Review

Severe Asthma: Definitions, risk factors and phenotype characterization

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SUMMARY. The correct diagnosis of asthma is usually made easily and most patients with asthma respond to therapy. Approximately 5-10% of patients with asthma, however, have disease that is difficult to control despite administration of maximal doses of inhaled medications. It appears that asthma is a heterogeneous disorder which presents not as a single disease but rather as a complex of multiple, separate syndromes that overlap. Although the various different phenotypes of asthma have been long recognized, they are still poorly characterized. Improved phenotypical characterization and understanding of the underlying pathobiology are necessary for linkage of specific genotypes with clinical disease manifestations, for possible development of biomarkers and for devising advanced, phenotype-targeted asthma treatment. This review reports on the asthma phenotypes that have been best described and analyses the methods used to define them. *Pneumon 2010, 23(3):276-292.*

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INTRODUCTION

Asthma is a chronic inflammatory disease of the airways characterized by recurrent episodes of symptomatic airflow obstruction and various degrees of hyperreactivity of the airways to non specific stimuli. The recognition that the disease has a chronic inflammatory component has directed treatment towards the early use of inhaled glucocorticoids, which typically produce significant reduction in inflammatory markers and improvement in pulmonary function. A subset of patients, however, in the range of 5% to 10%, with severe or refractory asthma[1] does not respond to glucocorticoid treatment. These patients account for 40% to 50% of the health costs of asthma and incur significant morbidity and decrement in their quality of life[2,3].

A phenotype is defined as "the observable characteristics of an organism resulting from the interaction between its genetic make up and the environment". Asthma probably consists of a collection of different phenotypes, rather than one single disease. These phenotypes are all generally categorized under the broad umbrella of "asthma" because they meet the simple criteria for clinical diagnosis of this disease. Studies now suggest that identifica-

tion of the phenotype of asthma in a specific patient can assist in individualized management and treatment. The better understanding of a phenotype is accompanied by improved insight into the genetic and environmental factors involved in the presentation of complex diseases such as asthma. The objective of this review is to define, through characterization of phenotypes, novel points at which immunological and pharmacological interventions can be introduced in the treatment of asthma

THE DEFINITION OF SEVERE ASTHMA

Severe asthma affects a small, but clinically and economically important, proportion of patients with asthma, who experience frequent and/or debilitating symptoms and limitation of their activities. These patients have frequent exacerbations and hospitalizations and account for over half of the costs of the disease and most of its mortality[4,5]. According to the definition of the Global Initiative for Asthma (GINA), patients should be classified as having severe persistent asthma when they experience daily symptoms, frequent exacerbations, frequent nocturnal asthma symptoms, limitation of physical activities, and forced expiratory volume in 1 sec (FEV_1) or peak expiratory flow (PEF) ≤60% predicted and PEF or FEV_1 variability ≥30% before initiation of treatment[4,5]. The GINA definition of severe asthma is imprecise, rendering the guidelines not particularly useful for most research purposes, with the result that investigators have developed more rigorous working definitions for severe asthma that can be implemented consistently in clinical studies. Several different working definitions of severe asthma have been employed in recent studies[6].

The American Thoracic Society (ATS) in 2000, through an expert workshop, developed a working consensus definition of severe asthma, which although not perfect, remains the "state of the art" in the field. According to the ATS recommendations, up to 10% of asthma patients may be classified as severe, based on the consensus definition of persistent symptoms, air-flow limitation, emergency care visits and treatment (Table I)[7,8].

The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study[9] used a working definition of difficult-to-control asthma. TENOR subjects were considered to have severe or difficult to treat asthma based on their physicians' diagnosis. Thus, even patients with mild or moderate asthma were eligible for inclusion in the study if their treating physicians considered their asthma difficult to treat and they met all the other inclusion criteria, namely care from their physician or healthcare provider for at least 1 year and increased use of the healthcare system (i.e., 2 or more unscheduled care visits for asthma or 2 or more oral steroid bursts) and/or high use of antiasthma medication (i.e., currently requiring 3 or more medications to control asthma, the need for high doses of inhaled steroids or current use of oral prednisone >5mg/day) in the previous 12 months. This approach may have a closer link to the clinical practice of asthma management, but has the disadvantage of variation, or inconsistency in implementation. Despite this limitation, the TENOR study showed that healthcare resource utilization among patients with asthma patients was highest in those who had severe asthma, suggesting that by adding measures of healthcare utilization to the traditional measures of asthma severity, further understanding of disease activity will be achieved.

According to the ENFUMOSA study[10], the definition of severe asthma was based on use of high-dose corticosteroid treatment and one or more exacerbations in the last year. Requirements for additional treatment, abnormal lung function, or specific measures of daily asthma control are not included in the definition. Consequently, the populations of patients with severe asthma enrolled according to the ENFUMOSA definition, although similar in steroid requirements, were different from those enrolled in studies according to the ATS consensus definition.

TABLE 1. The American Thoracic Society workshop consensus for definition of severe/refractory asthma

Major criteria
• Treatment with continuous or near-continuous (≥50% of year) oral corticosteroids
• Requirement for treatment with high-dose inhaled corticosteroids
Minor criteria
• Requirement for additional daily treatment with a controller medication,
• Asthma symptoms requiring short-acting β-agonist use on a daily or near-daily basis
• Persistent airway obstruction (FEV_1 <80% predicted; diurnal peak expiratory flow variability >20%)
• One or more urgent care visits for asthma per year
• Three or more oral steroid bursts per year
• Prompt deterioration with ≤25% reduction in oral or inhaled corticosteroid dose
• Near-fatal asthma event in the past

Severe asthma requires one or both major criteria and at least two minor criteria

It is apparent that, at present, the picture of the diagnosis of "severe asthma" or "severe refractory asthma" is complex. No single measure is a valid discriminator and even two or three variables in combination fail to differentiate moderate from severe asthma. The latest definition, given 2 years ago, is as follows: *"severe asthma is diagnosed in patients with refractory asthma that remain difficult to control despite a thorough re-evaluation of the diagnosis and after >6 months of close follow-up by a physician specializing in asthma"*[11].

Recently, guidelines have started to move away from the concept of severity of asthma and focus on monitoring and treatment according to levels of control. Asthma control represents the extent to which the clinical manifestations of asthma have been removed or reduced by treatment. Asthma severity is defined by the intensity of treatment required to achieve good asthma control and therefore should always be assessed only during treatment[5].

RISK FACTORS FOR SEVERE ASTHMA

Epidemiological studies have examined the relationship between possible risk factors and asthma severity. The Leiden Group (ten Brinke et al)[12], conducted a study in which 13 clinical and environmental factors, all potentially associated with recurrent exacerbations, were investigated in 136 patients with severe asthma. The results showed that frequent exacerbations in difficult-to-treat asthma are strongly associated with psychological dysfunction (OR 10.8), recurrent respiratory tract infections (OR 6.9), gastro-oesophageal reflux (OR 4.9), severe paranasal sinus disease (OR 3.7) and obstructive sleep apnoea (OSA) (OR 3.4). It was also found that atopic patients, in particular those with specific IgE to house dust mite or cockroach, had >10-fold increased odds for frequent exacerbations compared with nonatopic patients. Identification and management of these specific factors might result in reduction of exacerbation rate, improved quality of life and better control of the disease.

The ENFUMOSA study showed that female sex, obesity and the lack of atopy were associated with more severe disease expression, while no childhood risk factors were identified[10,13]. More recently, data from the TENOR study showed that factors associated with increased risk of exacerbation and hospital admission were younger age, female sex, non-white race, BMI ≥35 kg/m^2, post-bronchodilator FEV_1 <70% predicted, a history of pneumonia, diabetes, intubation for asthma and three or more steroid bursts in the previous 3 months[14]. A final risk score ranging from 0–18 was derived from the logistic regression model in this cohort, which was highly predictive of hospitalization or emergency department (ED) visits. Scores of 0–4 represent low risk, scores of 5–7 moderate risk and a score of ≥8 represents high risk (Table II)[15].

TABLE II. TENOR risk score for severe asthma exacerbations

Points	Variables
3	**Age yrs**
0:	≥60
1:	50–59
2:	35–49
3:	18–34
1	**Sex**
0:	Male
1:	Female
2	**Race/ethnicity**
0:	White
2:	Non-white
1	**BMI (kg/ m^2)**
0:	<35
1:	>35
2	**Lung function**
0:	Post % pred FVC >70
2:	Post % pred FVC <70
1	**Previous history of pneumonia**
0:	No history
1:	Previous history
1	**Currently has diabetes**
0:	No
1:	Yes
1	**Currently has cataracts**
0:	No
1:	Yes
1	**Ever intubated**
0:	No
1:	Yes
3	**Steroid bursts in last 3 months**
0:	0 steroid bursts
1:	1 steroid bursts
2:	2 steroid bursts
3:	>3 steroid bursts
1	**Nebuliser ipratropium bromide**
0:	No
1:	Yes
1	**Systemic corticosteroids**
0:	Less than every other day
1:	At least every other day
18	**Total possible score**

BMI: body mass index; FVC: forced vital capacity.

In contrast to the ENFUMOSA patients, the TENOR cohort had a very high rate of skin test positivity for allergy[16], and an association of IgE levels with asthma severity among younger patients[17]. In female children and adolescents, increased body weight was found to be associated with asthma severity[18].

Compared with low risk scores (0–4 points), a TENOR risk score of moderate magnitude (5–7 points) reflects a 3.5-fold higher risk of an emergency department visit or hospitalization; a high value (>8 points) reflects a 12-fold higher risk[14].

PHENOTYPICAL CATEGORIES OF SEVERE ASTHMA

Numerous classifications of asthma have been made, based on cause (allergic, nonallergic, occupational), pathology (eosinophilic, noneosinophilic), severity and physiological parameters (type I brittle, type II brittle)[19].

Allergic and non-allergic asthma are probably the best known and most commonly discussed phenotypes, but the determination of additional phenotypes has recently been considered necessary in asthma control. Asthma phenotypes based on age of onset, type of inflammation, pattern of severity and various other clinical characteristics have been recognized and used in clinical management, but they are poorly characterized and the underlying pathobiology is not well-defined.

A multiplicity of reviews or original studies have been published which report and analyse the broad categories of phenotypes[6,10,20-22]. A systematic review by S. Wenzel[23] proposes the classification of phenotypes into three categories: phenotypes defined by clinical or physiological criteria (severity-defined, exacerbation-prone, defined by chronic restriction, treatment-resistant, defined by age at onset), phenotypes related to specific triggers (aspirin or non-steroidal anti-inflammatory drugs, environmental allergens, occupational allergens or irritants, menses, exercise) and phenotypes defined by their pathobiology (eosinophilic, neutrophilic, pauci-granulocytic). This categorization is not intended to imply that there is no overlap between these groups; on the contrary, there is substantial interaction among the groups, as is shown from the common clinical picture of patients with asthma.

The aim of this review is to describe some of the characteristic features of the severe asthma phenotypes.

Severity-defined asthma

It has been suggested that definitions of asthma developed on the basis of lung function, symptoms and use of medication are not adequate for predicting either the course of asthma, the control of the disease or the response to treatment[24,25]. Treatment can significantly reduce asthma symptoms to a point where they are no longer troublesome. The term severe-refractory asthma is applied when there is inability of the appropriate treatment to reduce the symptoms to a sufficient degree for the patient to achieve good asthma control. For this reason, the severity of asthma must be evaluated only after at least six months of adequate treatment, but also after effective management of possible co-morbidities (rhinitis, gastro-oesophageal reflux, psychological dysfunction and others) and exacerbating environmental factors (allergens, occupational exposure)[26]. Poor compliance with treatment is also an important factor in patients with refractory asthma and must be taken into consideration before applying the phenotype of severe asthma to a specific patient.

Asthma severity may be influenced by the underlying disease activity and by the phenotype, both of which may be further described using pathological and physiological markers. These markers can also act as surrogate measures of future risk. Many biomarkers have been proposed for distinguishing between mild and severe asthma, but few have been confirmed by multiple studies. Such possible biomarkers include transforming growth factor β (TGFβ), interleukin (IL) 11, tumour necrosis factor α (TNFα), and IL-8[27-32]. Results from recent studies indicate that specific patterns of cytokines can be detected in bronchoalveolar lavage (BAL) from patients with asthma, which may in the future provide information for the more objective classification of asthma phenotypes, but this needs further investigation. This approach indicates that important new diagnostic and prognostic information is available in airway fluids and that future research in biomarker identification is likely to be fruitful.

Exacerbation-prone asthma

Almost all patients with asthma will have at least one moderate-to-severe exacerbation, but some patients with asthma appear to be predisposed to frequent exacerbations, which can be very severe. This exacerbation-prone asthma phenotype accounts for more than 40% of the patients with severe asthma in the Severe Asthma Research Programme (SARP) Database sponsored by the US National Heart, Lung, and Blood Institute[33]. Since exacerbation-prone asthma is a hallmark of severe disease and poor outcome, the identification of immunopathological

factors that distinguish this phenotype is important. In studies from SARP, logistic regression analysis results suggested that several factors independently contribute to the severe exacerbating phenotype, including low FEV_1, African race, early age at onset, and a history of exacerbation in response to aspirin or non-steroidal anti-inflammatory drugs, or before menses[34]. Other researchers have suggested that psychological disorders, including depression and anxiety, contribute to non-compliance and affect the frequency of exacerbations[35]. Patients with exacerbation-prone asthma appear to have a blunted dyspnoea response to worsening of airway obstruction, which can cause delayed recognition of symptoms[36,37]. This blunted dyspnoea response has been associated with an increase in eosinophilic inflammation, but conversely, other studies suggest that chronically high numbers of eosinophils in the airways are associated with increased susceptibility to exacerbations and with increased awareness of dyspnoea[38].

In the study of ten Brinke et al.[12], which was one of the most important studies on severe asthma with frequent exacerbations, the patients with frequent exacerbations experienced a total of 186 severe exacerbations, 37 hospital admissions, 335 hospitalized days and 69 emergency visits, in comparison with 24, 1, 10 and 15, respectively, in the control group with only one exacerbation in the last 12 months,. The patients with frequent exacerbations were significantly younger (mean 38 years vs 47 years) and had shorter asthma duration (median 12 years vs 24.5 years), and more often had a positive family history for asthma and a positive atopic status. No significant difference was detected between the groups in the daily dose of inhaled corticosteroid or smoking history. Bronchodilator reversibility and airway hyperresponsiveness were increased in the patients with more than three exacerbations compared with the control group, but this difference disappeared after correction for age and asthma duration.

Fixed airflow limitation (chronic airflow restriction)

Some patients with asthma present with marked airflow restriction but do not have serious symptoms or frequent exacerbations. Studies from the US National Heart, Lung, and Blood Institute Children's Asthma Management Program (CAMP) suggest that only a fraction of patients with childhood-onset asthma develops progressive loss of lung function over a 5-year period[39]. These children are more likely to be boys and are less allergic and less predisposed to exacerbations than the children with asthma who have no loss of lung function. Similar outcomes have been seen in the TENOR study of more than 4,000 patients with severe or difficult to treat asthma[24].

The findings of both CAMP and TENOR studies suggest that allergic features in asthma are more likely to be associated with exacerbation-prone or difficult to control asthma than with the phenotype associated with persistent severe airflow restriction. Whether or not allergic processes protect against profound loss of lung function is not known. No reported studies have differentiated patients with progressive loss of FEV_1 from those without, in terms of lung pathology, partly because there have been few longitudinal studies of asthma. Genetic studies have identified single nucleotide polymorphisms in ADAM33, IL-4, IL-4R and TGFβ1, each associated with lower than normal lung function. IL-4 single nucleotide polymorphisms have also been associated with near-fatal exacerbations of asthma.

Fixed airflow limitation is attributed to airway remodelling; a process that includes subepithelial basement membrane fibrosis, epithelial goblet cell hyperplasia, increase in blood vessels and proliferation of airway smooth muscle, along with increased mass because of hyperplasia and hypertrophy[40], and has been associated with the ADAM33 gene[41]. Observations suggest the presence of heterogeneous fibroblast types in asthmatic airways and distal lung[42].

A large subset has been identified of patients with severe asthma who manifest chronic airflow obstruction. The specific definition of chronic airflow obstruction varies, however; for example, ten Brinke et al[43] used a cutoff point of postbronchodilator FEV_1 <75% predicted, whereas Bumbacea et al[44] used a value of postbronchodilator FEV_1 <50% predicted. In both of these studies patients with chronic airflow limitation were older and had longer duration of disease. They also had elevated residual lung volumes consistent with air trapping, but normal diffusion capacity which is not suggestive of emphysema. Bronchial wall thickening seen on high-resolution computed tomography (CT) scan was associated with chronic airway obstruction. Patients with fixed airflow obstruction are often grouped under the heading of chronic obstructive pulmonary disease (COPD), and some international guidelines recommend classifying asthma with fixed airflow obstruction as COPD. Indeed, both COPD (induced by smoking or other noxious agents) and asthma may be associated with a decline in lung function that causes fixed airflow obstruction. Subjects with a history of asthma were found to have significantly more eosinophils in peripheral blood, sputum, BAL, and airway

mucosa; fewer neutrophils in sputum and BAL; a higher CD4+/CD8+ ratio of T cells infiltrating the airway mucosa, and a thicker reticular layer of the epithelial basement membrane. They also had significantly lower residual volume, higher diffusing capacity, higher exhaled nitric oxide (NO), a lower high-resolution CT scan emphysema score, and greater reversibility to bronchodilator and steroids. Thus, despite similar fixed airflow obstruction, subjects with a history of asthma have characteristics distinct from those with a history of COPD, and should be identified and treated[45].

Treatment (Steroid) resistant asthma

In most patients with asthma, glucocorticoid therapy influences inflammatory and structural cells beneficially, targeting sources of airflow limitation, including airway smooth muscle contraction, mucosal oedema, airway inflammation, increased mucus secretion and airway remodelling. Up to 10% of patients with asthma, however, demonstrate poor response to glucocorticoid therapy and experience frequent exacerbations and limitations of everyday activity and quality of life[46]. Corticosteroid-resistant or poorly-responsive asthma can be seen at all levels of asthma severity, but usually this phenotype of asthma is expressed in severe asthmatics, since the main treatment for asthma, the steroids, are not effective. Steroid resistant asthma was believed to be due to a defect in the response of the patient to corticosteroids that diminishes their anti-inflammatory effects. However, there are many different mechanisms for steroid resistance, as shown in recent studies, including decreased glucocorticoid receptor (GR) density, distorted affinity of ligand for the GR receptor, diminished capacity of the GR to bind with DNA, and increased expression of inflammatory transcription factors, e.g. NF-kβ and activator protein-1, that compete for DNA binding[47].

Increased gene transcription is associated with an increase in histone acetylation induced by histone acetyltransferase[48], while hypo-acetylation is correlated with reduced transcription or gene silencing which is controlled by histone deacetylases (HDACs). HDAC2-mediated GR deacetylation enables GR binding to the NF-kβ complex, thus reducing inflammatory gene transcription induced by NF-kβ[49]. A defect of GR deacetylation caused by impaired HDAC 2 has been proposed as a molecular mechanism causing glucocorticoid insensitivity through NF-kβ mediated gene expression. Loss of HDAC2 did not reduce GR nuclear translocation, GR binding to glucocorticoid response element (GRE) on DNA, or GR-induced DNA or gene induction, but it inhibited the association between GR and NF-kB[50]. HDAC activity and HDAC2 expression are decreased in lung macrophages and peripheral lung tissue obtained from patients with COPD, a disease relatively insensitive to steroids, and this reduction correlates with disease severity[51]. Ito et al., in 2006[50] showed that overexpression of HDAC2 was able to restore glucocorticoid sensitivity in steroid insensitive diseases such as COPD. Theophylline has been shown to restore HDAC activity and reverse steroid insensitivity in COPD[52]. Th-2 cytokines have also been proposed to play a part in severe corticosteroid refractory asthma with CD4+ T-cells from Patients with refractory asthma being less able to produce the anti-inflammatory cytokine IL-10 in response to dexamethasone than cells from patients sensitive to corticosteroids[26].

The types of inflammatory cells in the airways of some patients may predict responsiveness to glucocorticoid therapy[53]. The absence of eosinophils, as indicators of inflammation, predicts reduced response to corticosteroids. Multiple regression analysis revealed that sputum eosinophilia and FEV_1 were independent significant predictors of FEV_1 increase after treatment. Conversely, the FEV_1 and PD20 of asthmatics with low sputum eosinophilia were not positively affected by inhaled corticosteroid treatment. Neutrophil counts were higher in those patients with low baseline airway eosinophilia. Increased sputum neutrophils indicate poor response to steroids. These studies could possibly explain the poor response of people with asthma who smoke to corticosteroid therapy, since smokers are likely to have higher sputum neutrophil counts[54]. Other types of cells that are involved in steroid resistance are the peripheral blood mononuclear cells (PBMCs) and alveolar macrophages (AMs). These cells from patients with severe asthma are less sensitive to inhibition by dexamethasone of pro-inflammatory cytokines release, when compared with cells from patients with well-controlled non-severe asthma[55,56]. The mechanisms underlying this poor suppressive response to corticosteroids in severe asthma are unclear, but AMs from patients with severe asthma demonstrated a greater degree of activation of p38 mitogen-activated protein kinase (p38 MAPK). This serine-threonine kinase acts on a variety of substrates, including transcription factors, such as nuclear factor (NF)-B and activator protein-1, and has been implicated in inflammation, cell proliferation and cell death relevant to asthma pathophysiology[57]. Recent findings suggest that anti-IgE might benefit patients with glucocorticoid-resistant asthma[58]. On the other hand, strategies using

anti-TNFα have produced conflicting results[59], while a recent study by Wenzel et al[60] showed very disappointing results concerning this type of asthma. Further research is needed to identify additional and perhaps better non-invasive biomarkers related to this phenotype in order to move in the direction of targeted therapy.

Asthma defined by age at onset (occurrence through the lifespam)

The age at which a patient develops asthma differentiates phenotypes. Early onset or late onset asthma can both be associated with exacerbation-prone asthma, thus participating in the group of risk factors for severe asthma[61]. Asthma can begin at anytime during life; however, recent evidence indicates that most patients with asthma experience their first symptoms before the age of 5years.

The origins of childhood asthma lie in a complex interplay of genetics, environmental exposure and immune and pulmonary system development. Children with early onset asthma usually have a family history of atopy and/or asthma and a history of eczema. The maternal history is most strongly associated with susceptibility in the child, implying both genetic and environmental components[20]. Clearly, environmental exposures play a critical role in determining early disease susceptibility. Most 'early-onset' asthma, defined as onset before the age of 12 years, has an allergic component and patients develop symptoms after exposure to triggers[62]. Conversely, intrinsic asthmatics are probably a population with a great number of patients with late onset asthma[43]. Generally, early-onset asthma seems to be a more homogeneous disease than late-onset asthma, to which a mix of allergic, infectious and other factors contribute[33,61].

In many children, symptoms of asthma and wheezing improve with age, but 30% - 40% continue to have recurrent episodes as adults. Despite their longer disease duration, people with early-onset asthma appear to have marginally better lung function than those with late-onset disease. Miranda et al[62] reported findings in adult patients with late onset asthma who showed marginally worse lung function than those with early onset disease, despite a shorter overall duration of disease. In the study by Jenkins et al[63], the disease severity in children and adults whose onset of asthma occurred in childhood was related to disease duration, but this did not apply to patients with onset of asthma in adulthood. Burrows et al[64] noted that patients with adult-onset asthma display a steep loss in lung function soon after the diagnosis is made, followed by relatively stable lung function thereafter. The mechanisms involved in the apparent rapid decline in lung function among the adult-onset asthma patients are presently not understood. It is possible that some of these patients may have had unrecognized asthma for years, the diagnosis being made only after a significant degree of lung function loss. Alternatively, according to Jenkins et al[63], adult-onset asthma may be associated with a greater degree of airway inflammation and/or more repair processes, resulting in rapid airway remodelling. Ten Brinke et al[43] found that adult-onset asthma was a significant risk factor for chronic airway obstruction [odds ratio (OR) 3.3], and that patients whose asthma was late in onset were less likely to be atopic on skin testing, tended to have lower IgE levels, and had fewer symptoms with allergen exposure. These findings suggest that there may be significant pathophysiological, and perhaps mechanistic, differences between early-onset and late-onset asthma.

Allergic asthma

Allergic sensitization is the basis of allergic asthma and is one of the most common asthma phenotypes. The presence of allergic characteristics can be associated with better overall lung function, but with more exacerbations than non-allergic asthma. It is particularly common in childhood asthma, but is also frequently found in adults[65]. By 10 years of age, allergic asthma is the dominant form of the disease. A family history of asthma and early exposure to allergens are probably important in the initiation of allergic asthma, but the mechanisms by which some children develop asthma, while others have non-respiratory allergic manifestations are not understood[66]. The age of exposure to specific allergens is possibly critical in the process of developing asthma later in life; early exposure could be more relevant than later exposure. The findings of studies on exposure to high concentrations of cat allergen up till the age of 3 years imply that an immune response, not associated with asthma symptoms, can be induced and this situation should be considered to be a form of tolerance. There is evidence that children raised in a house with a cat are less likely to become allergic to cat allergens or to the development of asthma[67,68]. Also, early sensitization to dust mite allergens is more significant in relation to asthma than sensitization after 3 years of age[69,70].

The early phase of the response is triggered when an atopic individual encounters the allergen, and is characterized by release of both preformed and newly synthesized

mediators, such as leukotrienes (LT), histamine, prostaglandins and cytokines, which induce bronchoconstriction and oedema. The late phase is characterized by the influx and activation of lymphocytes and other inflammatory cells that, in turn, increase production of pro-inflammatory cytokines.

It appears that the immune response in allergic and, perhaps, in other forms of asthma, is heterogeneous, which probably contributes to heterogeneity in clinical phenotypes. Over 100 genes have been implicated in allergic asthma, but the genetics of the disorder are complex and are modulated by environmental exposures. None of the genes have been shown to contribute to risk in all populations.

Targeted therapies, such as immunotherapy or monoclonal antibody treatment, are available for the treatment of asthma. In studies of the IgE antibody, omalizumab, an allergic phenotype was defined only by the presence of allergen-specific IgE measured by skin-prick or serum testing[71,63]. Analysis of these and other trials, as well as clinical experience, suggests that not all people with allergic asthma diagnosed by these tests respond to anti-IgE therapy. Whether a better definition of allergic asthma or its biomarkers could enhance the ability to identify patients who will respond to this treatment, is not clear.

Occupational asthma

The occupational asthma phenotype might account for up to 15% of adult-onset asthma and can cause frequent severe exacerbations[12]. Occupational asthma does not differ in its clinical and pathological features from non-occupational asthma, but it has several sub-phenotypes which result from both immunological and non-immunological mechanisms. Immunologically mediated occupational asthma appears after a latency period of exposure necessary for the worker to acquire immunological sensitization to the causal agent. This type encompasses both occupational asthma that is induced by an IgE mechanism (most high- and some low-molecular-weight agents), and occupational asthma in which an IgE mechanism has not been demonstrated consistently (low-molecular-weight agents, such as diisocyanates, western red cedar, and acrylates). Nonimmunological occupational asthma is characterized by the absence of a latency period. It occurs after accidental exposure to high concentrations of a workplace irritant. This clinical entity has been defined as irritant-induced asthma. The most definitive form of irritant-induced asthma is "reactive airway dysfunction syndrome" (RADS) which occurrs after a single exposure to high levels of an irritating vapour, fume, or smoke. In addition, work-related asthma encompasses variant syndromes, including eosinophilic bronchitis and asthma-like disorders caused by exposure to organic dusts[73].

The airway inflammation in immunologically mediated occupational asthma is characterized by the presence of eosinophils, lymphocytes, mast cells and thickening of the reticular basement membrane[74]. In contrast, in occupational asthma caused by irritant chemicals, the pathological changes consist of fibrosis of the bronchial wall and epithelial denudation and fibrino-haemorrhagic exudates in the submucosa, without eosinophilic inflammation[75]. Although this type of occupational asthma can retreat if the patient promptly discontinues exposure to the offending agent, once the process is established, immunological phenotypes can continue independently of exposure[73].

Aspirin-induced asthma

Asthma that is induced by aspirin and other nonsteroid anti-inflammatory drugs is commonly referred to as aspirin-sensitive asthma (AS-asthma). It is among the most easily identified phenotypes because of the specificity of the trigger. Estimates vary, but prevalence is likely to be approximately 10–20% of the adult asthma population[76]. AS-asthma patients are likely to be female and suffer from more severe disease. It is associated with raised airway leukotrienes, and high numbers of eosinophils in both tissue and blood, but little evidence of atopy[77]. The most clinically distinctive patterns associated with aspirin sensitivity are severe rhinosinusitis and nasal polyps, and adult onset asthma. Nonsteroid anti-inflammatory drug sensitivity does not appear to be mediated by IgE, but is related to altered eicosanoid metabolism. Increased levels of cysteinyl LT and increased expression of CYSLTR1 are characteristic findings associated with this phenotype, suggesting that its pathogenesis may be related to an enhanced inflammatory response due to overexpression of cysteinyl LT and CYCLTR1[78].

Although this phenotype is very distinct clinically and pathologically, the underlying pathogenesis remains poorly understood. Genetic studies have shown that mutations in the LT synthesis pathway affect this phenotype, but these distinctions alone are not sufficient to explain the adult onset of the disease, which suggests an additional environmental (perhaps viral) element in its pathogenesis[23]. Recent studies have also suggested alterations in cyclooxygenase-2, prostaglandin E2 and

lipoxin metabolism. A number of single nucleotide polymorphisms (SNPs) have been identified in the leukotriene C4 synthase, 5-lipoxygenase, CYSLT1 and -2 genes, TBX21 (which encodes the transcription factor Tbet), and prostaglandin E2[78]. The cyclooxygenase-2 and thromboxane A2 receptor genes, while not associated with AS asthma per se, may all have functional effects.

The asthma in aspirin sensitive patients can be difficult to control, as it frequently does not respond well to corticosteroids. LT receptor antagonists can be helpful, but, as with other asthma phenotypes, not all patients respond well to this treatment option.

Peri-menstrual asthma

Hormonal disturbance is a risk factor for frequent severe exacerbations. Menses-related asthma is the least well characterized of the trigger-induced subtypes. It probably only occurs in a small proportion of women with asthma, but it can be severe. There is no generally accepted definition of perimenstrual asthma (PMA) and most authors have generally relied on self-reported worsening of asthma symptoms in the perimenstrual phase. Currently, PMA is defined as an increase in asthma symptoms or a decrease in lung function immediately preceding or during the menstrual phase of the female cycle. Perimenstrual worsening of asthma has been documented in 30% to 40% of asthmatic women[79].

Although a role of sex hormones in asthma pathogenesis has been assumed for some time, the actual hormonal mechanisms for these effects are not clear. Depending on the environment, both oestrogen and progesterone have the potential to act as proinflammatory or anti-inflammatory hormones.[80] Female sex hormones exert effects on several inflammatory mediators, on neutrophils, IL-8 and on monocyte chemotactic protein. An intriguing possible explanation for cyclic changes in the severity of asthma is that the TH1/TH2 balance varies with the menstrual phase, shifting more toward the TH2 profile in peripheral blood perimenstrually[79].

Oestrogens have been shown to alter cortisol production, clearance and metabolism. Progesterone exerts a competitive action with cortisol for the binding site of the corticosteroid-binding globulins, and oestradiol enhances corticosteroid-binding globulin production. Significant variation in theophylline levels caused by higher clearance during the menstrual phase compared with that during the follicular phase has been demonstrated.[79,81]

The following patient characteristics are associated with PMA: 1) longer menstruation, more pronounced premenstrual tension, and a higher incidence of allergic, infective and psychological factors, 2) increased severity of asthma (more symptoms, rescue medication, lower PEF and FEV_1), 3) up to 3 times more frequent visits to emergency departments for their asthma than men, and this is linked to the perimenstrual phase of their cycle, and 4) PMA attacks have also been associated with frequent hospitalizations and even mechanical ventilation.[79,81]

Inflammatory phenotypes

The understanding of asthmatic inflammation is perhaps the most important advance in elucidation of the pathogenesis of the disease and in deciding the appropriate treatment for asthma. This led to the widespread use of inhaled corticosteroids and their position as the gold-standard for asthma treatment. Inflammatory phenotypes of severe asthma can be characterized by persistence of eosinophilic or neutrophilic infiltration, although in some cases, no inflammatory infiltration is noted (paucigranulocytic).[23] These phenotypes are becoming increasingly associated with distinct clinical and physiological inflammatory and repair processes.[15,38]

Usually, inflammatory cells are present and activated in the airways of patients with severe asthma and persist despite treatment, but their relevance to the control and severity of the disease is largely unknown. These cells include not only eosinophils and neutrophils but T lymphocytes, mast cells and macrophages, while structural cells are also involved in the inflammatory reaction and remodelling in asthma.

Eosinophilic asthma

Eosinophilic asthma is the best studied pathological phenotype. Eosinophils have been reported, in various numbers, in the sputum, BAL and endobronchial biopsies of many people with asthma. Studies that have defined an eosinophilic phenotype by sputum or biopsy testing in patients with varying severities of asthma consistently show that around 50% of patients have eosinophilic involvement.[38]

Eosinophils may be an important biomarker of some key features of severe asthma. For example, Bumbacea et al.[43] related the presence of chronic airway obstruction with an increase of eosinophils in both the sputum (>2%, OR=7.7) and the blood (OR=6.3). Using criteria initially suggested by Wenzel and Busse,[7] severe asthma can be characterized as eosinophil positive (EOS +) or negative (EOS -), according to the presence or absence of eosi-

nophils in endobronchial mucosal biopsy; EOS- biopsies tend to be neutrophils enriched. The eosinophil, with its capacity to release a range of inflammatory mediators, is often seen as the principal inflammatory cell linked to airway dysfunction in asthma. Some researchers have suggested that eosinophilic inflammation increases with the severity of disease, but recent findings question the pivotal role of the eosinophil in asthma pathogenesis.[82,83] Persistent airway eosinophilia and T-cell activation in the presence of corticosteroids has been found in studies of chronic asthma[38,84,85] implying that corticosteroids are not adequately suppressing the inflammatory process. The ENFUMOSA study,[10] although unable to demonstrate significant differences in the circulating eosinophil count between the patient groups, found that the persistence of eosinophils in induced sputum and the presence of increased urinary LTE4 and EPX, despite inhaled and oral corticosteroid treatment, show that the inflammatory response in severe asthma is inadequately controlled. Miranda et al.[62] showed that 2/3 of the severe asthmatic patients in their study had biopsy evidence of eosinophil infiltration, in spite of long-term high-dose oral corticosteroid treatment, which suggests resistance to the beneficial anti-inflammatory effects of inhaled and oral steroids.

Persistent eosinophilic inflammation in severe asthma is often associated with adult-onset disease and with aspirin sensitivity. Patients with eosinophilic inflammation frequently have more severe symptoms, worse disease control, and a greater risk of exacerbations than patients with other pathological phenotypes of asthma.[25,86]

The mechanisms of eosinophilic inflammation are not well defined. Identification of an eosinophilic phenotype has traditionally been made by sputum analysis or endobronchial biopsy. Additionally, exhaled NO concentration has been proposed as a tool for identifying patients with persistent eosinophilic inflammation.[87,88] Generally, the exhaled NO concentration correlates with the number of eosinophils in sputum or biopsy samples, even in patients on high doses of corticosteroids[88]. Treatment strategies that use exhaled NO to control steroid dosage have been controversial in the past[89], but recent studies have produced satisfactory results on this issue[90,91].

Whether eosinophilia is a permanent phenotype or one dependent on the current treatment and level of disease control remains to be seen. Despite the evidence in support of a persistent eosinophilic phenotype in a proportion of patients with moderate-to severe asthma, two studies suggest that eosinophilic inflammation might be present in a greater proportion of patients with asthma than previously believed, since this inflammation could be present in a distal portion of the lung that is not assessed by standard methods. In one study, about 50% of patients with severe asthma that had previously been identified as non-eosinophilic were found to have eosinophilic inflammation in the distal lung[23,92].

Perhaps the greatest validation of the importance of defining a specific phenotype is that phenotypic assessment improves treatment. Studies that selected an eosinophilic endpoint in their design support the idea that identification and modification of the level of eosinophilic inflammation can lead to improved outcomes. Two large-scale, long-term studies have compared a basic "guidelines" approach to therapy with an approach in which the sputum eosinophil count dictated which intervention was used.[25,93] In these studies, treatment was designed to lower the number of sputum eosinophils to less than 3% of the total inflammatory cells. This led to fewer severe exacerbations of asthma and no overall change in the corticosteroid dose compared with the "guidelines"approach.

The mechanisms of eosinophilic inflammation are not well defined. Although both IL-5 and the chemokine eotaxin, both of which have eosinophilotactic activity, have been reported to be increased in asthma, studies that aimed to inhibit these pro-eosinophilic mediators were not accompanied by clinical efficacy.[82,94] Recent studies of targeted therapy, however, such as those using Mepolizumab, a humanized monoclonal antibody (mAb) with potent IL-5 neutralizing effects, performed specifically in a cohort with eosinophilic asthma, showed that in addition to reduction of eosinophils, a reduction of the number of exacerbations has also occurred.[95,96] Mepolizumab therefore, could be a potential treatment for eosinophilic diseases.

Neutrophilic asthma

Severe asthma may also be associated with neutrophilic inflammation,[10,97] but the precise role of neutrophils remains to be determined. Many patients with neutrophilic inflammation have concomitant eosinophilic inflammation seen on tissue biopsy, while sputum assessment might show a clear predominance of either neutrophils or eosinophils.[38] Neutrophilic asthma is seen most commonly in patients with severe disease and has been reported in autopsies of patients who died soon after the onset of a severe exacerbation.[98]

The cause of neutrophilic inflammation in asthma is not well understood. The association with severe asthma

could be caused by treatment with high doses of corticosteroids, which have been shown to decrease the apoptosis of neutrophils *in vitro*.[99] Neutrophilia may represent a continuous influx of cells from the bloodstream due to continuous antigenic stimulation of the bronchi, or it may be influenced by high levels of steroid treatment. Several mediators linked to neutrophil LT B4, IL-8, macrophage inflammatory protein-1a and TNFα) have been shown to be increased in severe asthma[97]. They induce neutrophil chemotaxis, activation and survival and upregulate endothelial adhesion molecules. Epidermal growth factor receptor (EGFR), a marker of epithelial stress/damage, is increased in proportion to disease severity. EGFR expression in the bronchial epithelium correlates with IL-8 indicating that EGFR can also contribute to this sustained neutrophilic inflammation[100].

This phenotype seems to be less responsive to corticosteroid therapy than eosinophilic asthma.[101] Anti-neutrophilic treatment has not been systematically studied. Thus no studies have successfully targeted treatment of this pathological phenotype .

Paucigranulocytic asthma

Asthma has been thought of as an inflammatory disease for the past 20–30 years, yet studies suggest that asthma can present in the absence of an identifiable influx of inflammatory cells such as eosinophils, neutrophils, or lymphocytes[38]. Inflammation might take less traditional forms, perhaps caused by activation of resident cells, such as mast, epithelial, or smooth muscle cells. Unfortunately, no biological markers have been identified for this paucigranulocytic phenotype. Some studies suggest that these patients do not respond to corticosteroid therapy, and might benefit from reduction in their corticosteroid dose[102], but the inflammation might increase during exacerbations in these patients or in response to corticosteroid dose reduction, resulting in the asthma becoming granulocytic in phenotype.

Genes and asthma

A number of genes have been identified that contain polymorphisms which influence immune or pulmonary development and response to environmental exposures, perhaps increasing the risk for development of asthma. Over 100 genes have been reported to be associated with asthma or related phenotypes. Among these are: NOS3, FCER1B, IL4RA, ADAM33, GRPA, SPINK5, ORMFL3, MYLK, ECP, CYLTR1, CD14 and some of the Toll-like receptors, among others.[103-107] In the period 2006-2007 alone, 53 novel candidate gene associations were reported[108]. It has been suggested that certain genotypes may be associated with asthma which persists into adulthood. One study found that Arg16–Gly27 homozygotes are more likely to have recurrent wheezing as adults; however, this genotype is of low frequency (3%) in wheezing adults[109]. Furthermore, the genotype of β2 adrenergic receptor affects the long-term response of β2 adrenergic agents and patients homozygotic to Arg-Arg mutations should possibly avoid β2 agents for the treatment of their asthma[110]. The genetics of asthma susceptibility is complex, with the same genotype sometimes conferring protection and sometimes risk depending on the environmental exposures.

Molecular phenotyping of severe asthma

It has already been mentioned above that at least some patients with severe asthma have been characterized by endobronchial biopsy as having either neutrophil-predominant inflammation or increased tissue eosinophils.[15,38] Eosinophil-positive patients, especially those with early-onset disease and associated airway remodelling, have been shown to have an increased incidence of near-fatal events, although other studies have found no clinical differences between the eosinophilic and non-eosinophilic phenotypes[23]. Together, these observations suggest that severe asthma is a pathologically heterogenous disorder, and an objective method for distinguishing clinically significant subtypes is still lacking.

The findings that patients with severe asthma have distinct inflammatory processes suggest that they may also express distinct airway cytokine profiles compared with patients with responsive asthma. Brasier AR, et al[22] investigated this hypothesis by examination of airway cytokine expression patterns in BAL from a matched group of patients with non-severe and severe asthma by using bead-based multiplex cytokine arrays (Luminex xMAP). The final intent of the researchers was to accurately define the asthmatic phenotypes, based on molecular profiles that may facilitate clinical investigation on the pathogenesis and treatment of asthma. Statistical analysis identified 4 groups, labelled G1 to G4, that differed between each other in more than 15 variables. These variables included the cellular features of BAL (pulmonary eosinophils, alveolar macrophages) and lung function measurements (lung function values, FEV_1 response to bronchodilation and sensitivity to methacholine). Patients in G1 had a significantly reduced FEV_1, FVC, and FEV_1 improvement after

bronchodilator therapy and high levels of IL-2 compared with the other groups, and a high proportion of asthma classified as severe by the ATS criteria. G2, the group with the best preservation of lung function was high in patients with non severe asthma according to ATS criteria and had high levels IL-1Ra. G3 had high levels of IP-10 and G4 had high levels of IL-2R and many other cytokines. The study by Brasier et al. identified 10 cytokines as being most important for identification of the G1 severe group. The rank order of these cytokines (from the most to the least informative) was IL-1Ra, MIP-1a, MIG, IL-15, IL-2R, IP-10, IL-4, IL-6, MCP-1, and IL-2. Classification methods for predicting methacholine sensitivity were developed, and hyperresponders could be predicted with 88% accuracy. The cytokines that contributed to this model were IL-2, IL-4, and IL-5. On the basis of this classifier, 3 distinct hyperresponder classes were identified that differed in BAL eosinophil count and PC20 methacholine.

This study provided a first proof of the concept that informative patterns of cytokines can be detected and interpreted in BAL from patients with asthma and may contribute to more objective classification of disease type. The authors' interpretion of these findings is that patients with asthma with apparently similar clinical characteristics are in fact composed of heterogeneous subtypes that can be further distinguished on the basis of BAL cytokine profiles. It appears that important new diagnostic and prognostic information is available in airway fluid, indicating that future research in biomarker identification will be informative.

Clustering of Phenotypes

Each patient with asthma shows characteristics of different phenotypes; this creates difficulties in the accurately selection of patients for participation in epidemiological or investigational studies, and for interpretation of the effects of different therapeutic strategies. Current descriptions of asthma phenotypes are limited by subjectivity and poor coherence. A robust system of classification that incorporates the multidimensionality of asthma is needed to identify subgroups with consistent patterns of disease[111]. An important study by Haldar et al.[112] has suggested that cluster analysis of asthmatic populations explains better the differences seen in the effects of treatment. In this study, clusters of a population managed in primary care with predominantly mild to moderate disease, were compared with a refractory asthma population managed in secondary care. Differences in asthma outcomes (exacerbation frequency and change in corticosteroid dose at 12 months) were compared between clusters in a third population with predominantly refractory asthma, either minimizing eosinophilic inflammation in the sputum (inflammation-guided strategy) or applying standard clinical care. According to this study, two clusters (early-onset atopic and obese, non-eosinophilic) were common to both refractory and mild to moderate asthma with greater severity of characteristics. Two other clusters characterized by marked discordance between symptom expression and eosinophilic airway inflammation (early-onset symptom predominant and late-onset inflammation predominant) were specific to refractory asthma. Inflammation-guided management was superior for both discordant subgroups, leading to a reduction in exacerbation frequency in the inflammation-predominant cluster and a dose reduction of inhaled corticosteroid in the symptom-predominant cluster. Using the sputum guided care, the obese, non-eosinophilic phenotype, for example, in the Haldar et al. study, common to populations of mild to moderate and refractory asthma, was characterized by symptoms that were not associated with eosinophilic airway inflammation. Given the recognized association between eosinophilic airway inflammation and steroid responsiveness in airway disease, the reported steroid resistance of asthma in obese patients may in part be explained by the lack of presence of eosinophils[113]. Using the conventional clinical strategy care, without examining the type of airway inflammation, overtreatment with corticosteroids for symptom improvement may be given, whereas, possible strategies for improving compliance could have a better effect.

The following section on specific patients' characteristics could possibly be explained by the above classification of asthmatic subjects and it is probable that different ways of management could have led to more effective treatment of asthma in these patients. Further investigation is needed for clarifying the difficulties in identification of phenotypes.

Characteristics of individual patients

Most asthmatic patients do not follow the characteristics of a single phenotype, but fit into many phenotypes. Two case studies are presented to illustrate this phenotype interrelationship.

The first case is that of a Greek woman who was born preterm in 1964 with low birth weight (1.5kg). She has a monozygotic sister with mild asthma. She is a lifelong non-smoker with asthma and rhinitis since infancy. She worked in a cotton mill from 1985 to 2000 when she

stopped because of difficulty in breathing. Her course was notable for frequent hospitalizations and emergency room visits for severe asthma attacks, but she has never required intubation. She experiences typical asthma symptoms of wheezing, cough and chest tightness in response to cold air, hot weather, fumes, and upper respiratory infection. Over the years she has developed significant GERD, OSA and weight gain, and since 2002 she has had nasal polyps and sinusistis. She is unable to taper methylprednisolone below 20mg/d without having more frequent asthma attacks. Besides methylprednisolone, her medication includes high-dose combination of steroids with long-acting β2 agent, salbutamol, a LT modifier, omeprazole, and calcium. Inhaled or systematic steroids were introduced at least 30 years after the start of her asthma. In 2005 she had 2 pregnancies that terminated early with embryonic death due to low HbSO2. She has normal IgE, so anti-IgE therapy is not an option. In 2006 she developed hyperthyroidism which is managed with thyroxine tablets and she became depressed but did not accept regular medication. She is seen weekly to monthly.

On examination, she is mildly Cushingoid. Chest CT scan has shown bronchiectasis. She does not have the Churg-Strauss syndrome. Recent spirometry shows FEV_1 of 0.67 L (34% predicted) and FEV_1/FVC 62%, with no bronchodilation response. Her PO_2 is 58 mmHg and PCO_2 rises to 50 mmHg (6.7 kPa). She uses O_2 every day. She is unable to perform everyday activities or walk freely, she has severe sinusitis and produces purulent sputum (culture shows *Haemophilus* and *Streptococcus*) and she is hospitalized 3 times /year.

This patient's asthma is corticosteroid-dependent, requiring high doses of oral corticosteroids, although control is never fully achieved, suggesting that she may have an element of corticosteroid resistance. Circulating eosinophils are not increased, but any effort to reduce steroids has been unsuccessful. This patient's asthma also belongs to the exacerbation-prone phenotype, as well as the fixed limitation of airflow phenotype and also, her occupational exposure to the endotoxin of cotton dust possibly aggravated her symptoms. Cotton work with long employment is associated with irreversible symptoms, longitudinal loss of lung function (decline of FEV_1 32.3ml/year and of FVC 20.1ml/year) and possibly severe pulmonary disability.[114,115] This patient is seriously depressed, without appropriate medication and, as documented above, psychological dysfunction is considered as one of the most important risk factors for frequent severe exacerbations.

The second case is that of a 53yr-old caucasiane man who presented with severe, persistent asthma asking to participate in a clinical research study on asthma. He is a lifelong non-smoker with asthma since the age of 40 years. He has never required intubation, but has required oral corticosteroids since 4 years ago to control his asthma. He currently complains of wheezing and chest tightness on minimal exertion. His medications included a combination of high dose steroids and LABA for maintenance and relief. Spirometry showed FEV_1 of 0.70 L (35% predicted) and FVC of 1.4 L (60% predicted). There was no response to bronchodilation. The diffusing capacity was normal. He also has OSA since 2004 and he is using CPAP, His PaO_2 was 68mmHg and he experiences serious exacerbations once a year. He requires daily oral steroids so as not to experience exacerbation, but after long term treatment with steroids there is no improvement in symptoms or change in lung function, suggesting a phenotype of fixed airflow obstruction due to asthma and possibly steroid resistance. This patient has late onset asthma, but shares many common characteristics with the previous female patient, although he had no aggravating occupational exposure, but he is not psychologically burdened or seriously depressed. He leads an almost normal life a quality not seriously impaired.

CONCLUSIONS

A number of asthma phenotypes have been described; however, these descriptions are not based on a clear understanding of the pathobiology of these phenotypes and it is often difficult to combine or compare studies, due to lack of a common definition or well-characterized description of the phenotype being studied.

Considerable progress has been made in recent years to define and understand the pathophysiology of asthma. As new treatment modalities for asthma become available, substantial effort is needed to define and understand which patients will respond to which treatment. Ongoing research efforts provide more insight into the relationship between genetics, environment, genotype-phenotype relationships and the pathophysiology of asthma; thus it should be possible to define more precisely clinical phenotypes based on pathological mechanisms and genetics. Targeted approaches will aid in the identification of better biomarkers for certain phenotypes.

The description of pathological phenotypes of asthma is in its infancy. In the future, more phenotypes will be identified and characterized through specific biomarkers.

By identifying asthma phenotypes, the application of more appropriate, more effective, and safer forms of treatment of each phenotype of asthma will be possible.

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