asthma and 34 control subjects using hypertonic saline challenge. A subgroup (23%) of patients had a sputum neutrophil profile with increased neutrophils without eosinophilia. Patients with isolated sputum neutrophilia responded less well to inhaled corticosteroids than the other subjects.


Markers of airway inflammation in peripheral blood, sputum, and mucosal biopsies were compared between 27 subjects with a history of chronic obstructive pulmonary disease and 19 subjects with a history of asthma with a similar degree of fixed airflow obstruction. The results show that the two groups of patients exhibit a different pattern of airway inflammation, suggesting that the type of airway inflammation in asthma does not change with the development of fixed airflow obstruction.


Airway mucosal biopsies were analyzed in 40 patients with asthma of different severity, in 10 patients with chronic obstructive pulmonary disease, and in 10 healthy control subjects. Multivariate analysis of the data showed that airway smooth muscle hypertrophy and fibroblast accumulation, but not epithelial damage, granulocyte infiltration, or thickness of subbasement membrane were selectively associated with severe persistent asthma.
50 Asthma


73 Espinosa K, Bosse Y, Stankova J, et al.: CysLT1 receptor upregulation by TGF-beta and IL-13 is associated with bronchial smooth muscle cell proliferation in response to LTD4. J Allergy Clin Immunol 2003, 111:1032–1040. This study shows that certain cytokines can enhance the expression of Cys-LT1 on bronchial smooth muscle cells and render these cells more responsive to LTD4 in terms of proliferation, which can be prevented by the Cys-LT1 antagonist montelukast. This might be an important mechanism involved in airway remodeling in asthma.


75 Leung DY, Bloom JW: Update on glucocorticoid action and resistance. J Allergy Clin Immunol 2003, 111:3–22. This is an extensive and very useful review on the mechanisms of glucocorticoid action and resistance, including an algorithm for management of glucocorticoid-resistant asthma.