Introduction

The American Thoracic Society (ATS) has a long history, originating as the American Sanatorium Association in 1905, which was established to promote the treatment and prevention of tuberculosis. Since then, the scope of our mission has widened, and the Society has become the premier professional society in respiratory medicine, with more than 15,000 members worldwide who are dedicated to advancing our clinical and scientific understanding of pulmonary diseases, critical illnesses, and sleep-related breathing disorders. Our members provide care for millions of people who suffer daily from asthma, chronic obstructive pulmonary disease, cystic fibrosis, sleep apnea, and lung diseases related to prematurity, to name a few.

In celebration of our 110th anniversary, the ATS journals and 2015 ATS International Conference will highlight many of the advances in patient care and research in adult and pediatric pulmonary, critical care, and sleep medicine. The **ATS Discoveries Series** is a new collection of articles and talks that features major scientific and clinical breakthroughs, which have changed the lives of the patients we treat, as told by leading scientists and clinicians. With input from our membership, the topics range from the development of bronchoscopy to the discovery of surfactant, from insights into asthma pathogenesis to the potential of lung regeneration.

The following article titled "Evolving Concepts of Asthma," by Marc Gauthier, M.D., pulmonary, allergy, and critical care medicine fellow; Anuradha Ray, Ph.D., professor of medicine and immunology; and Sally E. Wenzel, M.D., professor of medicine and director of the Asthma Institute, all at the University of Pittsburgh, is the second of the series published in the *American Journal of Respiratory and Critical Care Medicine*. I hope you enjoy learning about the seminal discoveries in respiratory medicine and their impact on patient care, now and in the future. Please be sure to read all of the articles in the Discoveries Series, which will appear not only in the "Blue" journal, but also the *American Journal of Respiratory Cell and Molecular Biology* and *Annals of the American Thoracic Society* during the coming months.

Thomas Ferkol, M.D.

Immediate Past President, American Thoracic Society

Evolving Concepts of Asthma

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Abstract

Our understanding of asthma has evolved over time from a singular disease to a complex of various phenotypes, with varied natural histories, physiologies, and responses to treatment. Early therapies treated most patients with asthma similarly, with bronchodilators and corticosteroids, but these therapies had varying degrees of success. Similarly, despite initial studies that identified an underlying type 2 inflammation in the airways of patients with asthma, biologic therapies targeted toward these type 2 pathways were unsuccessful in all patients. These observations led to increased interest in phenotyping asthma. Clinical approaches, both biased and later unbiased/statistical approaches to large asthma patient cohorts, identified a variety of patient characteristics, but they also consistently identified the importance of age of onset of disease and the presence of eosinophils in determining clinically relevant phenotypes. These paralleled molecular approaches to phenotyping that developed an understanding that not all patients share a type 2 inflammatory pattern. Using biomarkers to select patients with type 2 inflammation, repeated trials of biologics directed toward type 2 cytokine pathways saw newfound success, confirming the importance of phenotyping in asthma. Further research is needed to clarify additional clinical and molecular phenotypes, validate predictive biomarkers, and identify new areas for possible interventions.

Keywords: asthma; phenotyping; endotyping; clustering; biologic therapy

Asthma is defined by typical symptoms (wheezing, chest tightness, and/or shortness of breath), evidence of airway obstruction, and airway hyperreactivity or reversibility of obstruction (1). Although originally believed to be a single disease, it has been increasingly recognized as a complex of multiple phenotypes, each with a somewhat unique natural history, severity, and treatment response. This heterogeneity has led to challenges in treatment, especially in patients who respond poorly to current therapies. This review will explore the evolution of our understanding of asthma phenotypes and where current research is heading.

Historical Asthma

Asthma has been recognized throughout recorded history. The word asthma comes from the Greek ασθμα, ασθματος, meaning a "short-drawn breath, hard breathing, or death rattle," and thus, represented multiple breathing maladies rather than a single disease (2). Earliest descriptions of "asthma" come from the Hippocratic corpus, a collection of texts from 420 to 370 BCE assembled in Alexandria in the third century BCE (3). In *The Sacred Disease,* asthma is described as a complication of epilepsy, caused by phlegm from the brain lodging in the lungs, thereby blocking the airflow to the body. Despite this "humoral" view, there was also an early recognition of the association of asthma with environmental factors, including a relation to certain winds and worsening in certain geographical areas (4).

The first modern descriptions come from Sir John Floyer's treatise on asthma from 1698 (5) (Figure 1). Floyer, who had asthma, described the still predominant Hippocratic humoral pathology, but also described bronchial constriction as a cause for wheezing. He discussed his own asthma flares, providing some of the first descriptions of uncontrolled asthma. He also described his association of symptoms with regions and triggers, which was later identified as allergic asthma. His text remained popular throughout the next two centuries, but much remained poorly understood.

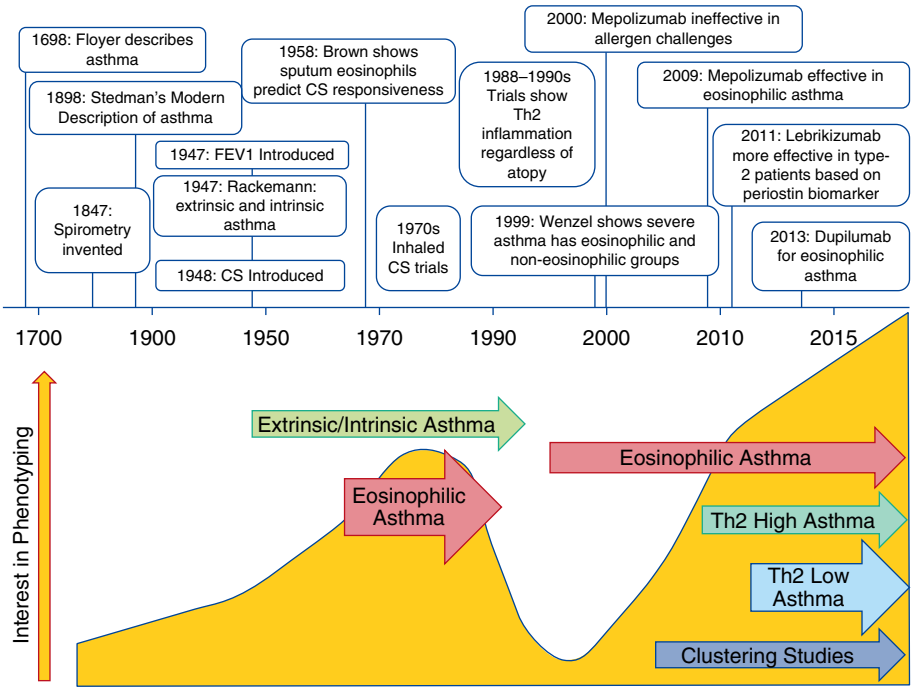

Figure 1. A timeline showing major events in the understanding of asthma and phenotyping. The timeline is "semilogarithmic" in scale, emphasizing the growing amount of research in the field with time. *Arrows* below represent the emergence of various phenotype strategies. Background shows the overall changing interest in asthma phenotyping over time. CS = corticosteroids.

Beginning in the late 19th century, a more formalized definition of asthma emerged, detailing an association with allergy and the concept of triggers (6). Although John Hutchinson introduced vital capacity measurements in the 1840s (7), time-dependent FEV was not introduced until 1947 (8). Bronchodilator responsiveness in FEV_1 emerged as a diagnostic criterion for asthma in the 1950s, although the sensitivity and specificity of this test were never formally addressed (9, 10).

Treatments, including epinephrine, anticholinergics, methylxanthines, and inhaled β-agonists were all introduced in the first half of the twentieth century (6). In 1952, McCombs (11) described the use of systemic corticosteroids (CS) and adrenocorticotropic hormone (ACTH) to prevent and treat asthma exacerbations, leading to widespread use. Due to systemic CS side effects, topical delivery was explored. In the 1970s, beclomethasone, which was previously used as a topical CS, was aerosolized and studied in 60 patients with asthma, 37 of them on long-term oral CS. Twenty-eight were able to stop oral therapy, and 19 of 23 patients not on oral CS had improved symptom control (12). A noninferiority trial showed that patients starting on oral or inhaled CS therapy had no difference in control (13). With further confirmatory studies (14), the era of inhaled CS therapy as standard of care began (15).

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As inhaled CS gained prominence, the underlying pathology of asthma was also explored. Historically associated with allergies, it was realized early on that not all asthma patients were atopic by skin prick testing (16). However, a population study from the 1980s showed strong correlation between age-adjusted blood IgE levels and asthma, which suggested that all asthma had an allergic component (17). Increased levels of the IL-2 receptor and the cytokines IL-3, IL-5, and granulocyte–macrophage colony–stimulating factor (GM-CSF), found in blood T cells of patients with asthma, promoted eosinophil survival, regardless of the presence of atopy (18). Examination of asthmatic bronchoalveolar lavage (BAL) fluid further showed that IL-2, -3, -4, and -5, and GM-CSF could be localized to T cells (19), which was consistent with previous work on inflammation from Th2 cells, a particular T-helper cell subclass (20). Further studies showed elevated levels of mRNA for IL-4 and IL-5 that were correlated with airway hyperreactivity in patients with asthma (21) and the increased presence of FcεRI receptors (a high affinity receptor for IgE) in the bronchial biopsies of patients with asthma, regardless of atopic status (22). In sum, these studies suggested allergic/Th2 driven disease as the cause for all asthma.

Identification of Th2 pathway cytokines in asthma led to an interest in directly targeted biologic therapy, especially because of the association between sputum eosinophilia and asthmatic disease (23). However, an allergen-challenge, placebo-controlled trial of an antibody to IL-5, despite reducing eosinophilia, failed to improve early or late asthmatic reactions or airway hyperreactivity (24). A larger study of persistent asthma, despite inhaled CS therapy, again showed no improvement in clinical outcomes despite significant reductions in blood and sputum eosinophils (25). Similarly, an antibody to the IL-4 receptor in moderate-to-severe asthma showed no differences in relevant asthma outcomes (26). These studies suggested either that Th2 cytokines were not important in asthma or that they were only important in a subset of patients.

Recognition was also emerging that traditional asthma medications did not work in all patients. Some inhaled CS trials showed either mixed benefits or had preselected patients with response to CS (12–14). Although inhaled CS were generally more effective than a leukotriene receptor antagonist, either or both medications failed in many patients (27). Similarly, 55% of children with mild-to-moderate asthma had no benefit from either inhaled CS or montelukast. This study was one of the first to find that certain biomarkers, including high fractional exhaled nitric oxide (F_{ENO}), blood eosinophil counts, and IgE predicted greater responses to inhaled CS (28). These findings supported the underlying differences in pathobiology that potentially contributed to different treatment responses.

Phenotypes in Asthma

Phenotypes are defined as the "observable properties of an organism produced by the interactions of the genotype and the environment." (29) An ideal molecular phenotype identifies common molecular pathways with common clinical characteristics. To be termed an "endotype," certain molecular pathways must be identified as critical to the clinical manifestations of the patients (30). Depending on the level of efficacy of targeted biologic therapies in the next several years, asthma endotypes may begin to emerge in which one or more of these pathways defines the disease.

Clinical and Inflammatory Phenotyping

Clinically distinct asthma "subgroups" have been recognized for years. In the 1940s, Rackemann (16) described two clinical asthmatic phenotypes. Extrinsic asthma was believed to be due to allergens from outside the body and associated with environmental exposures, atopy, and other allergic diseases, as well as younger age of onset; intrinsic asthma was postulated to be due to factors intrinsic to the body, was present regardless of season or environment, lacked atopy, and was associated with older age at onset (16, 31, 32). Age of onset has remained a key differentiator. In the 1960s, the triad reported by Samter and Beers (asthma, nasal polyposis, and aspirin sensitivity) identified a late-onset asthma phenotype associated with eosinophilia (33, 34). Forty years later, an endobronchial biopsy study of patients with severe asthma divided by early (<12 yr old) versus late age at onset showed that allergic symptoms and atopy were associated with early-onset disease, whereas late-onset disease had lower lung function for the duration of disease and more tissue eosinophils. Furthermore, a subset of patients with late-onset disease without eosinophils showed none of the typical subepithelial basement membrane (SBM) thickening suggestive of an alternative disease pathway (35). Statistical clustering further supported this concept because Haldar and colleagues identified a patient cluster with later onset and exacerbation-prone disease with high levels of sputum eosinophils (36).

Another early approach to phenotyping beginning in the late 1950s found that sputum eosinophils predicted response to CS therapy (23, 37). Later studies of inhaled CS confirmed this finding and argued that, in general, eosinophils were markers of a CS responsive asthma phenotype (38–40). A later study targeting CS therapy to sputum eosinophil counts rather than symptoms actually improved control (41). In contrast to studies in milder disease in which eosinophils predicted CS responses, Wenzel and colleagues examined endobronchial biopsies of 34 severe patients with CS refractory disease and found elevated tissue eosinophils in approximately 50% of these patients, with rare or no eosinophils in the remaining patients. Here, eosinophils were associated with greater likelihood of a previous near-fatal event, a higher number of transforming growth factor-β–positive cells in the tissue, and a thicker SBM (42). Importantly, these studies began to link molecular processes to a clinical phenotype.

This and earlier studies led to a growing realization that some patients responded poorly to CS and developed severe, poorly controlled disease. These patients, compared with CS responders, were reported to have higher levels of IL-4 and -5 in their BAL after CS therapy (43). Similarly, Adcock and colleagues showed that CS responders had greater glucocorticoid receptor availability in peripheral blood monocytes, further supporting differences in pathology (44). Numerous subsequent studies have clinically differentiated asthma subtypes or phenotypes, using characteristics such as airway obstruction and reversibility, presence of exacerbations, atopy/allergy (and other triggers), as well as age at onset.

Supporting these clinically based observations, a recent wave of statistical

clustering analyses of well-characterized asthma cohorts have appeared. In a cohort of more than 700 patients recruited through the Severe Asthma Research Program (SARP) that used 34 compressed variables, age at onset and lung function were found to be the most significant contributors to identifying 5 clinical asthma phenotypes. Three phenotypes were early onset, mild-to-severe "allergic" asthma, with atopy, and a history of allergic symptoms. Two additional phenotypes were identified: one was a very late-onset female, inflammatory, and obese phenotype; and the other was a very severe, generally later-onset phenotype with mixed inflammation (45). This "clinical clustering" was followed by an "immuno-inflammatory" clustering not included in the first approach (46). Wu and colleagues examined nearly 400 SARP patients with clinical-physiologic data who underwent bronchoscopy, BAL cell counts/differentials, allergy skin testing, and measurements of F_{ENO} and IgE. Using more than 100 variables, this study again showed the relative importance of age at onset, but also added inflammatory variables, particularly neutrophilic inflammation and F_{ENO}, to define 6 subject clusters (1 healthy control and 5 asthma clusters). The primary difference between these inflammatory clusters and the previous clinical clusters was the "statistical" recognition of a late-onset, highly eosinophilic cluster associated with nasal polyposis and sinusitis, suggestive of later onset eosinophilic asthma, and even the triad reported by Samter and Beers (33, 34). Several additional clustering approaches have been reported, including one from Europe, which supported stability of some clusters (primarily early onset/allergic) and the instability of others over time (47). Finally, a study clustering patients in the Childhood Asthma Management Program suggested that clustering may help identify responders to specific asthma therapies, despite a minimal relationship to inflammatory markers (48).

Despite varied results in these studies, consistently relevant variables and even phenotypes have emerged. Age at disease onset, especially as related to allergy, and the presence of eosinophils remain consistent markers of distinct phenotypes (45–47). Traditional early-onset allergic asthma associated with clear precipitating factors is also consistently observed across studies. However, considerable variability exists in clusters related to later onset disease, such as obesity and neutrophilic inflammation.

Molecular/Physiologic Phenotyping

The alternative to clinical phenotyping involves using molecular disease pathways to identify patient groups who respond to certain therapies (49). Traditional clinical phenotyping for atopy and/or allergy was insufficient to identify patients most likely to respond to the IgE antibody omalizumab. Inclusion criteria in most trials specified evidence of atopic asthma, as defined by elevated total and specific IgE levels. Although statistical benefit was seen with treatment, responses were heterogeneous, because not all patients with allergic asthma responded to therapy (50, 51). Thus, despite findings suggestive of atopic/allergic asthma, IgE did not appear to be a driver of disease in many of these patients. A *post hoc* analysis showed that the patients most likely to respond were those that had low lung function and were treated with high-dose CS therapy, but it could not identify an inflammatory or molecular mechanism (52).

Type 2 Hi Asthma

Although the cytokines IL-4, -5, and -13 were initially identified as originating from Th2 CD4 T cells, further evidence showed that these cytokines and others in the Th2 pathway could be produced by non-Th2 cells, such as basophils, mast cells, and eosinophils (53, 54). This recognition led to a relabeling of this inflammatory state as type 2, rather than Th2, to reflect their more diverse immunologic origin.

The ability to perform molecular profiling on well-characterized asthma populations has contributed to an evolving ability to "molecularly" phenotype asthma. The first broad molecular profiling study of airway epithelial cells in mild asthma yielded limited results, with only small differences between asthma and healthy controls (55). However, the authors found three differentially expressed genes (*CLCA1*, *SERPINB2*, and *periostin*) regulated *in vitro* by the type 2 cytokine IL-13. Following up, Woodruff and colleagues reevaluated the brushings from 42 patients with mild to moderate asthma and 28 healthy controls using quantitative polymerase chain reaction for these three genes, clustering patients on the basis of the expression of this type 2 signature. Surprisingly, approximately 50% of the asthma patients were classified as type 2 Hi, whereas the others (type 2 Lo) were clustered with the healthy, nonatopic controls. Importantly, type 2 Hi asthma was associated with consistent clinical and inflammatory characteristics, including increased blood and airway eosinophilia, airway hyperresponsiveness, a thickened SBM, higher IgE levels, and higher tissue expression of IL-5 and -13 (56). However, the most important finding was an association with a response to inhaled CS. The type 2 Hi phenotype had robust improvement in FEV_1 with a moderate dose of fluticasone, whereas the type 2 Lo phenotype had no improvement. This renewed interest in biologic studies that targeted a specific type 2 Hi asthma.

Studies of biologic therapies targeted to specific patient populations using various biomarkers began to emerge (Table 1). The first of these studies revisited mepolizumab, an antibody to IL-5 that in a broad asthma population had previously been largely ineffective (25). In contrast, treatment in patients with severe eosinophilic asthma (many with late-onset/sinus-related disease) significantly reduced asthma exacerbations (57). Further studies showed that anti–IL-5 (or IL-5R) therapy targeted to patients with blood or sputum eosinophilia consistently decreased exacerbations, daily oral CS dose, and in some cases, also improved symptoms and lung function (58, 59). Similarly, using eosinophilia as a guide, dupilumab (an antibody to the receptor IL-4Rα) significantly reduced loss of asthma control when background therapy was withdrawn, with additional improvements in FEV_1 and asthma symptoms (60). Finally, lebrikizumab (an antibody to IL-13) showed only modest benefits in all patients, but it showed a robust improvement in FEV_1 in those with high-serum periostin levels, which is a marker of type 2 inflammation (61). F_{ENO} worked similarly well as a type 2 Hi biomarker in this study, and was significantly suppressed by lebrikizumab and dupilumab, confirming the biologic effect of the drugs. Similar results were reported with tralokinumab when identifying patients by their high sputum IL-13 levels (62). Finally, in a retrospective analysis, even the currently

Table 1. Biologic Agents in Asthma and Potential Biomarkers

Pathway	Biologic Agents Approved or in Trials	Biomarkers Predicting Response to Therapy	Biomarkers Modulated by Therapy	Reference(s)
IgE	Omalizumab	F_{ENO} Blood eosinophils Periostin	F_{ENO} Sputum eosinophils	Hanania *et al.*, 2013 (63)
IL-4/IL-13	Pitrakinra (competitive antagonist) Dupilumab (receptor antibody)	F_{ENO} Sputum eosinophils Blood eosinophils	F_{ENO}	Wenzel *et al.*, 2007 (81) Wenzel *et al.*, 2013 (60)
IL-13	Lebrikizumab Tralokinomab	Periostin F_{ENO} Eosinophils Sputum IL-13 (periostin surrogate)	F_{ENO}	Corren *et al.*, 2011 (61) Piper *et al.*, 2013 (62)
IL-5	Mepolizumab Reslizumab Benralizumab	Sputum eosinophils Blood eosinophils	Sputum eosinophils Blood eosinophils	Flood-Page *et al.*, 2007 (25) Haldar *et al.*, 2009 (57) Pavord *et al.*, 2012 (58) Bel *et al.*, 2014 (59) Nair *et al.*, 2009 (66) Ortega *et al.*, 2014 (74) Castro *et al.*, 2011 (75) Castro *et al.*, 2014 (76)

Definition of abbreviation: F_{ENO} = fractional exhaled nitric oxide.

available biologic, omalizumab (targeted to IgE) was more efficacious in patients with evidence of type 2 inflammation, as measured by blood eosinophils, serum periostin, or F_{ENO} (63, 64). Overall, these studies began to link type 2 biomarkers to responses to type 2 targeted therapy, supporting a type 2 Hi molecular phenotype.

Type 2 Hi Biomarkers

These striking efficacy findings sparked interest in biomarkers to predict disease severity and response to treatment (Table 1). Asthma biomarkers were identified as early as the mid-twentieth century when Brown described an association between the presence of sputum eosinophils and response to CS therapy (23, 37), followed by studies that confirmed this association and demonstrated its predictive value (28, 38, 39, 41, 65). Because of the association between eosinophils and IL-5, sputum eosinophils successfully predicted response to drugs that targeted IL-5 (57, 66), with reductions in sputum eosinophils associated with therapeutic response (25, 57, 66). Despite this, recent studies that examined the relationship between sputum eosinophilia and elevated airway type 2 cytokines (IL-4, -5, and -13) found strong specificity but low sensitivity, suggesting that some patients have elevated type 2 signatures without sputum eosinophilia (67).

Because sputum eosinophils are technically difficult to measure, interest in blood eosinophils arose (68, 69). Blood eosinophils have been similarly linked to elevated type 2 cytokines in the airways, although not as robustly as sputum eosinophils (67). Blood eosinophilia has been linked to worse outcomes in asthma (70, 71), more severe disease (72, 73), and is predictive of CS responsiveness (28, 65). Blood eosinophilia also predicts response to anti–IL-5 therapy (mepolizumab, reslizumab, and benralizumab) and IgE therapy (omelizumab) (58, 59, 63, 64, 66, 74–76), and decreases with treatment (24, 57, 59, 66, 74–76). As a result, blood eosinophils have largely replaced sputum eosinophils as a type 2 biomarker in clinical trials.

F_{ENO} has also been of interest as a type 2 biomarker. The primary enzyme driving F_{ENO} levels, inducible NO synthase, is upregulated by IL-13 (77) and IL-4 (78). Elevated F_{ENO} is similarly associated with worse asthma symptoms (72, 79), need for CS (80), and is predictive of responsiveness to CS therapy (28, 65). The relationship between eosinophilia and F_{ENO} is complex (40, 67, 78). Although some correlations exist, marked reduction in blood and sputum eosinophils through anti–IL-5 approaches had no impact on F_{ENO} (57). Similarly, reduction in F_{ENO} through IL-4Ra– or IL-13–directed approaches, while consistently reducing F_{ENO}, had no effect on blood eosinophils and tended to increase them (60, 61, 81).

Periostin, a new biomarker of interest, was initially identified in microarray and polymerase chain reaction studies (55). Follow-up studies have suggested association with sputum eosinophilia (82), increased airway expression in asthma, and an association with Th2 inflammation (67). Periostin successfully predicted response to IL-13 targeted therapy (61), in addition to predicting response to omalizumab (63). However, its utility as a response marker is uncertain.

Although further clinical studies are needed for all these biomarkers, it is likely that several of these, alone or in combination, will be useful in identifying patients for therapy using type 2–targeted therapies. Because of the high predictive value and ease of measurement of blood eosinophils, it is likely that they will serve as an initial biomarker to predict response to biologic agents targeting Il-4, -5, and -13. The role of periostin and F_{ENO} in targeting type 2 biologic therapy is less clear, although the change in F_{ENO} after dupilumab therapy correlates well with improvement in FEV_1. Thus, whether high F_{ENO} will be a better predictor for IL-4/-13 directed therapy or whether blood eosinophils will be a better

predictor of anti–IL-5 responses remains unclear. It is likely that clinical and research experience will eventually identify a panel of biomarkers that best predicts response to these biologic therapies.

Complex Type 2 Phenotypes

Despite the rise in success of targeted biologics for type 2 asthma, not all patients with type 2 Hi asthma respond to these therapies. Although anti–IL-5 showed efficacy in oral CS-dependent patients, there was still a substantial subgroup of patients in whom minimal effects were observed (59). Similarly, anti–IL-4 and/or -13 approaches remain unstudied in patients with very severe asthma. Further investigation into possible subgroups of type 2 Hi asthma remains important. A recent study by Modena and colleagues found several patient clusters among patients with elevated F_{ENO} that were suggestive of a type 2 Hi process, including one with a possible type 1 signature (83). Thus, even patients with type 2 Hi asthma may be grouped into additional subphenotypes who may selectively respond better to certain targeted approaches.

Type 2 Lo Asthma

Although the bulk of recent successful biologic treatment trials have been directed at type 2 cytokines, nearly half of patients with asthma lack evidence for this pathway (42, 56). The inflammatory processes associated with this broad phenotype remain unclear. Neutrophilic inflammation may play some role, but its meaning may differ on whether it is seen with or without eosinophils (84, 85). Biopsy studies showed patients without eosinophilic inflammation have a thinner SBM, suggesting an alternative pathology, whereas studies by Wenzel and colleagues (42) and Baines and colleagues (86) showed differences in gene expression in sputum from patients with neutrophilic versus eosinophilic asthma. These studies argue for a role for neutrophilic inflammation in some asthmatic phenotypes. Importantly, these patients are consistently found to be largely refractory to steroid treatment, and thus, they have limited treatment options (38, 39). Considerable work on mice has suggested a role for IL-17 in this neutrophilic inflammation (87, 88), but human data supporting the importance of this pathway, including the minimal efficacy of an anti–IL-17R antibody in moderate-to-severe asthma, is lacking (89, 90). Some studies have shown potential benefit with macrolide therapy in these patients, which decreases IL-8 levels and neutrophil activation (91). Macrolides have shown modest clinical efficacy in neutrophilic asthma phenotypes and in those with the type 2 Lo phenotypes, where neither eosinophils nor F_{ENO} were elevated (92). Currently, the exact pathophysiology of this pathway and whether the increased neutrophils identify the underlying pathologic state or are a marker of high CS use in a disease that is refractory to CS remains unclear. In our recent study, Th1 inflammation, together with a low Th17 and Th2 response, was detected in almost 70% of patients with severe asthma (93). A role for IFN-γ in increased airway hyperreactivity is suggested, using a mouse model of the disease.

Obesity-related asthma may also present as non–type 2 asthma. Obesity represents a difficult area in asthma, because it can be both a comorbid feature and possibly a causal feature of the disease. Increasing obesity is associated with worsening asthma, although the relationship of obesity with asthma pathobiology may differ by age at onset, with later onset of obese asthma reflecting a more causal role for obesity, whereas with earlier age of onset, obesity may be more of a comorbidity (94, 95). The pathobiology of obesity-associated asthma may involve chest wall biomechanics and airway compliance (96, 97), poor response to medications due to obesity, and adipose-related inflammatory activity (97, 98).

Similarly, smoking-related asthma may also represent a unique phenotype with neutrophilic predominance and type 1 inflammation seen in some studies (99). These patients are often poorly responsive to asthma therapies, but may benefit from smoking cessation (99).

Conclusions

It has become increasingly clear that asthma represents a heterogeneous disease with multiple phenotypes representing different pathobiologies, natural histories, symptom

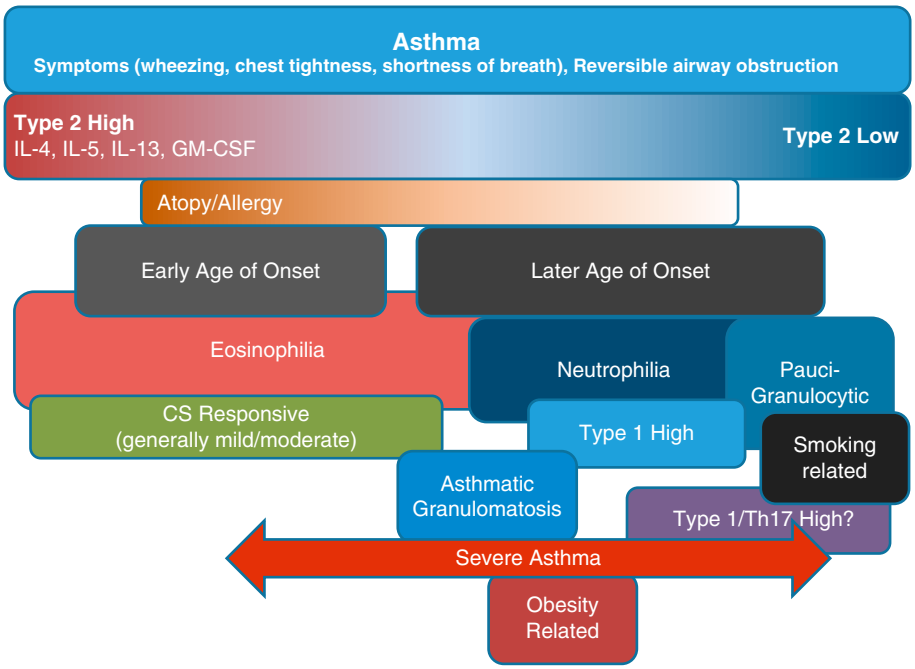

Figure 2. An example of current asthma phenotypes as they relate to inflammatory type (type-2 high or low) and other variables. Note that many phenotypes overlap because currently there is no clear demarcation between these groupings. Patients may exhibit clinical or pathologic features of multiple groups, emphasizing the limitations in the current understanding of phenotypes and the ability to use them routinely in clinical practice at this current stage. CS = corticosteroids; GM-CSF = granulocyte–macrophage colony–stimulating factor.

burden, and responses to therapy (Figure 2). The importance of these differences has been underscored by the failure of one-size-fits-all approaches to asthma care, from the lack of efficacy of CS in some patients with severe asthma to the initial failure of untargeted biologic therapy. Although our current molecular understanding of these phenotypes remains limited, ongoing studies are generating new and novel hypotheses for testing in clinical trials. Well-characterized large populations of diverse asthma patients with longitudinal follow-up are likely to add new information on molecular networks, including their inception and stability. Improved animal models reflecting the diversity of asthma will help test the importance of these pathways. In combination, this research will enable us to better characterize the phenotypes that make up the disease of asthma, and allow us to develop and target individualized therapies to the right patients. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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