Asthma in the elderly: Current understanding and future research needs—a report of a National Institute on Aging (NIA) workshop

Nicola A. Hanania, MD, MS, (Co-chair),[a]* Monroe J. King, DO, (Chair),[b]* Sidney S. Braman, MD,[c] Carol Saltoun, MD,[d] Robert A. Wise, MD,[e] Paul Enright, MD,[f] Ann R. Falsey, MD,[g] Sameer K. Mathur, MD, PhD,[h] Joe W. Ramsdell, MD,[i] Linda Rogers, MD,[j] David A. Stempel, MD,[k] John J. Lima, PharmD,[l] James E. Fish, MD,[m] Sandra R. Wilson, PhD,[n] Cynthia Boyd, MD, MPH,[e] Kushang V. Patel, PhD,[o] Charles G. Irvin, PhD,[p] Barbara P. Yawn, MD, MSc,[q] Ethan A. Halm, MD, MPH,[r] Stephen I. Wasserman, MD,[i] Mark F. Sands, MD,[s] William B. Ershler, MD,[t] and Dennis K. Ledford, MD,[b] for the Asthma in the Elderly workshop participants‡ *Houston and Dallas, Tex, Tampa and Jacksonville, Fla, Providence, RI, Chicago, Ill, Baltimore, Bethesda, and Gaithersburg, Md, Tucson, Ariz, New York, Rochester, and Buffalo, NY, Madison, Wis, San Diego and Palo Alto, Calif, Bellevue, Wash, Gladwyne, Pa, Burlington, Vt, and Rochester, Minn*

Asthma in the elderly is underdiagnosed and undertreated, and there is a paucity of knowledge on the subject. The National Institute on Aging convened this workshop to identify what is known and what gaps in knowledge remain and suggest research directions needed to improve the understanding and care of asthma in the elderly. Asthma presenting at an advanced age often has similar clinical and physiologic consequences as seen with younger patients, but comorbid illnesses and the psychosocial effects of aging might affect the diagnosis, clinical presentation, and care of asthma in this population. At least 2 phenotypes exist among elderly patients with asthma; those with longstanding asthma have more severe airflow limitation and less complete reversibility than those with late-onset asthma. Many challenges exist in the recognition and treatment of asthma in the elderly. Furthermore, the pathophysiologic mechanisms of asthma in the elderly are likely to be different from those seen in young asthmatic patients, and these differences might influence the clinical course and outcomes of asthma in this population. (J Allergy Clin Immunol 2011;128:S4-24.)

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The proportion of persons older than 65 years in the United States is currently about 13% but is projected to grow from about 40 million in 2005 to more than 86 million by 2050, accounting for 25% of the population. The age group with the largest growth will be those older than 85 years, which is estimated to be more than 1 million by 2050.[1,2] In 2004, the US prevalence of asthma for those 65 years or older was 7%, with 1,088,000 reporting an asthma attack in the previous 12 months.[3] Older asthmatic patients are more likely to be underdiagnosed, undertreated,[4,5] and hospitalized than younger asthmatic patients.[3] They also have the highest death rate (51.3 per million persons) of any other age group.[6] Older women are hospitalized more than twice as often as older men.

Asthma in older adults is superimposed on a background of aging-related changes in respiratory and immune physiology and often on multiple diseases and conditions common in older age.

*These authors contributed equally to this work.

‡The Asthma in the Elderly workshop participants are shown in Appendix 1.

From [a]the Section of Pulmonary and Critical Care Medicine, Asthma Clinical Research Center, Baylor College of Medicine, Houston; [b]the Division of Allergy and Immunology, Department of Medicine, University of South Florida, Tampa; [c]Brown University, Providence; [d]Northwestern University, Chicago; [e]Johns Hopkins University, Baltimore; [f]the University of Arizona, Tucson; [g]the University of Rochester, Rochester; [h]the Department of Medicine, Section of Allergy, Pulmonary, and Critical Care, University of Wisconsin, Madison; [i]the University of California–San Diego, San Diego; [j]New York University School of Medicine, New York; [k]GlaxoSmithKline, Bellevue; [l]Clinical Pediatric Pharmacology, Nemours Children Clinic, Jacksonville; [m]Genentech, Gladwyne; [n]Stanford University School of Medicine, Palo Alto; [o]the National Institute on Aging, Bethesda; [p]the University of Vermont, Burlington; [q]the Department of Family and Community Health, University of Minnesota, Rochester; [r]the University of Texas Southwestern Medical Center, Dallas; [s]the Department of Veteran Affairs Medical Center and the University of Buffalo, State University of New York; and [t]the Institute for Advanced Studies in Aging, Gaithersburg.

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Reprint requests: Monroe J. King, DO, Division of Allergy and Immunology, Department of Medicine, University of South Florida, 7674 Cumberland Ct, Largo, FL 33777. E-mail: m.james.king@me.com.

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Abbreviations used
ADL: Activities of daily living
COPD: Chronic obstructive pulmonary disease
FVC: Forced vital capacity
GERD: Gastroesophageal reflux disease
hMPV: Human metapneumovirus
LOA: Late-onset asthma
LSA: Longstanding asthma
LTM: Leukotriene-modifying agent
NIA: National Institute on Aging
NO: Nitric oxide
RSV: Respiratory syncytial virus
TENOR: The Epidemiology and Natural History of Asthma

Recognizing the paucity of research, the many challenges that exist in the recognition and treatment of asthma in older adults, and the opportunity to bridge geriatrics and the clinical specialties that focus on asthma, the National Institute on Aging (NIA) sponsored a Workshop on Asthma in the Elderly in Herndon, Virginia, on September 8 and 9, 2008. The workshop was planned by a committee of 6 physician-scientists from US academic institutions or from the Division of Geriatrics and Clinical Gerontology in the NIA. The planning committee selected speakers and participants for their expertise in asthma, pulmonology, allergy/immunology, primary care, emergency medicine, geriatrics, and/or gerontologic science (see the list of participants in Appendix 1). The immediate goals of this workshop were to summarize the current understanding of the mechanisms of asthma in older persons and to identify knowledge gaps and research opportunities leading to improved medical care and health outcomes for older persons with asthma. These research opportunities are discussed in the body of this report and summarized in Table I.[7-9]

In addition, the NIA, in collaboration with the National Heart, Lung, and Blood Institute and the National Institute of Allergy and Infectious Diseases, recently issued a set of program announcements inviting research proposals on asthma in older adults (http://grants.nih.gov/grants/guide/pa-files/PA-10-263.html, http://grants.nih.gov/grants/guide/pa-files/PA-10-264.html, and http://grants.nih.gov/grants/guide/pa-files/PA-10-265.html).

BIOLOGY OF AGING

It is a central principle of gerontology that aging itself is not a disease.[10] Yet there are physiological changes within organs, tissues, and cells that result in diminished functional reserve and thereby increased susceptibility to stressors, disease, or both. A second principle is that these aging changes are highly variable and account for the great constitutional heterogeneity among older persons from very "fit" to very "frail." In fact, the concept of frailty, both its causes and consequences, has become a focus of concentrated gerontologic investigation.

Aging at the cellular level

At the root of age-associated physiological changes are a number of genetic, epigenetic, and environmental factors.[11] Molecular damage accumulates over time, and the capacity for DNA repair decreases.[12] Cellular senescence, which is believed to be the consequence of accumulated DNA and protein damage and reduced proliferative capacity, is becoming increasingly understood at the molecular level.[13] However, just how this correlates with the phenotypic changes of advanced age remains incompletely understood.[14]

There has been much written about cellular senescence and the events that lead to cell death.[15-17] After a finite number of divisions, normal somatic cells invariably enter a state of irreversibly arrested growth, a process termed *replicative senescence*.[18] In fact, it has been proposed that escape from the regulators of senescence is the antecedent of malignant transformation. However, the role of replicative senescence as an explanation of organismal aging remains the subject of vigorous debate. The controversy relates, in part, to the fact that certain organisms (eg, *Drosophila* species and *Caenorhabditis elegans*) undergo an aging process, yet all of their adult cells are postreplicative.

What is clear is that the loss of the proliferative capacity of human cells in culture is intrinsic to the cells and not dependent on environmental factors or even culture conditions.[18] Unless transformation occurs, cells age with each successive division. The number of divisions turns out to be more important than the actual amount of time passed. Thus cells held in a quiescent state for months, when allowed back into a proliferative environment, will continue approximately the same number of divisions as those that were allowed to proliferate without a quiescent period.[19]

The question remains whether this *in vitro* phenomenon is relevant to animal aging. One suggestive observation is that fibroblasts cultured from samples of old skin undergo fewer cycles of replication than those from young skin.[20] Furthermore, when various species are compared, replicative potential is directly and significantly related to lifespan.[21] An unusual β-galactosidase with activity peaks at pH 6 has proved to be a useful biomarker of *in vitro* senescence because it is expressed by senescent but not presenescent or quiescent fibroblasts.[22] This particular β-galactosidase isoform was found to have the predicted pattern of expression in skin from young and old donors, with measurably increased levels in dermal fibroblasts and epidermal keratinocytes with advancing age.[22] The nature of the expression of this *in vivo* biomarker of aging in other tissues will be important to discern.

Pathways to frailty

For clinical investigators, frailty has proved hard to define primarily because of the seemingly insurmountable heterogeneity inherent in geriatric populations on the basis of these variable rates of organ system decrease and the presence or absence of 1 or more diseases.[9] Yet, regardless of the pathway taken to frailty, the clinical picture has common features, including a reduction in lean body mass (sarcopenia), loss of bone mass (osteopenia), cognitive impairment, functional decline, and anemia. On the basis of data derived from large cohorts of elderly patients, Fried et al[23] have offered an operational definition of frailty incorporating an assessment of 5 specific characteristics to ascribe a frailty index. On this 5-point scale, a score of 3 or more has been shown to be independently predictive of a range of adverse clinical outcomes, including acute illness, falls, hospitalization, nursing home placement, and early mortality.[23-25] Furthermore, simple performance measures, such as the assessment of walking speed, are predictive of important outcomes, including survival.[26]

With the phenotype better defined, attention has shifted to pathophysiology. Although frailty can occur in the absence of a diagnosable illness, the fact that some become frail and others do

TABLE I. Identified future research needs

The aging lung
Large, longitudinal, and more complete studies to determine the effects of aging on the function of the respiratory system
Improved knowledge about lung structure-function relationships in older age using techniques of imaging and measures of lung function not requiring effort (eg, high-resolution computed tomographic scanning and forced oscillation)
Improved assessment of lung processes underlying airflow limitation attributable to aging versus COPD or asthma, especially in asthmatic patients who smoke
Studies to examine the effects of aging in ethnic groups and the role of gender
Epidemiology, effect, diagnosis, and management
Determine the true prevalence and cost of asthma in the older population
Develop a uniform definition of asthma to be applied to health care records that will distinguish asthma from COPD and mixed asthma/COPD
Evaluate evidence-based treatment algorithms for older asthmatic patients, such as those developed by the National Heart, Lung, and Blood Institute and Global Initiative For Asthma guidelines[7]
Assess the effect of asthma treatment, including direct medical costs of care, indirect costs of care, and value of treatment in improving quality of life[8,9]
Assess the effect of comorbid conditions, especially COPD and congestive heart failure, on asthma[9]
Characterize phenotypes of elderly asthma with regard to responses to therapy and long-term outcomes based on age of onset, duration of disease, and environmental triggers
Develop algorithms for electronic medical record systems that are asthma-specific
Evaluate effects of current asthma medications in older patients compared with younger patients
Identify pharmacogenetic determinants of response to asthma medications in older adults
Identify simpler and safer drug delivery systems and schedules for older adults
Develop simple methods to differentiate COPD from asthma exacerbations in older adults
Epigenetics and environmental and microbiological triggers
Understand how environmental or aging-related factors affect epigenetic changes in asthma in older adults
Identify differences between older and younger asthmatic patients or between LSA and LOA with regard to inflammation, remodeling, intracellular mechanisms, responses to environmental pollutants, and allergy sensitization and their effects on the metabolism and action of asthma drugs
Identify naturally occurring age-related changes in airway cellular patterns
Develop animal models of age-related airway inflammation
Understand the significance of allergy sensitization associated with asthma in older adults (eg, through larger prospective studies)
Identify the utility of allergy tests, either skin tests or serum specific IgE measurement, in reflecting allergy sensitization in older adults
Identify the role of the microbiome in patients with LOA
Understand the role of non-IgE mechanisms in older adults' inflammatory responses to inhalant allergens or pollutants (eg, T_H17 lymphocytes producing IL-17 or protease receptor responses to molds and dust mites)
Determine the roles of adaptive versus innate immune mechanisms on asthma development, progression, and response to treatment in older adults
Determine whether there are environmental pollutants peculiar to institutional settings
Identify viruses and other microbiological agents responsible for, and the mechanisms by which they cause, asthma exacerbations in older adults, which might lead to the development of vaccine- or antiviral drug–based interventions
Determine effects of asthma medications, viral or bacterial load, or allergy status on susceptibility to exacerbations in older patients
Define rates of infection and specific pathogens in older asthmatic patients
Distinguish roles of innate immunity in eosinophilic versus neutrophilic asthma

not suggests an inherent or acquired variability in homeostatic pathways. Recent evidence from observational studies has raised suspicion that dysregulated inflammatory processes are involved in, if not central to, the variable patterns of aging. Increased serum levels of certain proinflammatory cytokines, most notably IL-6, are increasingly present with advancing age and to a greater extent with frailty.[27,28] Furthermore, the appearance of this and other inflammatory markers has been associated with a number of adverse clinical outcomes, including decreased strength and mobility, falls, dementia, and mortality.[27]

Life expectancy, lifespan, and maximum survival

From the perspective of those who study aging, there is an important distinction made between median (life expectancy) and maximum lifespan. Over the past several decades, with the advent of modern sanitation, refrigeration, and other public health measures, including vaccination and antibiotics, there has been a dramatic increase in median survival.[29] Early deaths have been diminished, and more patients are reaching old age. In the United States today, life expectancy now approaches 80 years.[30] Median survival is what concerns public health officials and health care providers, but for those studying the biology of aging, it is maximum survival that is the focus of greatest attention. It is worthwhile to note that it has been estimated that if atherosclerosis and cancer were eliminated from the population as a cause of death, about 10 years would be added to the average lifespan, yet there would be no change in maximum lifespan.[31]

Although several theories have been proposed, none suffice to account for the complexities of aging. Lifespan is finite and varies generally from species to species and much less so within species. Mice live, on average, 2½ years, monkeys 30 years, and human subjects about 90 years. Among species, larger animals generally live longer than smaller animals, but within species, smaller animals are likely to live longer. It is clear that aging is not entirely explained by DNA sequence. For example, mice and bats have only 0.25% difference in their primary DNA sequence, but bats live for 25 years, 10 times longer than mice. A commonly held notion is that regulation of gene expression accounts for a longevity difference between species.

It is now clearly established that certain specific genes can alter lifespan, at least in lower animals, but whether these same genes regulate "aging" is still in question. For example, transgenic *Drosophila* species expressing increased copies of the free radical scavenging enzymes superoxide dismutase and catalase live on average a third longer than the appropriate controls.[32] In even lower species (eg, yeast and nematodes) the identification of specific genes that influence lifespan[33,34] has led to the optimistic impression that analogous genes in higher organisms will lead greater insights into the aging process. Yet the identification and functional analysis of analogous genes in human subjects remains elusive.

The oldest human being alive today is approximately 120 years old. What is intriguing is that the record has remained stable and unchanged by the public health initiatives mentioned above. In fact, there has been some recent data presented that the maximum survival is actually decreasing in the United States.[35,36] What is interesting is that, unlike the public health initiatives in human subjects in which median but not maximum survival has been enhanced, experimental interventions in lower species have resulted in prolongation of maximum survival. As mentioned above, transgenic *Drosophila* species producing extra copies of superoxide dismutase and catalase survived about 33% longer than controls,[32] and similarly, the maximum survival in C57BL/6 mice fed a calorically restricted diet enhanced by 50% or more.[37,38] The true mechanisms of aging might well be uncovered with a better understanding of how these interventions affect longer survival.

Future research in aging should attempt to improve our understanding of the basic biology of aging and interventions that retard the aging process. There is a need for the development and application of a standardized definition of frailty for future clinical investigation. Investigations directed at the role of comorbidities in accelerating the aging process are important. Furthermore, future research should focus on the development of cellular and animal models of typical, delayed, and accelerated aging and of large collaborative networks in which populations and resources can be shared to study aging and frailty. Leveraging on well-characterized existing cohorts, when possible, is recommended.

THE AGING LUNG

The lungs, like other organs, age and exhibit continued loss of function as a person grows old. Lung function is traditionally assessed by means of a number of standardized methods. The most common measurement used is spirometry with the determination of FEV_1 and forced vital capacity (FVC). FEV_1 and FVC both show continuous decreases of between 25 and 30 mL with each year of life after about age 20 years.[39] The cause of this decrease is usually attributed to the loss of the driving forces for airflow as a result of reduced respiratory muscle performance, loss of static elastic recoil, or both.[39,40] The decrease in FEV_1 in asthmatic patients is largely a function of the decrease in FVC because of the increase in residual volume.[41] Stiffening of the chest wall and reduced respiratory muscle performance result in a decrease in total lung capacity and an increase in residual volume because of ever-increasing closing volume.[42] Accordingly, these aging processes lead to airflow limitation that might be hard to distinguish from an active disease process.

Not all older persons are able to perform spirometry, especially those with decreased cognition, coordination, and frailty. In addition, spirometry is effort dependent, and the very old can tire quickly. Techniques of imaging and measures of lung function not requiring effort (ie, forced oscillation) should be used in future studies to extend our knowledge about lung structure-function relationships at the very end of life.

Bronchodilator responses are known to be less marked in the elderly, perhaps as a consequence of the aging effects attributed to the emphysema-like state of the senile lung[43]; however, this would not explain the slow temporal response to bronchodilators. Other studies do not find such age-related bronchodilator differences. Furthermore, although methacholine responsiveness has been reported to increase with aging, the exact mechanism for this is not apparent.

Increased incidence and prevalence of many lung diseases occur with age. Alterations in immune function increase the risk of many of these diseases. Studies of systemic immunity suggest that sustained antigenic stress over a lifetime leads to a decrease in naive T-cell numbers, an accumulation of memory T cells, and a decrease in T-cell repertoire and B-cell functions but a lesser decrease in innate immunity.[43,44] Little is known about what happens to the immune/inflammatory pathways in older asthmatic patients. The immune system changes seen with aging will be discussed in more detail in the section on pathophysiology.

IMPACT OF ASTHMA IN THE ELDERLY

In the United States the National Health Interview Survey asks questions regarding lifetime history of asthma, current asthma prevalence, and asthma attacks in the last 12 months.[3] For all age groups, asthma prevalence has been steadily increasing since 1980. For the 65 years and older age group, asthma is consistently more prevalent in female than male subjects.[3] The National Center for Health Statistics tracks data on physician encounters for asthma. The National Ambulatory Medical Care Survey reported that those 65 years or older have the second-highest rate of outpatient office visits after those aged 0 to 4 years. Those 65 years and older did not have significantly different emergency department visits than the other adult groups. The 65 years and older age group accounts for a greater proportion of hospitalizations (23%) than the size of its population (13%) would indicate.

Not surprisingly, the elderly population is a high user of medical resources for the treatment of asthma. Hospitalizations and emergency department visits are more common for these patients than for other adult cohorts. Some of the increased costs are related to comorbid disease. For example, the presence of comorbid chronic obstructive pulmonary disease (COPD) increases the risk of an asthma-related hospitalization in Medicare patients 3.6-fold, respiratory medical costs almost 6-fold, and total medical costs 2-fold. Elderly female subjects appear at greater risk than elderly male subjects.[45-48]

Asthma mortality increased steadily from 1980 until it peaked in 1998. The highest mortality rates for asthma occur in the 65 years and older group. In fact, the increase in asthma mortality between 1979 and 1989 was primarily driven by the 65 years and older group. In addition, the decrease in asthma mortality between 1999 and 2005 was most evident in this age group. Elderly women with asthma tend to have higher mortality rates than elderly men with asthma.

One reason for the increasing prevalence of asthma in the elderly might be the improved longevity of the population. Also, increased office visits for asthma in the elderly might be

TABLE II. Possible mechanisms of asthma in the elderly

	Age of onset	Genetic role	Infection	Allergy	Inflammation	Environment
LSA	Child or young adult (<40 y)	Likely gene-environment	Viral: rhinovirus and RSV	Likely	T_H2 driven, eosinophilic	Allergens, day care and school, workplace
LOA	Adult (>40 y)	Likely epigenetic, including oxidative stress, shortened telomeres	Viral: RSV, influenza, and bacterial (eg, *Chlamydia pneumoniae*), microbial superantigens	Unlikely	T_H1 or T_H2 driven, neutrophilic and/or eosinophilic, innate immunity, T_H17, proteases	Workplace, dwelling type (house, apartment, institutional)

responsible for fewer attacks. Increasing hospital admissions might account for decreased mortality. By continuing to gather surveillance data on asthma, reasons for these trends could become clearer. In addition, surveillance data help to focus intervention efforts in areas of greatest need.

In the Cardiovascular Health Study, a large community-based cohort of subjects older than 65 years, questions were asked that were relevant to asthma and provided more insight into the prevalence and effect of asthma in this population.[5,49,50] *Definite asthma* was defined as a positive response to the questions indicating that the patient had current asthma and that a physician confirmed the diagnosis. *Probable asthma* was defined as a history of wheezing in the past year associated with chest tightness or breathlessness. Excluding smokers and those with a diagnosis of congestive heart failure, 4% of subjects had definite asthma, and 4% had probable asthma. Among those who smoked, 11% had definite asthma, and 14% had probable asthma. Among nonsmokers, 185 subjects were identified who had definite or probable asthma; 76% were women, and 20% were older than 80 years. The age of asthma onset was spread approximately evenly among decades. Twenty-seven percent had late onset of disease after age 60 years, and 25% had onset of disease before age 20 years. As expected, respiratory symptoms in the older asthmatic subjects were more prevalent, with a 2- to 5-fold increase in cough, phlegm, wheezing, and dyspnea. Dyspnea on exertion was 1.6-fold more likely to be present in asthmatic patients than in those without the diagnosis. Lung function was reduced in those with a diagnosis of asthma. Mean FEV_1 was 77% of predicted value in those with definite asthma and 89% of predicted value in those with probable asthma compared with 96% in those who did not have asthma. Forty-one percent of those with a diagnosis of asthma had airflow obstruction below the fifth percentile for the age group, and peak flow lability was increased. Elderly asthmatic patients reported the most common trigger was a viral infection in 58% compared with animal allergies in 30%. Two thirds reported seasonal worsening. Asthma had a significant effect on quality of life, with 35% of patients with definite or probable asthma reporting a fair or poor health status compared with 17% of elderly patients without asthma. Sixty percent of patients with definite asthma reported seasonal allergic rhinitis compared with only 30% in the nonasthma group. Despite the high prevalence and morbidity of asthma in this population, inadequate treatment was common. Only 40% of those with definite asthma had a rescue albuterol inhaler, and only 30% had inhaled corticosteroid use.[5,49,51,52]

PATHOPHYSIOLOGY AND RISK FACTORS

The pathophysiology of asthma in the older adult is poorly understood and understudied. Many questions about this issue remain: Is asthma the same disease in older adults as it is in children and younger adults? Is late-onset asthma (LOA; asthma that starts in middle age or older) different from longstanding asthma (LSA; asthma of early onset that has persisted into older adulthood)? If LOA and LSA are the same disease, then the diagnosis and treatment should be similar. However, if LOA and LSA are different phenotypes or at least have a different cause and pathophysiology, then the diagnosis and treatment might differ (Table II).

Epigenetics, aging, and asthma

The traditional view of disease susceptibility has been expanded to include epigenetics to account for the influence of environmental factors and aging on the genomic blueprint. *Epigenetics* is defined as heritable changes in gene expression that occur without alterations in DNA sequence. It is the process by which genotype interacts with environment to produce a phenotype and explains differences between cells, tissues, and organs despite identical genetic information. Genes function in a milieu determined by the developmental and environmental history of the cell, which constitutes the epigenotype.[53,54] Epigenetic changes or marks can play a major role in human disease.[55,56] The most common examples of epigenetic marks are DNA methylation of CpG islands by DNA methyltransferases and chromatin modification of histone proteins, particularly acetylation by histone acetyltransferases and histone deacetylases.[57,58] The function of epigenetic changes is to regulate gene expression. Epigenetic changes are known to contribute to cancer and autoimmune disease and are thought to contribute to common diseases, including cardiovascular disease, diabetes, and the loss of response to stress caused by aging.[59]

Asthma is a markedly heterogeneous disease, and recent evidence suggests that environmentally induced epigenetic changes contribute to asthma phenotypes and that airway inflammation in patients with asthma and COPD might involve epigenetic regulation.[57,58,60] Methylation patterns and chromatin structure change with age and are thought to contribute to the increase in the incidence of common diseases that begin in middle age.[55,61] The incidence of asthma in the elderly resembles the incidence of common diseases. Moreover, characteristics and asthma drug response in the elderly asthmatic patient differ from those seen in childhood asthma. Compared with younger cohorts, elderly asthmatic patients have a higher prevalence, higher rates of bronchial hyperreactivity, more severe asthma, and a lower prevalence of atopy. The symptoms of elderly asthmatic patients are more difficult to control with drug therapy, and these patients have steroid resistance and might respond better to leukotriene receptor antagonists compared with inhaled corticosteroids.[62-71] The contribution of epigenetics to differences

observed between elderly asthmatic patients and younger cohorts is unknown. Unlike genetic variants that contribute to disease, epigenetic changes can be reversed and therefore represent potential drug targets.[72]

Role of airway inflammation

Older asthmatic patients are less responsive to albuterol treatments given in the emergency department and are more frequently admitted for hospitalization.[73] Thus it appears that the responsiveness to treatment is diminished and the severity of asthma exacerbations is greater. The exact reason for these disparities is not known.

Immune cell function decreases with aging, a property often termed *immunosenescence*.[74] One often-confusing aspect of immunosenescence is the observation that aging might be associated with opposing immunologic effects. For example, T-cell secretion of IL-2, IL-4, or IFN-γ has been shown to be both decreased with aging and also increased with aging.[75] It is likely that both phenomena are correct but are dependent on the context of the immune function. Thus the effect of aging on T-cell function in the context of allergen stimulation might be different than the effects of aging on T-cell function in the context of viral infection. Given that asthma is an inflammatory disorder of the airway, it is of interest to determine whether asthmatic airway inflammation of the elderly might differ from that of younger asthmatic patients and thus represent a distinct phenotype of asthma. These changes might have implications for susceptibility to exacerbations because of viruses or other pathogens, as well as response to treatment.

The aging process has been shown to exhibit changes in airway inflammation. An examination of the cellular composition of bronchoalveolar lavage fluid from 19- to 83-year-old subjects without a history of allergies, pulmonary disease, or gastroesophageal reflux showed increased airway neutrophilia, as well as increased numbers of $CD4^+$ T cells.[76,77] The T cells also appeared to be more activated in the elderly, with increased expression of HLA-DR and CD69. The increase in airway neutrophils with aging has also been observed in asthmatic patients.[78] Because there is a phenotype of severe asthma characterized by a predominantly neutrophilic airway inflammation,[79] the question arises as to whether the increased presence of neutrophils contributes to greater asthma severity in the elderly.

Some of the prominent inflammatory cells recruited into the airway in asthmatic patients are eosinophils, neutrophils, and T cells, which are capable of secreting numerous inflammatory mediators, including leukotrienes and cytokines. It is not known whether immunosenescence affects the production of these mediators in elderly asthmatic patients, either at baseline or during an exacerbation of symptoms. Furthermore, it is not known whether age-related changes in their production would have any implication for the clinical presentation or management of asthma in the elderly. Peripheral blood eosinophils were isolated from younger (20-40 years old) and older (55-80 years old) subjects for *in vitro* functional assays. The eosinophil effector functions of degranulation and superoxide production were diminished in the older compared with the younger asthmatic patients.[78] In another study examining the expression of neutrophil mediators in younger and older asthmatic patients, there was decreased baseline expression of leukotriene B_4 in the sputum of older asthmatic patients despite greater numbers of neutrophils.[80] Whether these findings have implications during an asthma exacerbation has yet to be determined. Nevertheless, the results demonstrate age-related changes in the function of an inflammatory cell considered pathognomonic for allergic asthma and raise the question of whether additional effects of immunosenescence are relevant to airway inflammation in asthmatic patients.

There have been several studies of animal models to address age-related changes in the airway inflammation induced by allergen challenge of sensitized aged animals (see Experimental approaches section below). These studies yielded conflicting results, and there is concern that the animal models do not accurately represent the chronic features of human asthma with seasonal allergen exposure and intermittent exacerbations. The aged animals were both sensitized and challenged at old age, which is in contrast to the typical elderly human asthmatic patient who might be exposed to allergens for several decades.

Role of allergy

Typically, nasal and ocular symptoms on exposure to allergens diminish with age. Allergen-triggered asthma symptoms also diminish with age. The Epidemiology and Natural History of Asthma (TENOR) study examined the natural history of asthma in older (>65 years old) compared with younger patients and found that older asthmatic patients had lower total IgE levels, fewer positive skin prick test responses, and less concomitant allergic rhinitis or atopic dermatitis.[81] Several studies have demonstrated age-related decreases in total IgE and allergen-specific IgE levels,[82-87] suggesting that this might be the explanation for the decrease in allergy symptoms. There is also evidence for an age-related decrease in skin prick test responses to allergens.[88] However, the relationship between total IgE levels and allergic disease persists in the elderly, such that subjects with greater IgE levels remain more likely to have allergic rhinitis or asthma.[89,90]

Given the changes in allergic inflammation with aging, one might conclude that asthma in the elderly should be milder. However, there are several other common triggers for exacerbations of asthma, including irritants (eg, cold air) and respiratory tract infections. Estimates suggest that up to 80% of asthma exacerbations in adults are caused by viral upper respiratory tract infections.[91]

The role of environmental exposures and allergy in older asthmatic patients is largely unknown. In the general population, evidence regarding the effect of indoor pollution on asthma is summarized in "Clearing the air: asthma and indoor air exposure" by the Institute of Medicine for the Environmental Protection Agency published in 2000.[92] Evidence was reported for asthma development related to house dust mites and for asthma development associated with environmental tobacco smoke in preschool children. The report also showed evidence for causation of asthma exacerbations for house dust mite, environmental tobacco smoke (in preschool children), cat, and cockroach; an association with exacerbations was found for dogs, fungi, formaldehyde, and rhinovirus. In addition, evidence associating exacerbation of asthma-related symptoms with self-reported damp air was reported in a review of damp indoor spaces and health.[93,94]

There are only a few studies that have evaluated the role of atopy in elderly patients with asthma. One large national study of allergy skin tests that included older adults[95] and several small studies of allergy skin tests in older adults with asthma[81,96-103]

TABLE III. Studies examining allergy in patients with early-onset asthma versus those with LOA

Location/date	No.	Mean age (y)	Mean age of onset (y)	Positive skin test response (%)	Positive serum specific IgE level (%)
Providence, RI, 1991[97]	25	>70	<43 (n = 13)	62	ND
			>70 (n = 12)	0	
Rochester, Minn, 1997[102]	63	>65	<40 (n?)	56	ND
			>41 (n?)	21	ND
			>65 (n?)	20	ND
Boston, Mass, 1997[101]	46	61	49 ± 15.7	ND	24 (cat)
					21 (Der p 1)
Boston, Mass, 1997[101]	33	61	61	ND	18 (cat)
					21 (Der p 1)

ND, Not done.

were reviewed. Allergy skin test results were positive in 8% to 12% of all older adults. The prevalence of positive skin test results or specific IgE levels to at least 1 allergen in older adults with asthma ranged from 0% to 75%. Those whose asthma had an unknown age of onset ranged from 27% to 60%, those with onset before age 41 years ranged from 56% to 62%, and those with onset greater than age 41 years ranged from 0% to 24% (Table III).[97,101,102]

Although there were no studies of allergen room exposure or bronchial challenge in older adults, neither prick-puncture skin test results nor specific IgE levels predicted the nasal challenge response to dust mites.[104] Safety concerns for allergen challenges in older adults are unresolved. Technical limitations of allergens, environmental measurements, and age-specific norms and cutoff levels for laboratory and physiologic tests are needed.

A few epidemiologic studies suggest an association between outdoor environmental exposures and emergency department or hospital admissions in older adults.[105,106]

In summary, studies of the general population suggest a causation or association between indoor air pollutants and allergy exposure and asthma. There are several small studies suggesting higher levels of positive allergy test results in older adults with asthma than in the general population of older adults. When age of onset is considered, asthma with an early onset (<41 years of age) has a much higher association with positive allergy test results than late-onset asthma.

Role of viral respiratory tract infections

Viral respiratory tract infections are common precipitants of asthma exacerbations during childhood. In approximately 80% of children with acute asthma exacerbations, a respiratory tract virus can be detected, with rhinovirus being the most frequent pathogen identified.[107] Although it is likely that viruses also lead to exacerbations of asthma in older adults, comprehensive studies regarding the rates and specific pathogens are lacking. Several issues have made defining the role of viruses in adult asthmatic patients problematic and include difficulty distinguishing COPD from asthma, lack of sensitive diagnostic tests, and issues with asymptomatic infection. A number of investigators have explored the incidence of viral infection in adult asthmatic patients.[91,108,109] Older studies using viral culture and serology for diagnosis demonstrated infection rates of 10% to 29%.[109] In contrast, more recent studies, which include RT-PCR, have shown significantly higher infection rates of 44% to 55%.[91,108] Similar to results found in children, rhinoviruses are the most frequently detected pathogen. Few older persons were included in these studies, in which the mean ages of subjects were 30 to 39 years.

The incidence of acute respiratory tract infections decreases steadily with advancing age, and rates of viral infection in older adults are influenced by place of residence.[110] Among community-dwelling older adults, rates of acute respiratory tract infections are roughly 1% to 2% per year, whereas rates in senior day care centers and long-term care facilities are substantially higher at 6% to 11%.[111] In addition, the epidemiology of respiratory tract infections can be quite complex in these semiclosed populations, with multiple pathogens circulating simultaneously.[112] Influenza A, respiratory syncytial virus (RSV), and human metapneumovirus (hMPV) are the most commonly identified viruses among older persons hospitalized with acute cardiopulmonary conditions.[113,114] Most patients who require hospitalization during a viral respiratory tract infection have underlying heart and lung conditions. Although studies to date have largely focused on the role of viruses in COPD exacerbations, it is reasonable to extrapolate infection rates and specific pathogens from these studies to older adults with asthma. Johnston,[115] in Ontario, Canada, found a seasonal peak in emergency department visits for all acute respiratory tract infections, as well as exacerbations of both COPD and asthma, for persons younger and older than 50 years. All the common respiratory tract viruses have been associated with COPD exacerbations, and depending on the methodology and season of study, the specific rates of influenza, RSV, parainfluenza viruses, coronaviruses, hMPV, and rhinoviruses vary.[116,117] Wheezing appears to be a common symptom in older adults infected with any of the respiratory tract viruses, particularly RSV and hMPV, and 7% of adults hospitalized with RSV will have a discharge diagnosis of asthma.[114,118]

Because most adult infections represent reinfection, the viral load in respiratory secretions tends to be low, making detection with conventional techniques difficult. Viral culture and rapid antigen testing, which can be used successfully in children, have poor sensitivity in older adults. The use of molecular diagnostics has vastly improved the ability to detect a number of viruses, such as RSV, parainfluenza, and rhinoviruses, and allows the detection of hitherto uncultivable agents, such as hMPV and coronaviruses.

Viral infections appear to aggravate reactive airway disease through a number of different mechanisms. It has been postulated that viral infection disrupts the negative feedback loop of acetylcholine on the M2 receptor, leading to increased levels of acetylcholine and increased constriction of bronchiolar smooth muscle.[119] Infection of the respiratory epithelium also induces chemokines, cytokines, and immune and growth factors, which result in a proinflammatory state.[120,121] Immunosenescence might affect the ability of older adults to clear viruses efficiently, and thus greater and more prolonged inflammation can result.

In summary, respiratory viral tract infections are common among older adults and are likely precipitants of acute asthma exacerbations. Furthermore, viral respiratory tract infections might likely precipitate the onset of LOA, although this needs to be further examined.[122] Comprehensive studies regarding the rates and specific pathogens are lacking in older adults. Distinguishing COPD from asthma, lack of sensitive diagnostic tests,

and issues with asymptomatic infections make it difficult to define the role of infections in older adults.

DIAGNOSIS OF ASTHMA IN THE ELDERLY

Clinical assessment

Classic symptoms of asthma in the elderly are mostly similar to those seen in younger asthmatic patients.[4,96] Data on the clinical features of asthma in the elderly have been derived from both longitudinal community surveys and case studies.[5,64,97,98,122-124] Most patients complain of episodic wheezing, shortness of breath, and chest tightness. These symptoms are often worse at night and with exertion and, like those in younger asthmatic patients, are often precipitated by an upper respiratory tract infection. In fact, the majority of elderly patients who have asthma after age 65 years have their first asthmatic symptom preceded immediately by or concomitant with an upper respiratory tract infection.[122] Asthma can often be triggered by environmental exposures, such as aeroallergens, irritants (cigarette smoke, household aerosols, and paints), strong odors (perfumes), and inhalation of metabisulfites (found in beer, wine, and food preservatives). Asthmatic symptoms can also be triggered by medications, such as aspirin, nonsteroidal anti-inflammatory agents, angiotensin-converting enzyme inhibitors, or β-blockers, which are commonly used by this patient population. This emphasizes the need for the physician to perform a comprehensive review of medications taken by the older asthmatic patient.

Studies have consistently shown that elderly patients and their physicians frequently overlook symptoms caused by asthma.[5,73,125] Several factors contribute to the underdiagnosis and misdiagnosis of asthma. One reason, as shown in large community studies, is that most patients first have asthma in childhood or adolescence, and many physicians have had the misconception that asthma is a childhood disease. Another important reason is that the symptoms of asthma are more commonly associated with other diseases seen in this age group. The symptoms of asthma in the elderly are therefore nonspecific and might be caused by conditions that mimic asthma. The differential diagnosis of asthma in the elderly is greater than seen in younger asthmatic patients and includes congestive heart failure, emphysema and chronic bronchitis (COPD), chronic aspiration, gastroesophageal reflux disease (GERD), and tracheobronchial tumors. Comorbid illnesses and the psychosocial effects of aging might also profoundly affect the diagnosis, clinical presentation, and care of asthma in the elderly. One particular diagnosis that is often difficult to detect and frequently overlooked by the patient and physician until the condition is advanced is upper airway obstruction, including the extrathoracic and intrathoracic central airways. Common causes of upper airway obstruction include malignancy, infection, inflammatory disorders, trauma, and extrinsic compression related to enlargement of adjacent structures (eg, an enlarged thyroid gland). It appears that malignancy and benign strictures related to airway instrumentation (eg, endotracheal intubation and tracheostomy) are becoming increasingly more prevalent in the older age group.

Distinguishing chronic asthma from COPD can be very challenging, and in some patients asthma cannot be distinguished from COPD with widely available diagnostic tests. The management of these patients might have similarities to that of asthma. The distinction between LOA and COPD can be difficult to define precisely. The Lung Health Study showed that methacholine-induced airways reactivity is present in many patients with mild-to-moderate COPD (ie, 63% of men and 87% of women). Approximately 85% of patients with tobacco-related COPD demonstrate bronchodilator reversibility at least once on repeated testing sessions. The distinction between COPD and asthma can be confounded by either the coexistence of the 2 common disease entities, the progression of common pathobiologic mechanisms induced by different environmental agents, or different disease mechanisms leading to an overlapping clinical syndrome.

It has been known for more than a century that early-morning wheezing is a prominent symptom of congestive heart failure. It has been called cardiac asthma because it can mimic the clinical picture of typical asthma. The usual symptoms of gastroesophageal reflux in the elderly, such as vomiting and heartburn, might be absent. In a study of elderly patients with esophageal reflux proved by means of intraesophageal pH monitoring, chronic cough, hoarseness, and wheezing were present in 57% of patients.[126] In addition to causing asthma-like symptoms, there is also evidence that GERD might be a cause of worsening asthma.

Shortness of breath is a common symptom in the elderly and is most commonly caused by heart or lung diseases. It is usually experienced during exertion. Shortness of breath at rest is not typical of heart disease or lung diseases, such as COPD or interstitial lung disease, except in advanced stages. When present, it should prompt an investigation for asthma because sudden bronchospasm can cause respiratory distress at rest or exercise. Paroxysmal nocturnal dyspnea, which is typical of congestive heart failure, is found in a smaller number of elderly patients with asthma. Many elderly patients limit their activity to avoid experiencing dyspnea, and others assume that their dyspnea results from their aging process and thus avoid seeking medical attention early in their disease process. However, aging *per se* does not cause dyspnea, and a cause needs to be always pursued in assessing an elderly patient who complains of breathlessness.

There are several other reasons why the diagnosis of asthma in the elderly might be delayed or not made at all. Elderly patients have been shown to have a reduced perception of bronchoconstriction,[127] and this might delay medical intervention. Many elderly patients are fearful of having an illness and dying and are reluctant to admit they are having symptoms. Underreporting of symptoms in the elderly might have many causes, including depression, cognitive impairment, social isolation, denial, and confusing symptoms with those of other comorbid illnesses.

Cough is a very prominent symptom and might occasionally be the only presenting symptom. Wheezing, on the other hand, might not be as prominent, and its presence is not very specific and does not correlate with severity of obstruction. Physical examination in elderly patients with asthma is usually nonspecific and might misguide the diagnosis: a negative examination result does not rule out asthma, and wheezing can be found in a number of conditions, such as COPD, recurrent aspiration, and "cardiac asthma" (congestive heart failure).

Two distinct clinical presentations have been described for asthma in the elderly. These are based on the onset and duration of the disease state.[97,124,128] Patients with LOA start having asthma symptoms for the first time when they are 65 years of age or older (some studies have suggested middle age or older). Some studies of elderly asthmatic patients have shown that, as a group, as many as 40% will have their first attack after the age of 40 years.[97,98,129]

Patients belonging to this group tend to have fewer atopic manifestations, higher baseline FEV_1, and a more pronounced bronchodilator response than those with LSA. Patients with LSA start having asthma symptoms early in life. Patients belonging to this group tend to have a higher incidence of atopic diseases, more severe and irreversible or partially reversible airway obstruction, and more hyperinflation. The duration of the disease in this group is an important determinant of severity and of the development of irreversible airflow obstruction.[128]

Longitudinal studies of asthmatic populations, whether new onset or long standing, have shown that remission from asthma is uncommon in older groups, occurring in less than 20% of patients.[130] This contrasts with asthma in children and adolescents, in whom remission of asthma symptoms is common, especially in the second decade of life, and might be seen in as many as 60% to 70% of patients.

Physiological assessment

Objective measures to confirm the diagnosis of asthma are uncommonly performed in primary care settings. Inhalers are prescribed for patients who are evaluated for asthma-like symptoms, and during a follow-up visit, the patient is asked whether the controller inhaler reduced the frequency of asthma symptoms or whether the albuterol inhaler quickly relieved the symptoms. Such an empiric approach might work most of the time for young patients with mild asthma but is more likely to result in an incorrect diagnosis, poorly efficacious treatment, or unnecessary medication side effects in older patients.

The onset of wheezing, shortness of breath, and cough in an elderly patient is likely to cause concern. Although the adage "all that wheezes is not asthma" is true at any age, it is especially true in the elderly. Diagnosis based on objective measures is essential. Moreover, lung function testing, even in the presence of minimal symptoms, is especially important in this age group because there is thought to be an age-related reduction in the perception of exertional dyspnea in the elderly.[125] An older patient with chronic, untreated, severe airway obstruction caused by asthma might reduce activity to avoid dyspnea and stoically deny impairment of activity. This might reflect either neurocognitive function or changes in lifestyle that favor sedentary activities.

There exist some barriers to lung function testing in the elderly. Spirometry might be difficult to perform in some situations because of physical or cognitive impairments. However, 80% to 90% of elderly persons are able to perform good-quality spirometry when tested by skilled technologists.[129-133] The Global initiative for Obstructive Lung Disease guidelines for diagnosing the airway obstruction of COPD by using a fixed FEV_1/FVC ratio of less than 0.70 caused a high misclassification rate in older persons.[134] However, almost all computerized spirometers automatically calculate the appropriate lower limit of the normal range for FEV_1/FVC ratio and for FEV_1 by using race-specific National Health and Nutrition Examination Survey III reference equations.

In addition, it is hard to define the lower limits of predicted normal values in this age group. Although complete reversibility of airflow obstruction is frequently seen with young asthmatic patients, most elderly asthmatic patients show incomplete reversibility despite continuous intense therapy, and many show fixed airflow obstruction as if they have COPD. However, objective measures of lung function, such as spirometric and peak flow measurements, are generally underused in elderly patients, and this also contributes to the delay or absence of diagnosis.[134,135] Lung function testing is especially important in this age group because of the age-related reduction in the perception of dyspnea seen in the elderly.[127] Spirometry is easily performed to determine that FEV_1 and FEV_1/FVC ratio are demonstrated with the timed vital capacity maneuver. The flow-volume loop, which also measures inspiratory flow, is especially useful when the cause of respiratory tract symptoms is not known and an upper airway obstruction is in the differential diagnosis. Although it might be difficult to perform spirometry in the elderly in some situations because of physical and poor cognitive impairment, studies have demonstrated that between 82% and 93% of elderly patients are able to perform the test properly.[131-135] On the other hand, it might be more difficult to define the lower limits of predicted normal values in this age group. Traditionally, an FEV_1/FVC ratio of less than 70% increases the probability of asthma in an elderly patient with asthma symptoms, but this ratio normally decreases with age because of a decrease in elastic recoil, and a ratio lower that 70% might be a normal finding.[136]

A brisk response to a short-acting bronchodilator might demonstrate the second cardinal feature of asthma: reversible airflow obstruction (ie, "a responder"). When airflow obstruction is found in an elderly patient, attempts should be made to demonstrate reversibility after the inhalation of a short-acting β-adrenergic agent, such as albuterol. Evidence of reversibility (postbronchodilator FEV_1 or FVC increases of >12% and 200 mL) increases the probability of a diagnosis of asthma. Elderly asthmatic patients, however, might have an impaired β-agonist bronchodilator response because the number of β-adrenergic receptors on smooth airway muscles is decreased with aging.[137] Although the bronchodilator response to inhaled β-agonists decreases with age,[138] this is not the case with anticholinergic agents.[139]

Airway obstruction might be absent at the time of testing, and further testing might be needed to facilitate the diagnosis. Bronchoprovocation testing with a methacholine challenge can be useful, and it is a safe and effective method to uncover asthma in older adults.[140,141] A negative test result will rule out asthma; a positive test result must be interpreted and include an assessment of pretest probability.[142] In addition, some studies have shown that bronchial responsiveness is heightened in older adults, and therefore aging might be an independent factor that influences airway responsiveness.[143] There is a relationship between the degree of bronchial hyperresponsiveness and prechallenge pulmonary function; a low FEV_1 predicts heightened responsiveness.[144] Other factors that might contribute to heightened airway responsiveness in the older population are atopy and current or previous smoking history.

Peak expiratory flow variability might be helpful in the diagnosis and follow-up of younger patients with asthma, but poor coordination and muscle weakness in some elderly patients might lead to an inaccurate reading.[52,145] A prospective study did not demonstrate any advantage of peak flow monitoring over symptom monitoring as an asthma management strategy for older adults with moderate-to-severe asthma when used in a comprehensive asthma management program.[146] Other tests, such as measuring the carbon monoxide diffusing capacity of the lung, have been advocated to distinguish between asthma and COPD because the diffusing capacity of the lung is reduced by parenchymal destruction found with emphysema. However, studies have shown that differences in lung function tests, although

statistically significant, cannot be used clinically to separate the 2 groups of subjects because of a large overlap.[147]

There is growing evidence that the airway function of young and middle-aged asthmatic patients decreases at a greater rate than that of healthy subjects.[148-150] The rate of decrease increases with increasing age and in those who smoke cigarettes.[149,151] In patients with LOA, there is evidence that lung function is reduced even before a diagnosis is made and decreases rapidly shortly after diagnosis.[98,152] Thereafter, it remains fairly stable. Although the effect on older asthmatic patients with LSA is variable, in a random survey of 1200 elderly asthmatic patients older than 65 years, only 1 in 5 patients had normal pulmonary function (FEV_1 >80% of predicted value), whereas a similar number showed moderate-to-severe airflow obstruction (FEV_1 <50% of predicted value) after an inhaled short-acting bronchodilator.[153] Because structural changes of emphysema are minimal in elderly asthmatic patients, except if they are previous smokers, airway remodeling is thought to be the main cause of fixed airflow obstruction.

Role of nitric oxide

Nitric oxide (NO) is a gas generated by the action of NO synthase from the substrates molecular oxygen and arginine. It was originally identified as a biologically important signaling molecule with the properties of an activity previously described as endothelial-derived relaxing factor. This molecule is important in regulating vascular integrity and blood flow and is thought to be a regulator of vascular smooth muscle relaxation.

More recently, it has been found that NO can be generated by a variety of inflammatory cells, including polymorphonuclear leukocytes, mononuclear cells, and, importantly, eosinophils. This finding led to the identification of NO as a molecule present in exhaled breath. Studies of NO exhalation have found that it is increased in infection and inflammation of the airway. Although high levels of NO are found in nasally expired air, studies in pulmonary inflammation have avoided this by redirecting airflow through the oral airway. It has been found that exhaled NO reflects airways inflammation and particularly eosinophilic inflammation. Exhaled NO levels are increased during the allergy season in atopic subjects. Inhaled glucocorticoids promptly suppress exhaled NO and do so in conjunction with suppression of eosinophilic inflammatory infiltrates. Studies have demonstrated that monitoring exhaled NO might permit better regulation of asthmatic symptoms, exacerbations, and total steroid use than treatments based on guidelines or symptoms. Furthermore, increases in exhaled NO levels might predict asthma exacerbations.[154] It is of interest that NO levels in expired air decrease after bronchoconstrictive stimulation of asthmatic airways.

Little is known of the effects of age on NO levels in the expired air. It appears that NO production and vascular responses to NO might be diminished in the elderly, but that effect might be overcome by exercise to increase fitness. An unanswered question in airways biology is whether NO is causative of airways dysfunction, a marker for this dysfunction, or an ineffective homeostatic response to airways constriction.[155-159]

Challenges in defining asthma in the elderly

There is agreement that asthma is both a common and underrecognized health problem for the elderly that leads to impairments of lung function and quality of health and life. The first question that needs to be addressed is why we need to make such a diagnosis rather than just treat the symptoms. There are reasons that physicians must strive to assign a diagnosis to a patient with a symptom complex. The patient is given relief by letting him or her know what is wrong by giving the illness a name, which implies a cause, establishes a prognosis, and initiates a treatment plan. Moreover, advancement of the understanding of epidemiology, natural history, pathobiology, and treatment require a definable disease entity. Whether the threshold for diagnostic criteria is set at a high level of sensitivity, a high level of specificity, or a high level of accuracy depends entirely on the costs and benefits of an incorrect diagnosis versus a missed diagnosis. For example, enumeration of a disease might require a high level of accuracy, whereas diagnosis of an uncommon and difficult-to-treat disease (eg, metastatic cancer) ought to be highly specific. The diagnosis of a common and easily treatable disease (eg, vitamin deficiency) ought to be highly sensitive, even if there is a risk of overdiagnosis. Asthma tends to be one of those disorders that is relatively easy (although not inexpensive) to treat and has morbid consequences if left untreated, suggesting that the diagnostic criteria ought to be highly sensitive.

Although medical students are taught the rigorous discipline of data collection, differential diagnosis, and test confirmation, most physicians do not practice this way. In practice, physicians typically rely on a constellation of signs and symptoms along with demographic characteristics and recent experiences to establish diagnoses through the process of pattern recognition.

There are no shortages of official definitions of asthma, and modifications seem to be added every year. Most of these definitions involve the definition of a clinical syndrome (episodic cough, wheezing, and dyspnea), an underlying pathophysiology (airway hyperresponsiveness, variable, and reversible airflow obstruction), an underlying biological process (chronic eosinophilic or neutrophilic inflammation of the airways), and an associated morbid anatomy (basement membrane thickening, smooth muscle hypertrophy, and mucus cell metaplasia).

Given this, why is it so challenging to diagnose asthma in the elderly? First, the syndrome of asthma is often confused with other common diseases in the elderly, such as COPD, congestive heart failure, paroxysmal arrhythmias, pulmonary emboli, recurrent aspiration, and GERD.

Second, asthma can often coexist with these other conditions, and it can be impossible to determine which of the 2 conditions is responsible for the patient's ill health. This diagnostic confusion can be amplified by the different manifestations of asthma in the elderly. Elderly asthmatic patients can be insensitive to exertional dyspnea because of a sedentary lifestyle. They tend to be less atopic and have an incomplete response to bronchodilators. The elderly without asthma tend to show some signs suggestive of asthma: slower emptying of the lung during forced expiration, decreased lung elastic recoil, and a higher prevalence of nonspecific airways reactivity.

The hope that formal testing of airways reactivity would prove useful in diagnosing asthma has led to disappointment. In young adults a history of asthma, wheeze, or treatment for asthma plus a positive methacholine challenge test result is highly specific for asthma (99%) but misses about half of the asthmatic population.[160]

In epidemiologic studies that have examined various criteria for diagnosing asthma, it turns out that the solution is relatively

simple. Patients who answer yes to the question "Have you ever had asthma?" have nearly 100% specificity and 48% to 100% sensitivity when compared with those receiving an independent expert's diagnosis.[161,162]

The problem of diagnosing asthma in the elderly is more complicated because of the overlap with COPD. Asthma is typically considered a disease of onset in youth driven by atopy and eosinophilic inflammation causing reversible airflow limitation. COPD, in contrast, is considered to be a disease of onset in middle age driven by cigarette smoking and neutrophilic inflammation and leading to irreversible airflow limitation. As evidence presented in this workshop has shown, asthma in the elderly displays many of the features of COPD. The disease can have its symptomatic onset late in life, often is only partially reversible, and is associated with neutrophilic inflammation. Moreover, the current cohort of elderly patients has a high prevalence of past smoking, reflecting the health habits in the United States in the 1940s and 1950s.

The failure to deal with the population of elderly patients who have overlapping signs of asthma and COPD is not just a matter of classification of disease. It has significant health consequences in that such patients are systematically eliminated from clinical trials and are not covered by treatment guidelines. Little is known about how best to treat the elderly patient with asthma who smokes or the elderly patient with COPD who has reversible airflow limitation.

This confusion is manifest by diagnostic coding in older Medicaid patients. Of those who were hospitalized with an initial diagnosis of COPD, 43% had an asthma diagnosis within 3 years. Of those who had an initial hospital diagnosis of asthma, 46% had a diagnosis of COPD within 3 years. Price et al[161] attempted to develop a discriminant function using clinical and demographic information that would separate patients with COPD from those with asthma by using strict physiologic criteria. Although several discriminating characteristics were found, the best diagnostic criteria were only 78% sensitive and only 75% specific.

We need to ask whether it really is important to make the distinction between asthma and COPD in the elderly in terms of prognosis or treatment. One study by Hansen et al[136] suggests that regardless of whether a person is given a diagnosis of asthma or COPD, the prognosis is mostly determined by the impairment in FEV_1.

MONITORING ASTHMA IN THE ELDERLY

Standardized monitoring tools

There are a number of ways to measure the effect of asthma in both young and elderly patients. Assessments of symptoms, functional limitations, quality-of-life measures, and risk of adverse events are several that have been suggested by current asthma guidelines.[163] In addition, measuring a patient's satisfaction with his or her asthma symptom control and overall asthma care has been advocated.

The use of objective measures of asthma control and satisfaction can be especially important in the elderly because the perception of symptoms might be impaired with advancing age. In addition, many elderly patients unconsciously accommodate to their symptoms or assume that the symptoms are a function of the aging process itself. Because the number of unscheduled ambulatory visits, emergency department visits, and hospitalizations are high in elderly asthmatic patients,[164,165] and quality-of-life scores are low in elderly patients with persistent asthma when compared with those with mild asthma or no asthma at all,[5] careful assessment of asthma control is essential in this age group. Despite severe symptoms and physiologic impairment, most elderly patients with asthma can lead active productive lives if their asthma is appropriately managed. In fact, when elderly patients with severe or difficult-to-treat asthma have been identified by a physician's assessment, they appear to do better than younger patients. In the TENOR study, despite lower lung function, older asthmatic patients (mean age, 72 years) had lower rates of unscheduled office visits, emergency department visits, and corticosteroid bursts.[81] Patients reported in the TENOR study received more aggressive care than younger adults, including higher use of inhaled and oral corticosteroids, and this undoubtedly had an effect on outcomes.

The tools to measure asthma outcomes include questionnaires and other self-report tools, such as diaries and standardized medical history forms. Standardized questionnaires that assess asthma impairment include the Asthma Control Test,[166,167] the Asthma Control Questionnaire,[168,169] the Asthma Therapy Assessment Questionnaire,[170,171] and others.[172-175]

There are many tools available to clinicians to assess the quality of life of asthmatic patients.[176-183] Unfortunately, these psychometric instruments that claim to measure the same outcomes might produce disparate results, and none have been targeted for the elderly. In general, results that measure several domains are more accurate when a composite score is derived rather than when subscores of specific domains are compared. Medical, administrative, and pharmacy records have also been used, especially to study larger asthmatic populations; these have proved useful for the assessment of a patient's change over time and to measure group differences.

Clinical trials of asthma therapy and educational, self-management, and health services interventions have used psychometric instruments to assess elderly patients with asthma. In most of these studies, however, the majority of subjects are younger. There are no studies that have specifically determined the reliability and validity of these instruments in elderly persons. This is true of patient-satisfaction measures that have been used to assess asthma care.[184-186] This is much needed because using lung function testing to measure outcomes has potential limitations in this age group. There are difficulties in defining normal predicted values at a very advanced age, and many patients with physical or cognitive impairment cannot reliably perform these tests. It is hopeful that newer biomarkers of lung inflammation have a particular role to play in the assessment of asthma control in the elderly.

Tools assessing physical function: Self-reported and objective

A major goal of geriatric and gerontologic research is to reduce the decrease in cognitive and physical function and prevent disability among older adults. Accordingly, many functional status measures have been developed and used to understand the disabling process, as well as to evaluate interventions to prevent functional decline. It is useful to identify instruments that measure functional limitations and disability to investigate the functional consequences of asthma in older adults and to understand the pathway from asthma to disability. Functional limitations are restrictions in performing basic physical and mental actions at the whole-person level (eg, walking or climbing stairs),

whereas disability refers to limitations or difficulty in performing socially defined roles or tasks of everyday living in a given environmental context (eg, grocery shopping or bathing).[187,188] Both self-reported and objective measures can be used to measure these different stages of disablement.[189]

Self-reported measures can provide an indication of how well a patient is functioning in daily life and provide an assessment of care needs. These measures incorporate self-perception of function and can assess adaptations made to compensate for decrements in function.[190] For disability assessment, self-reported difficulty or inability to perform basic activities of daily living (ADL) is commonly used. For example, a composite score of 8 ADL items has been used as an outcome to evaluate the efficacy of a program to prevent functional decline in frail older adults.[191] Other composite scores assessing difficulty in ambulation, stair climbing, transferring, upper extremity function, and basic and instrumental ADLs have been developed.[192] These comprehensive instruments of function and disability are amenable to computer adaptive testing.[193]

Several objective measures of physical performance are used in studies of older adults and in disease-specific patient populations. Tests of physical performance eliminate subjective attitudinal differences in the patient's reporting of physical function limitations. They have the advantage of providing an objective measure for comparisons across populations.[194] These tests are sensitive to change over time and can detect decrements in function that might not be observed with self-reported instruments. Many studies in older adults have used physical performance tests as predictors of adverse health events, as well as outcomes.

For example, the Short Physical Performance Battery, which consists of timed balance, walking, and chair-rise tasks, is a powerful predictor of disability, nursing home admission, and mortality.[195,196] The Short Physical Performance Battery was also used as a screening instrument to identify functionally limited older adults and as an outcome in a randomized controlled trial of exercise.[197] Increasingly, objective measures of physical function are used to summarize the effect of total disease burden, including subclinical conditions and impairments, and to identify physiologic reserve that might help some older adults cope with disease burden. Clinically meaningful differences have been established for commonly used performance measures.[198]

MANAGEMENT OF ASTHMA IN THE ELDERLY

The goals of asthma therapy in elderly patients are not different from those for younger asthmatic patients.[96] They are to treat acute symptoms, prevent chronic symptoms, decrease emergency department visits and hospitalizations, preserve normal activity level, and optimize pulmonary function with a minimal adverse effect from medications.[163,199,200] Optimal management should also focus on improving health status (quality of life) in these patients, which is often complicated by depressive symptoms and side effects from the drugs commonly used for asthma.[201] Unlike many younger adults who might require no medication or just as-needed β-agonist therapy for occasional symptoms, most older asthmatic patients need continuous treatment programs to control their disease. At a time when memory loss is common and financial resources are often limited, many older patients require complicated and frequent dosing with multiple expensive drugs. Unfortunately, this has led to a significant rate of noncompliance among the elderly population in general.[45] Sex, socioeconomic factors, educational level, marital status, and severity of disease do not seem to be good predictors of compliance in elderly asthmatic patients. In summary, there are many challenges in the treatment of asthma in the elderly, which include a greater propensity to experience adverse events from medication use, as well as potential drug interactions with medications used for the treatment of comorbidities,[4,96] and thus it is particularly important to treat any disease in the elderly, including asthma, with a minimum of therapy while attaining maximum efficacy.

A thorough understanding is required regarding which medications will be most effective in the treatment of asthma in the elderly to achieve this balance. Because many current therapeutic options and those in development for asthma focus on specific inflammatory cells and mediators, any age-related changes in the airway inflammatory milieu will likely affect their therapeutic efficacy. Therefore a rigorous characterization of age-related changes in airway inflammation will facilitate the management of asthma in the elderly.

Pharmacologic interventions

The therapeutic approach to asthma in elderly patients does not differ from what is recommended for young patients. Statements on the standard of care for treating asthma have been published by the National Institutes of Health and are widely used as guidelines.[163,199] Treatment protocols use step-care pharmacologic therapy based on the intensity of asthma symptoms and the clinical response to these interventions. As symptoms and lung function worsen, step-up or add-on therapy is given. As symptoms improve, therapy can be stepped down. In this age group special attention should also be given to the potential adverse effects of commonly used medications.

Corticosteroids are capable of reducing airway inflammation, thereby improving lung function, decreasing bronchial hyperreactivity, reducing symptoms, and improving overall quality of life. Oral corticosteroids should be avoided if possible because they place the patient at risk for bone fracture and increased likelihood of cataracts, muscle weakness, back pain, bruising, and oral candidiasis.[202] Many studies have shown that inhaled corticosteroids are safe and effective treatment for persistent asthma, but none have specifically targeted the elderly population. Long-term use of inhaled corticosteroids has been associated with a good safety profile, but higher doses of inhaled steroids (eg, >1000 μg/d) are capable of causing hypothalamic-pituitary-adrenal axis suppression. Local adverse effects, such as hoarseness, dysphonia, cough, and oral candidiasis, do occur but can usually be avoided by the use of a spacer or holding chamber with the metered-dose inhaler and by rinsing the mouth after each use. Despite the pivotal role of inhaled corticosteroids in asthma, many elderly patients are undertreated with this group of medications.[5,203]

Leukotriene-modifying agents (LTMs) are also asthma controllers. These agents have been shown to be effective in preventing allergen-induced asthma, exercise-induced asthma, and aspirin-induced bronchospasm. Studies on their use in the elderly are limited. When compared with LTMs, low-dose inhaled corticosteroids have favored the latter. The LTMs might also reduce asthma exacerbation rates and the need for steroid bursts. The LTMs are generally very safe.[66,204]

β-Adrenergic agents are important medications in the acute and chronic management of asthma. Elderly patients with asthma

might be less responsive to certain bronchodilators compared with younger patients.[73,138]

Inhaled short-acting β_2-adrenergic agonists are the treatment of choice for the acute exacerbation of asthma symptoms. Despite the minimal systemic absorption seen with these agents, slight tachycardia might be observed. This is presumably because of vasodilatation, which results from the stimulation of β_2-receptors in vascular smooth muscle. Tremor can also occur and is especially troublesome in the geriatric patient. Tremor is thought to be caused by stimulation of β_2-receptors in skeletal muscle. In general, they have been proven to be safe and effective in all age groups.[205] However, β-agonists can cause (1) a dose-dependent decrease in serum potassium levels and (2) a dose-dependent increase in the QT interval on electrocardiography. Because sudden death from ventricular arrhythmia can be caused by both of these mechanisms, as well as being a complication of ischemic heart disease, the use of β-agonists in the elderly should be closely monitored. Short-acting β_2-agonists should be used for rescue of symptoms, whereas long-acting agents should be used as maintenance medications only as an add-on to inhaled corticosteroids and never as stand-alone therapy.

Anticholinergics, such as inhaled ipratropium, a short-acting bronchodilator, and tiotropium, a bronchodilator with 24-hour action, have an excellent safety profile in the elderly. They should be considered when additional bronchodilator therapy is necessary; however, their role in long-term maintenance of asthma in the elderly has not been established.

Theophylline is an effective bronchodilator and has some anti-inflammatory properties. However, its use has been greatly reduced over the past decade because of safety concerns, especially in the elderly. The narrow therapeutic range of theophylline, the frequency of concomitant illnesses that alter theophylline kinetics, and many drug interactions that affect the clearance of theophylline make it essential to closely monitor blood theophylline levels in older asthmatic patients. Theophylline toxicity can cause seizures and cardiac arrhythmias, such as atrial fibrillation, supraventricular tachycardia, ventricular ectopy, and ventricular tachycardia. The most common cause for theophylline toxicity is a self-administered increase in medication.

Nonpharmacologic interventions

Controlling triggers. Measures should be taken to avoid triggers that can cause worsening of symptoms. As with asthma at any age, education concerning avoidance of aggravating factors that can lead to severe bronchospasm is very useful. Although aeroallergens are less important in provoking symptoms in the elderly than in young patients, a program implementing environmental control measures, such as avoiding or minimizing aeroallergen exposure, should be instituted in patients with documented sensitivity to specific allergens. However, such programs might not be successful in all cases, especially because lifestyle changes in the elderly population might be difficult.

The most important provocative factors include viral respiratory tract infections and irritants, such as cigarette smoke, paints, varnish, and household aerosols. Pharmacologic agents that are often prescribed for concomitant illnesses (ischemic heart disease and hypertension), such as β-adrenoreceptor antagonists (β-blockers), can also provoke bronchospasm.[206] This includes both noncardioselective agents (propranolol, pindolol, and timolol) and, to a lesser extent, cardioselective agents (metoprolol and acebutolol). Topical β-blockers are also widely used in the elderly to reduce intraocular pressure in wide-angle glaucoma. With such treatment, sufficient systemic absorption might cause fatal status asthmaticus.[207] The severity of β-blocker–induced bronchoconstriction correlates with the severity of underlying airflow obstruction and the degree of bronchial reactivity and might be reduced by the use of a cardioselective topical β-blocking agent, such as betaxolol.[208] Aspirin and nonsteroidal anti-inflammatory agents might precipitate acute bronchospasm in certain asthmatic patients, and angiotensin-converting enzyme inhibitors might cause dry cough in some, worsening the symptoms of asthma. GERD should also be considered a cause of worsening asthma symptoms.

Asthma education. The complexity of the prescription regimen (number and frequency of medications), coupled with the memory loss and cognitive dysfunction that might be present in this group of patients, contribute partially to poor compliance with therapy.[4,96]

Patient education is an effective tool and should be an integral part in the management of asthma.[209] Active participation by a patient and family members in monitoring lung function, avoidance of provocative agents, and decisions regarding medications provide asthma management skills that give that patient the confidence to control his or her own disease. Mastering the technique of an inhaled medication delivery device is a challenging problem in elderly patients, and the great majority of elderly patients are unable to properly use the metered-dose inhaler, even after proper instruction.[210-213] Use of dry powder devices, although simpler, requires the generation of an adequate inspiratory flow that might be suboptimal in frail patients and those with severe airway obstruction. In such situations the use of spacer devices or nebulizers might be beneficial. Patients should recognize the rationale behind using the different medications, the correct way to use them, and their side effects, and polypharmacy should also be avoided. Asthma in the elderly can be effectively managed, and despite severe symptoms and physiologic impairment, most patients can lead active and productive lives.

A demographic study of 380 low-income elderly persons in Chicago found that 26 (10%) without a previous diagnosis of asthma or emphysema had symptoms compatible with those of obstructive lung disease.[214] Of patients with a previous diagnosis, only 18% were compliant with medications, and this was largely due to the cost of medications. In addition, health care use was high in this population. Telephone intervention offers a simple option in the management of elderly patients with asthma. It has been shown that asthma care by means of telephone triage of adult asthmatic patients can lead to a higher percentage of asthmatic patients being reviewed at less cost per patient and without loss of asthma control when compared with usual routine care in the outpatient clinic.[215] However, it has not been determined whether such an intervention could improve asthma care specifically in persons aged 65 years or older. The following study was designed to evaluate this question.

Fifty-two elderly asthmatic patients who used their rescue inhalers more than twice a week and had at least 1 emergency department or urgent care visit in the previous year were randomized to an intervention or control group.[216] All patients received 2 telephone calls over a 12-month period. The intervention group received an asthma-specific questionnaire, and the control group received a general health questionnaire. Medication use and health care use were evaluated at the beginning and end of

a 12-month period. The study was completed by 23 control and 25 intervention subjects. Baseline data were similar in both groups. After 12 months, 72% (n = 18) of the intervention group was taking an inhaled corticosteroid compared with 40% (n = 10) of the control group. The intervention group had fewer emergency department visits when compared with the control group. Sixty-four percent (n = 16) of the intervention group had an asthma action plan compared with 26% (n = 6) of the control group. This study provides evidence that using a simple telephone questionnaire can successfully improve asthma care in the elderly. By empowering the elderly with the appropriate knowledge regarding their asthma, an appropriate discussion about their asthma care can be initiated with their primary care physicians.

Pulmonary rehabilitation. Although pulmonary rehabilitation is recommended as the standard of care for patients with COPD, there are only a few studies that evaluate the benefit of rehabilitation for asthmatic patients, and none of these consider elderly asthmatic patients. One study looked at the effects of a 10-week outpatient rehabilitation program for 58 asthmatic patients after 3 years.[217-219] They found that 39 of 58 subjects continued to exercise regularly all 3 years; there was a decreased number of emergency department visits and a decrease in asthma symptoms. Further studies are needed to assess empowerment strategies for elderly patients with asthma, as well as the potential benefits of pulmonary rehabilitation on morbidity and mortality.

AREAS OF RESEARCH

Experimental approaches

Asthma pathogenesis is complex and incompletely understood. Research into the pathophysiologic mechanisms is made more difficult by multiple factors, including the heterogeneity of the disease itself, variable presentations in different stages of life, and the lack of highly relevant animal models.[220-224] In the last decade, increasing interest in asthma in the elderly has triggered more intensive investigation in both human and animal systems by using ever more sophisticated immunologic methodologies.

Early investigation with rats revealed a lack of total and allergen-specific IgE in response to ovalbumin.[225] This was born out by several later *in vivo* studies.[226-228] IgG subset analysis (IgG_1 vs IgG_2) provided further support for this phenomenon. IgG_1, correlating in the mouse to a T_H2 response (vs IgG_2 [T_H1]) was shown to follow a similar pattern.[227,228] Recent studies[226-228] of cytokine profiles in aged rodents compared with young control animals enhanced the paradigm that age resulted in less robust T_H2 cytokines, particularly IL-4, IL-5, and IL-13, in favor of T_H1 gene and protein expression.[227,228] This pattern was not fully supported in a recent chronic murine asthma model[229] wherein IL-5 was greater in aged sensitized mice, making the picture more complex. IFN-γ, a key T_H1 cytokine, has been consistently overexpressed in aged versus young rodents.[226-229]

Eosinophilia, which is considered a key component of (allergic) asthma, was more pronounced in younger versus older animals (bronchoalveolar lavage fluid, lung tissue, or both) after most,[226-228,230] although not all,[229] sensitization paradigms.

Molecular genetics and T-cell subset analysis has allowed further insight into possible mechanisms underlying the waning T_H2 response observed in most models.[227-229] Specifically, elderly mice appear to have more memory T cells, less activated $CD4^+$ T_H2 cells, and less activated monocytes.[227,228] Resident goblet cells also appear to express upregulation of mucin and mucin gene expression.[229] A key to the impaired T_H2 response was recently found in the GATA3 pathway.[228] Elderly mice do not phosphorylate components of the extracellular signal-regulated protein kinase/mitogen-activated protein kinase pathway, resulting in lack of downstream signaling with GATA3, with subsequent impairment of promoter regions for key T_H2 cytokines, including IL-4. This could be an overarching explanation for many findings in the elderly asthmatic patient, including less IgE (IL-4 and IL-13 are needed for opening switch regions for IgE production); IL-4 and IL-13 are highly associated with airway hyperreactivity, and IL-5 is associated with eosinophil activation, survival, and, to a lesser extent, trafficking.

Finally, airway hyperreactivity has been universally found to be greater in young versus aged animals.[226-229,231] The mechanisms might be complex, including both an altered key cytokine milieu and alterations in muscle function at the muscarinic receptor level.[231-233]

Clinical and translational research

Research into the pathogenesis of asthma in recent years has led to the discovery of a number of novel, potentially important targets for the development of new treatment options. Much of this research has focused on T_H2 lymphocyte–driven processes underlying allergic asthma and its characteristic eosinophilic airway inflammation. Abundant information supporting this research has been derived from bronchial biopsy and bronchoalveolar lavage studies largely carried out in a young adult population. It is recognized, however, that the role of allergy and allergic triggers in asthma diminishes with age.[69,234] In addition, LOA is often less reversible, more severe, and frequently occurs in response to a viral respiratory tract infection.[153] A distinct asthma phenotype characterized by normal airway eosinophil numbers has been described.[235] Moreover, normal airway eosinophilia might also be associated with abnormal sputum neutrophilia.[236,237] Recent studies have shown that neutrophilic asthma might be associated with activation of innate immune pathways in contrast to the adaptive immune response associated with T_H2-mediated allergic asthma.[238] Thus alternative immune pathways involving natural killer T or T_H17 lymphocyte subtypes have been hypothesized as being potentially important in the pathogenesis of asthma, particularly in adult-onset asthma.[239,240] Just as the discovery of T_H2-related pathways has led to important leads in drug discovery for allergic asthma, further clinical research into these alternative pathways should be carried out with the goal of identifying new and exciting targets for future drug discovery. This research should focus not only on the discovery of new molecular targets but also on the identification of noninvasive biomarkers that will help predict the success of any new therapy in an individual patient.

SUMMARY AND CONCLUSIONS

Asthma is an important disease in the older adult, affecting 7% of the population older than 65 years, which is understudied and frequently underdiagnosed. There are data to suggest that asthma in older adults is phenotypically different from that in young patients, with a potential effect on the diagnosis, assessment, and

management in this population. This workshop brought together many disciplines to further our current understanding, resolve gaps in knowledge, and explore future areas of research and education. Table I lists specific areas in need of research and study.

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APPENDIX 1.

Planning Committee	
Chair:	**Co-chair:**
Monroe James King, DO Asthma, Allergy and Immunology CRU University of South Florida Largo, Fla	Nicola A. Hanania, MD, MS Section of Pulmonary and Critical Care Medicine Asthma Clinical Research Center Baylor College of Medicine Houston, Tex
Members	
Sidney S. Braman, MD Warren Alpert Medical School, Brown University Division of Pulmonary, Critical Care, and Sleep Medicine Rhode Island Hospital Providence, RI	Carol Saltoun, MD Northwestern Feinberg School of Medicine Chicago, Ill
Susan G. Nayfield, MD, MSc Geriatrics and Clinical Gerontology Program National Institute on Aging Bethesda, Md	Robert A. Wise, MD Johns Hopkins University Baltimore, Md
Participants	
Alexander Auais, MD Genentech, Inc Gladwyne, Pa	Jerome A. Dempsey, PhD University of Wisconsin School of Medicine Medical Sciences Building Madison, Wis
Cynthia M. Boyd, MD, MPH Division of Geriatric Medicine and Gerontology Johns Hopkins Department of Medicine Baltimore, Md	Paul Enright, MD The University of Arizona Tucson, Ariz
Ellen Brown American Lung Association Washington, DC	William B. Ershler, MD Harbor Hospital Baltimore, Md
Carlos A. Camargo, MD, DrPH Massachusetts General Hospital Boston, Mass	Ann Regina Falsey, MD University of Rochester School of Medicine Rochester General Hospital Rochester, NY
James E. Fish, MD Immunology, Tissue Growth and Repair Genentech Gladwyne, Pa	Carlos A. Vaz Fragoso, MD (OAIC) Clinical Epidemiology Research Center VA Connecticut Healthcare System West Haven, Conn
Paul Garbe, DVM, MPH Air Pollution and Respiratory Health Branch Division of Environmental Hazards and Health Effects National Center for Environmental Health, CDC Atlanta, Ga	Janet Holbrook, PhD, MPH Center for Clinical Trials Johns Hopkins University Baltimore, Md
Lydia Gilbert-McClain, MD Division of Pulmonary and Allergy Products US Food and Drug Administration Silver Spring, Md	Charles G. Irvin, PhD Vermont Lung Center University of Vermont Burlington, Vt
Ethan A. Halm, MD, MPH University of Texas Southwestern Medical Center Dallas, Tex	Dennis K. Ledford, MD University of South Florida College of Medicine James A. Haley VA Hospital Tampa, Fla
Robert G. Hamilton, PhD Johns Hopkins University School of Medicine Johns Hopkins Asthma and Allergy Center Baltimore, Md	Charlene Levine American Lung Association Washington, DC
Sameer K. Mathur, MD, PhD Department of Medicine Section of Allergy, Pulmonary and Critical Care University of Wisconsin School of Medicine Madison, Wis	John J. Lima, PharmD Clinical Pediatric Pharmacology Nemours Children's Clinic Jacksonville, Fla
Jeanne Moorman, MS Centers for Disease Control Atlanta, Ga	Katherine Pruitt American Lung Association Washington, DC

(continued)

APPENDIX 1. *(Continued)*

Enid R. Neptune, MD Division of Pulmonary and Critical Care Medicine Institute of Genetic Medicine Johns Hopkins School of Medicine Baltimore, Md	Joe W. Ramsdell, MD Division of General Internal Medicine University of California, San Diego San Diego, Calif
Amy Pastva, PT, PhD Department of Cell Biology Duke University Durham, NC	Charles Reed, MD (keynote speaker) Department of Medicine Mayo Medical School Rochester, Minn
Kushang Patel, PhD Laboratory of Epidemiology, Demography, and Biometry National Institute on Aging Bethesda, Md	Theodore Reiss, MD Merck & Co, Inc Rahway, NJ
Sergei Romashkan, MD Clinical Trials Branch Geriatrics and Clinical Gerontology Program National Institute on Aging Bethesda, Md	Linda Rogers, MD NYU School of Medicine Bellevue Hospital Asthma Clinic New York, NY
Mark F. Sands, MD University at Buffalo, State University of New York Division of Allergy/Immunology Buffalo General Hospital Buffalo, NY	Michael L. Terrin, MD, CM, MPH University of Maryland School of Medicine Baltimore, Md
David A. Stempel, MD GlaxoSmithKline Bellevue, Wash	Sandra R. Wilson, PhD Stanford University School of Medicine Department of Health Services Research Palo Alto Medical Foundation Research Institute Palo Alto, Calif
Stephen I. Wasserman, MD University of California−San Diego San Diego, Calif	Barbara P. Yawn, MD, MSc Department of Family and Community Health University of Minnesota Rochester, Minn
NIH representatives	
National Institute on Aging (NIA)	
Basil Eldadah, MD Geriatrics Branch Geriatrics and Clinical Gerontology Program National Institute on Aging Bethesda, Md	Ying Tian, MD, PhD Geriatrics Branch Geriatrics and Clinical Gerontology Program National Institute on Aging Bethesda, Md
Evan Hadley, MD Geriatrics and Clinical Gerontology Program National Institute on Aging Bethesda, Md	
National Institute of Allergy and Infectious Diseases (NIAID)	
Gang Dong, MD, PhD Division of Allergy, Immunology and Transplantation NIAID/NIH Bethesda, Md	Peter J. Gergen, MD, MPH NIH/DAIT/AAIB Bethesda, Md
National Heart Lung and Blood Institute (NHLBI)	
James P. Kiley, MD Division of Lung Diseases National Heart Lung and Blood Institute Bethesda, Md	Virginia Taggart, MPH Division of Lung Diseases National Heart Lung and Blood Institute Rockledge II, Room 10042 Bethesda, Md
National Institute of Nursing Research (NINR)	
Karen Huss, PhD NINR/NIH Bethesda, Md	