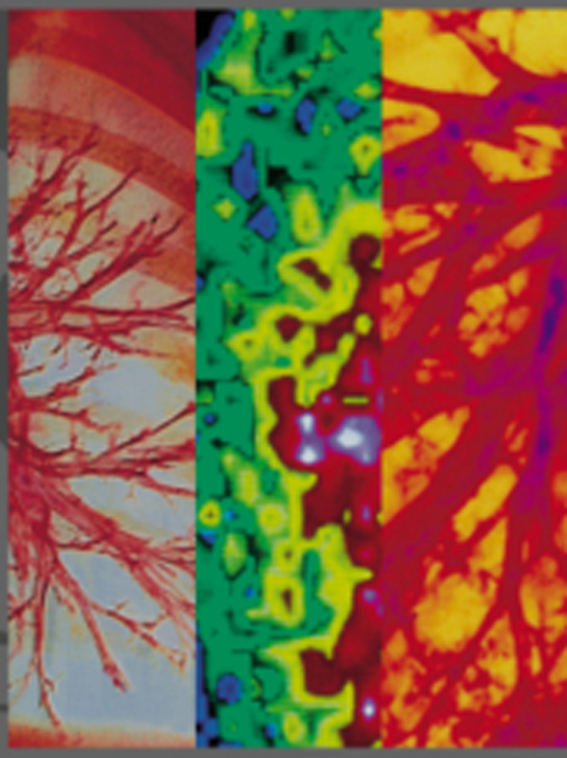
Asthma and COPD



Basic Mechanisms and Clinical Management

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Asthma and COPD

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Contents

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Foreword

During the last century, transmissible and acute diseases dominated the interests of the research, clinical, and public health communities. Looking back, we can only marvel at the progress that has been made. Indeed, some contagious diseases have been eradicated, totally or virtually, in many parts of the world. Deaths from some acute events, such as myocardial infarction and stroke, have declined remarkably. As a result, quality of life, economic power, and life expectancy have all increased in a number of countries. Over the past 20 years in the United States, for example, life expectancy increased by about six years owing to a reduction in death rates of most major conditions.

Chronic diseases of the airways, however, have worked against this favorable trend in life expectancy. Although death rates from asthma are relatively low, chronic obstructive pulmonary disease has a very significant impact on the total number of deaths worldwide. In the United States, it accounted for about 110,000 deaths in 1999, ranking as the fourth most common cause of mortality.

Of even greater concern than the death toll from asthma and COPD is their considerable impact on those who live with these chronic diseases. Because of their lingering nature, they constitute an extraordinary burden that reduces the quality of life for the patients and many around them. Furthermore, these diseases have a negative impact on the economic potential of society, especially in developing countries. The burdens on the healthcare system are readily measurable – hospitalizations, emergency room visits, prescription drugs, respiratory therapy, long-term care, among others. But perhaps even more significant are the limitations that these diseases impose on the ability of their victims to fulfill their roles in school, in the workplace, and in the community, to care for their loved ones and, in many cases, even to care for themselves. The strength of a society resides in the independence and productivity of its people, and these qualities, in turn, hinge upon the people's good health. Asthma and COPD are ominous threats to the strength of societies worldwide.

At the end of the twentieth century, several events occurred that may lead to a transformation of this sad situation. First and foremost, the international scientific community began to arrive at the realization that the path to achievement of its ideal goal – elimination of the main cause of COPD, cigarette smoking – would be a rocky one and that its pursuit must be coupled with an intensive research effort to control and conquer this disease.

With regard to asthma, an extraordinary research effort has yielded a greater understanding of the pathogenesis of this disease and a new armamentarium of therapeutic approaches that have proven to be remarkably effective. But there is no room for complacency!

Another defining event has been a greater realization of the importance of chronic diseases, especially asthma and COPD, in the newly developed interests of the World Health Organization. This has been largely due to the work of Drs Murray and Lopez.[1] They gave the research and public health communities great cause for alarm by demonstrating that the ranking of societal and individual burden from chronic respiratory diseases will rise from twelfth to fifth between the years 1990 and 2020.

We, and the public at large, can only applaud the response of these communities. This book is further evidence of that response. First, it presents the best and newest of what is known about these two diseases. The roster of international contributors is stellar. In addition, the volume is comprehensive: all aspects of these two very prevalent diseases are addressed. The reader will soon recognize the complexity of the issues and appreciate the wonderful job that the text does of making them understandable. The most important and innovative feature of this volume, however, is its comparison, where appropriate, of the two diseases. Of course, asthma and COPD are different, but they also share a number of characteristics, and understanding one can greatly help us understand the other.

In 1971, the CIBA Foundation sponsored a debate on "Identification of Asthma".[2] One participant led an extensive discussion on the definition of asthma and how it may be differentiated from chronic bronchitis. At its conclusion, another participant wisely observed: "The question that clinicians have to ask themselves before they can apply rational treatment is this: What is the mechanism?"

By comparing and contrasting asthma and COPD, this book helps answer that question. In the end, it is the patients and the societies in which they live who will benefit from this contribution

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Bethesda, Maryland

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Preface

Asthma and chronic obstructive pulmonary disease are amongst the two commonest chronic conditions in the world today and both are predicted to increase. Because of their high prevalence and chronicity, these diseases impose an enormous and growing economic and social burden. Enormous strides have been made in our understanding of the basic mechanisms of asthma, with a much better appreciation of the inflammatory mechanisms involved and how this underlies the clinical features of the disease. This is one of the reasons why the management of asthma has improved enormously. Currently available medications are highly effective in most asthmatic patients, although there remain a small group of patients who are still not adequately controlled on existing treatments. But although asthma medications are very effective, many patients with asthma continue to have problems and asthma is still a common cause of hospital admission and time lost from work. There is therefore a need for further research in asthma and for the development of new and even more effective therapies.

Although COPD is just as large a problem as asthma, there has been less attention given to this disease, and our understanding of the underlying basic mechanisms are far less advanced than for asthma. COPD has a very high morbidity and mortality and is a growing problem, particularly in developing countries. Treatment is less effective than in asthma, and none of the existing medications is able to reduce the progression of the disease. COPD is still commonly treated as poorly responsive asthma, yet the inflammatory process and effects are very different and there is little reason to think that the same treatments should be effective. There is a pressing need for much more research into underlying mechanisms of COPD, in order to identify novel therapies in the future. Management issues in COPD are also different in many respects from those involved in asthma.

Two of us (PJB and NCT) were involved in editing a book on *Asthma: Basic Mechansism and Clinical Management*. This was most successful and ran to three editions. In considering the next edition we thought that it would be very useful to include COPD as no other book had taken both these diseases together. In putting together this new volume on *Asthma and COPD: Basic Mechanisms and Clinical Management* we invited the two North American editors in order to make the book more international. We have retained the structure of the original *Asthma* book, but have added new chapters that are relevant to COPD. However, we have asked authors to consider both diseases in preparing their chapters. Of course, there is far more information about basic mechanisms pertinent to asthma than to COPD, but we hope that by contrasting this information and identifying areas of uncertainty, this may act as a stimulus to further research in COPD.

We hope that this new book will be useful to researchers and to clinicians and will serve as a useful reference source. The format has been changed to make it more attractive and more easily read. Despite the advance of on-line publications on the Internet, we feel that there is still an important place for definitive reference books as a source of information. We would like to thank Margaret MacDonald and Simon Crump of Academic Press for all their help in putting together this book and we hope that you will enjoy the result.

Peter J. Barnes	*Jeffery Drazen*	*Stephen Rennard*	*Neil C. Thomson*
London	*Boston*	*Omaha*	*Glasgow*

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Dedication

PROFESSOR ANN WOOLCOCK, AO, MD, FRACP, FAA (1937–2001)

We would like to dedicate this book to the memory of Ann Woolcock who sadly died on 17 February 2001. Ann contributed an important chapter on Asthma Management in Adults, and this was the very last thing that she wrote before her death.

Ann Woolcock was Professor of Respiratory Medicine at the University of Sydney, Australia, and Director of the Institute of Respiratory Medicine, which she had founded at the Royal Prince Alfred Hospital. She qualified in medicine at the University of Adelaide in 1961. She set up the Respiratory Laboratory at the Royal Prince Alfred Hospital in Sydney; then, after a period of research at McGill University in Montreal, established the Institute of Respiratory Medicine in 1982. A multidisciplinary Clinical Research Centre was recently established in Sydney, and directed by Ann.

Ann was a world leader in respiratory medicine and probably had more influence on modern asthma management than anyone else in the last decade. She trained a generation of leading investigators in respiratory medicine in Australia. Her research on the epidemiology and management of asthma was internationally recognized. She never lost her contact with and concern for patients who were devoted to her. She published extensively in international journals and was in great demand as a speaker at international meetings.

Her enormous contributions in respiratory medicine were recognized by many international awards, including Distinguished Achievement awards from the American Thoracic Society and the European Respiratory Society and the Simms Commonwealth Travelling Professorship. She was made an Officer of the Order of Australia in 1989, was elected a Fellow of the Australian Academy of Sciences in 1992 (the first practicing female clinician to achieve this honour), and was a corresponding member of the French Academy of Medicine. She was awarded an honorary degree at the University of Ferrara Italy only two weeks before her death.

Ann had an extraordinary influence throughout the world. She was an inspirational lecturer, iconoclast, and visionary, who advanced respiratory medicine almost more than any other, by stimulating new ideas and challenging conventional approaches. She was one of the first to promote the idea of guidelines in asthma therapy based on good clinical research. More than any other she recognized the need to integrate basic research into our understanding and management of asthma, and this is clearly visible in her chapter. It is very fitting that this book should be dedicated to her memory.

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PART I

Definitions, Epidemiology and Genetics of Asthma and COPD

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Definitions

Chapter 1

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Until recently, the presence or absence of *reversibility* was considered to be the key distinction between asthma and chronic obstructive pulmonary disease (COPD) – with reversible airflow obstruction the hallmark of asthma, and irreversible airflow obstruction the hallmark of COPD. Better understanding of both diseases has brought new definitions that acknowledge the overlap and highlight the similarities and differences between them. The important change in our understanding is the recognition that chronic inflammation underlies both diseases. The nature of the inflammation differs, however, as does the response to anti-inflammatory medications, as described in detail in later chapters.

DEFINITIONS

Asthma

In the most recent US asthma guideline, the Expert Panel 2 Report,[1] asthma is defined as:

> *A chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, in particular, mast cells, eosinophils, T lymphocytes, neutrophils, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night and in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyperresponsiveness to a variety of stimuli.*

COPD

In the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines,[2] COPD is defined as:

> *A disease state characterized by progressive development of airflow limitation that is not fully reversible. The airflow limitation is usually progressive and usually results from an abnormal response of the lungs to noxious particles or gases.*

SIMILARITIES AND DIFFERENCES

Over the past 30 years, thinking about asthma and COPD has swung between the concept of asthma and COPD belonging to a spectrum of diseases that all cause airflow obstruction, to the concept of them as very different diseases, and most recently to them both being inflammatory diseases with important similarities and differences. The present thinking is illustrated in **Fig. 1.1** from the GOLD guidelines, which shows both diseases causing airflow limitation, but through a gene–environment interaction involving different sensitizing agents, different cell populations in the inflammatory response, and a spectrum of reversibility. The airflow limitation resulting from the inflammatory process ranges from completely reversible (the asthma end of the spectrum) to completely irreversible (the COPD end of the spectrum).

Table 1.1 highlights the most important similarities between asthma and COPD. Both are chronic inflammatory diseases that involve the small airways and cause airflow limitation; both result from gene–environment interactions;

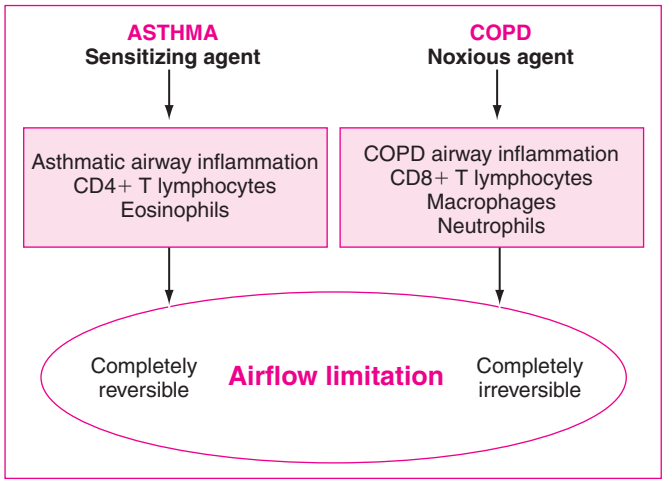

Fig. 1.1. Schematic of the genesis of airflow obstruction in asthma and COPD.

Table 1.1. Similarities between asthma and COPD

Both are chronic diseases
Inflammation present in both
Airflow obstruction
Involvement of the small airways
Mucus
Bronchoconstriction
Both are consequences of gene–environment interaction

and both are usually characterized by mucus and bronchoconstriction.

Although the similarities are striking, it is the differences between the two diseases that define their natural histories and clinical presentations. The key differences are contrasted in **Table 1.2**.

The first obvious difference is that the diseases involve different anatomic sites in the lungs. COPD affects both the airways and the parenchyma; asthma affects only the airways. The small airways are involved in both diseases, and the structural changes at this level are responsible for much of the lung function impairment associated with these diseases. Also, an important difference anatomically is that emphysema, an irreversible, destructive, parenchymal disease, is variably present in COPD, but is not present in asthma.

Perhaps the single most important difference between the two diseases is the nature of the inflammation: it is primarily eosinophilic, CD4-driven in asthma and neutrophilic, CD8-driven in COPD.[1,2] The nature of the inflammation in turn affects the response to pharmacological agents. There is ample evidence now that inhaled corticosteroids are effective against the eosinophilic inflammation that is characteristic of asthma,[1–5] but largely ineffective against the primarily neutrophilic inflammation seen in COPD – although this is not a completely consistent finding.

The natural histories of asthma and COPD are very different. COPD is a chronic and *progressive* disease that is characterized by airflow limitation that is *not fully reversible* and by an accelerated decline in lung function. Asthma is a chronic disease, but it is usually not considered a progressive disease, and it is not usually characterized by an accelerated decline in lung function, unless there are other risk factors such as smoking.[9,10] The airflow limitation is fully reversible in the early stages of asthma but, at least in a subset of asthmatics, may become progressively less reversible as the disease becomes longstanding.[11]

The difference in the gene–environment interaction in the two diseases has already been alluded to: in asthma, the inflammation is a response to inhaled allergens. In COPD, the inflammation is a response to noxious particles and gases.

DIFFERENTIATING BETWEEN ASTHMA AND COPD

It would be easy to differentiate between asthma and COPD if the latter occurred only in smokers and asthma in nonsmokers. In fact, there is a clear diagnostic bias on the part of physicians, with COPD more likely to be diagnosed in men and asthma in women.[11] It is important to emphasize that both conditions may coexist in an individual, so many will have the clinical and pathophysiological features of both diseases. This makes differentiating the diseases sometimes challenging for the clinician, especially in older adults who are or have been smokers.

The clinician can be guided by information in the clinical history, such as smoking history, age of onset of symptoms, history of atopic conditions, and description of acute episodes of shortness of breath (see **Table 1.3**).

Asthma usually has its onset in early childhood. However, adult-onset asthma does exist, and many are unable to remember childhood events that would provide a clue to the early stages of asthma. Therefore, unless symptoms are continuous from childhood, the onset of asthma symptoms in adult life may be hard to interpret, especially in the presence of other risk factors such as smoking. COPD typically becomes clinically apparent in the sixth and seventh decades of life. If an individual is physically active, he or she may notice reduced exercise tolerance earlier.

Table 1.2. Differences between asthma and COPD

Characteristic	Asthma	COPD
Anatomic site of disease	Airways involved	Airways and parenchyma involved
Nature of inflammation	Eosinophilic, CD4-driven	Neutrophilic, CD8-driven
Reversibility of airway obstruction	Mostly reversible	Mostly irreversible
Response to inhaled corticosteroids	Inflammation reduced	Inflammation mostly nonresponsive
Progression of disease	Chronic, but not characterized as progressive	Progressive airflow obstruction
Decline in lung function	Normal or slightly accelerated	Accelerated
Gene–environment interaction	Allergens are main drivers of inflammation	Particles and gases are main drivers of inflammation

Table 1.3. Clinical features of asthma and COPD

Clinical feature	Asthma	COPD
Age of onset	Usually early childhood, but may have onset at any age	Mid–late adult life
Smoking history	May be non-, ex-, or current smoker	Usually smoker or ex-smoker
Atopy	History of atopic disorder(s) common	Not a prominent feature
Exacerbations	Common at all levels of severity except mild intermittent	Increase in frequency with increasing severity of disease
Family history	Of atopic disorders or asthma commonly present	Not usually a feature
Lung function	Normal in mild intermittent and mild persistent; airflow obstruction present at all other steps	Airflow obstruction a hallmark of COPD
Reversibility of airflow obstruction	Characteristic of asthma	Poorly reversible
Peak flow variability	Characteristic of asthma, usually > 20%	Often does not vary at all
Diffusing capacity	Usually normal	Abnormal when there is emphysema

COPD in developed countries is mostly a disease of smokers. This is not necessarily true in developing countries where other risk factors, such as heavy outdoor and indoor/occupational air pollution, may be important risk factors that are causally related to COPD.[2] The relationship between asthma and smoking is complex. Individuals with asthma may be nonsmokers, smokers, or ex-smokers. Since asthma genes and genes leading to the susceptibility to develop airflow obstruction with smoking are common in the population, the likelihood that an individual may have both is high.

One of the unresolved questions about asthma relates to the nature of the complex relationship between asthma and atopy. Most asthmatics are atopic, but not all atopic individuals have asthma. A history of atopic disorders, such as allergic rhinitis or eczema, is therefore common in asthma, but is not a characteristic of COPD. As noted above, because asthmatic/atopic genes are widespread in the population, it is not unusual for atopic disorders to coexist with COPD, but it is not a characteristic of the disease as it is for asthma.

Pulmonary function tests can also provide guidance. Both diseases are characterized by airflow obstruction except in the early or mild stages. In asthma, lung function is still normal in patients with mild intermittent or mild persistent disease.[1] COPD, in comparison with asthma, is defined by airflow limitation, and this becomes progressively greater as the disease advances. **Fig. 1.1** shows the spectrum of reversibility ranging from completely reversible (asthmatic end) to completely irreversible (COPD end). Clinically, reversibility is defined as ≥ 12% increase in FEV_1 (and at least 200 mL) over baseline.[12] If clear-cut reversibility of airflow limitation is found, asthma is likely to be present. If the airflow limitation is irreversible, COPD is likely to be the diagnosis.

OVERLAP BETWEEN ASTHMA AND COPD

Not acknowledged in the definitions is the fact that longstanding asthma can lead to airway remodeling and partly irreversible airflow obstruction. So, in many (but not all) with longstanding asthma, there is an appreciable component of chronic irreversible airflow obstruction with reduced lung function and incomplete response (or at least, not complete reversibility) to a short-acting bronchodilator or to oral or inhaled corticosteroids.[13,14] This complicates the diagnosis of asthma in older adults, and requires that the goals of treatment be modified since maintenance of normal lung function can no longer be a realistic goal. Not clear yet is whether early and aggressive treatment with anti-inflammatory drugs can prevent remodeling, or in what proportion of individuals with longstanding asthma remodeling occurs.

Whether longstanding asthma with remodeling can be called COPD is intensely controversial. In so far as there is irreversible or poorly reversible airflow obstruction in the remodeled lungs, the term seems appropriate. Conceptually and practically, the recognition that remodeling is a feature of longstanding asthma in many (but not all) reinforces the notion that these diseases constitute a spectrum of disease, as illustrated in Figure 1.1, ranging from fully reversible to fully irreversible.

EXACERBATIONS

The definition of asthma highlights the importance of exacerbations as a feature of asthma, and emphasizes the fluctuations of the disease.[1] The definition of COPD does not include any mention of exacerbations.[2] Nevertheless, they may be as important in the natural history of COPD as

they are in asthma[15–17] and account for approximately 70% of the COPD-related costs in the US.[2]

The commonest causes of exacerbations of COPD are infections of the tracheobronchial tree and air pollution,[2,18–21] but the causes of about one-third of severe exacerbations cannot be identified. The commonest symptom of an exacerbation of COPD is increased breathlessness, often accompanied by wheezing, chest tightness, increased cough and sputum, change in color and/or tenacity of sputum, and fever. Enquiring about the nature, frequency, and length of exacerbations is an important part of the clinical history in COPD since exacerbations are an important contributor to the erosion of quality of life in severe disease, and should therefore be an important focus of management.

LIMITATIONS OF THE DEFINITIONS

Definitions for both asthma and COPD have limitations since they can reflect only our current understanding of the diseases, which is quite limited. Both diseases will continue to be redefined as our understanding of them deepens, and as new effective preventive strategies and treatments become available.

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Epidemiology

Chapter 2

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This chapter discusses the epidemiology of both asthma and chronic obstructive pulmonary disease (COPD). After briefly contrasting the disease definitions, the chapter reviews incidence and prevalence data, risk factors, and natural history.

DEFINING THE DISEASES

Asthma

The study of asthma epidemiology has been plagued by lack of consensus regarding standards for diagnosis. Most definitions have included variable airflow obstruction; but asthma is a clinical syndrome, without a gold standard for its diagnosis. Epidemiology studies have used questionnaires to assess for the presence of disease, but are limited by recall and misclassification bias.

Some have suggested that symptoms should be assessed in conjunction with airway hyperresponsiveness.[1] Others argue that airway hyperresponsiveness and symptoms should be analyzed separately owing to the poor correlation between clinical asthma and hyperresponsiveness.[2] Population-based epidemiology studies have demonstrated a low sensitivity of airway hyperresponsiveness for detecting asthmatic phenotypes, versus a sensitivity of greater than 90% in clinic studies.[3] A standard definition of asthma is as a chronic inflammatory disease of the airways with variable reversible airflow obstruction.

Beyond definitions, there are differences between languages for the words used to describe asthma symptoms. A novel solution to this problem has been used in the International Study of Asthma and Allergies in Children (ISAAC), which includes an asthma video questionnaire demonstrating clinical signs of asthma as an attempt to improve uniformity in surveying for asthma.[4]

COPD

Before describing epidemiological trends for obstructive lung disease, agreement on definitions should be achieved such that trends in incidence, prevalence, morbidity, and mortality can be properly ascribed.

COPD includes chronic bronchitis and emphysema, and is characterized by airway obstruction that is fixed or only partially reversible. The degree of airflow obstruction assigned to a given patient depends upon the guidelines used, with some defining mild obstruction as a FEV_1 greater than 65%, 70%, or 80% of predicted.

As in the case of asthma, the lack of international standardization of criteria for diagnosis in COPD makes understanding relative incidence and prevalence more challenging. This is well illustrated by a study by Viegi et al.[5] who compared the prevalence rates of COPD in a general population in the Po Delta Valley using European Respiratory (ERS) criteria, American Thoracic Society (ATS) criteria, and standard clinical criteria. In subjects 25–45 years of age:

- ERS criteria revealed a 10.8% prevalence of COPD;
- ATS criteria revealed a 27% prevalence;
- clinical criteria showed a 9.9% prevalence.

Similarly, in subjects aged 46 years or more:

- ERS criteria revealed a 12.2% prevalence;
- ATS criteria had a 57% prevalence;
- clinical criteria showed a 28.8% prevalence.

This example highlights the difficulty of comparison between international studies and the effort to understand COPD on a global scale. If such discrepant results are obtained within a single population, then the difficulty of comparison between populations is very clear.

In summary, both asthma and COPD lack gold standards for diagnosis, which would facilitate epidemiological studies. As a result, comparison of studies of asthma and COPD between populations and between countries must be viewed in the light of differences in criteria used for disease diagnosis.

INCIDENCE

Asthma is predominantly a disease of childhood, with more than 17.3 million persons having asthma in the United

States, 12 million are children of less than age 16. In childhood, incidence rates for asthma are highest among the youngest age groups[6,7] and among male children until puberty.[8–11] In a recent study of an adult Swedish population, Toren and Hermansson[12] found the incidence rate for adult-onset asthma to be highest among females of all ages greater than 20, with an incidence of 1.3 per 1000 person-years; among women 16–20 years of age the rate was 3 per 1000 person-years. Analysis of data from a prospective cohort study in Finland demonstrated no increase in incidence for asthma from 1982 to 1990 in adults aged 18–45 years.[13] Early investigation into the increasing prevalence of asthma in the United States was noted in a review of medical records from Olmsted County, Minnesota, where the annual incidence of asthma was found to increase from 183 per 100,000 in 1964 to 284 per 100,000 in 1983. The most significant increase was in children aged 1–14 years, suggesting a potential cohort effect early in life. Despite this increased incidence in asthma among children from 1964 to 1983, constant rates were observed among adults.[6]

Although these data indicate that asthma incidence is increasing, minimal information is available for trends in COPD incidence. Incidence rates for asthma and COPD vary with the age of the population. Asthma is commonly diagnosed in early childhood; COPD is commonly diagnosed after age 60.

PREVALENCE

Recent trends in the prevalence of obstructive lung disease are suggested by an analysis of the National Health and Nutrition Examination Survey (NHANES III).[14] This included subjects with asthma, chronic bronchitis, and emphysema (**Fig. 2.1**). In this cohort, outcome measures included a physician diagnosis of chronic bronchitis, asthma or emphysema, respiratory symptoms, and low lung function. Of note, for the purposes of evaluating this cohort the investigators defined low lung function as present when both the FEV_1/FVC ratio was < 0.70 and the FEV_1 was less than 80% of predicted. Of the investigated population of 20,050 adults, 6.8% had low lung function as thus defined; 7.2% of the population had an FEV_1/FVC ratio less than 0.70 with an FEV_1 greater than 80% predicted, and were not included as having low lung function. Of the entire population, 8.5% reported obstructive lung disease.

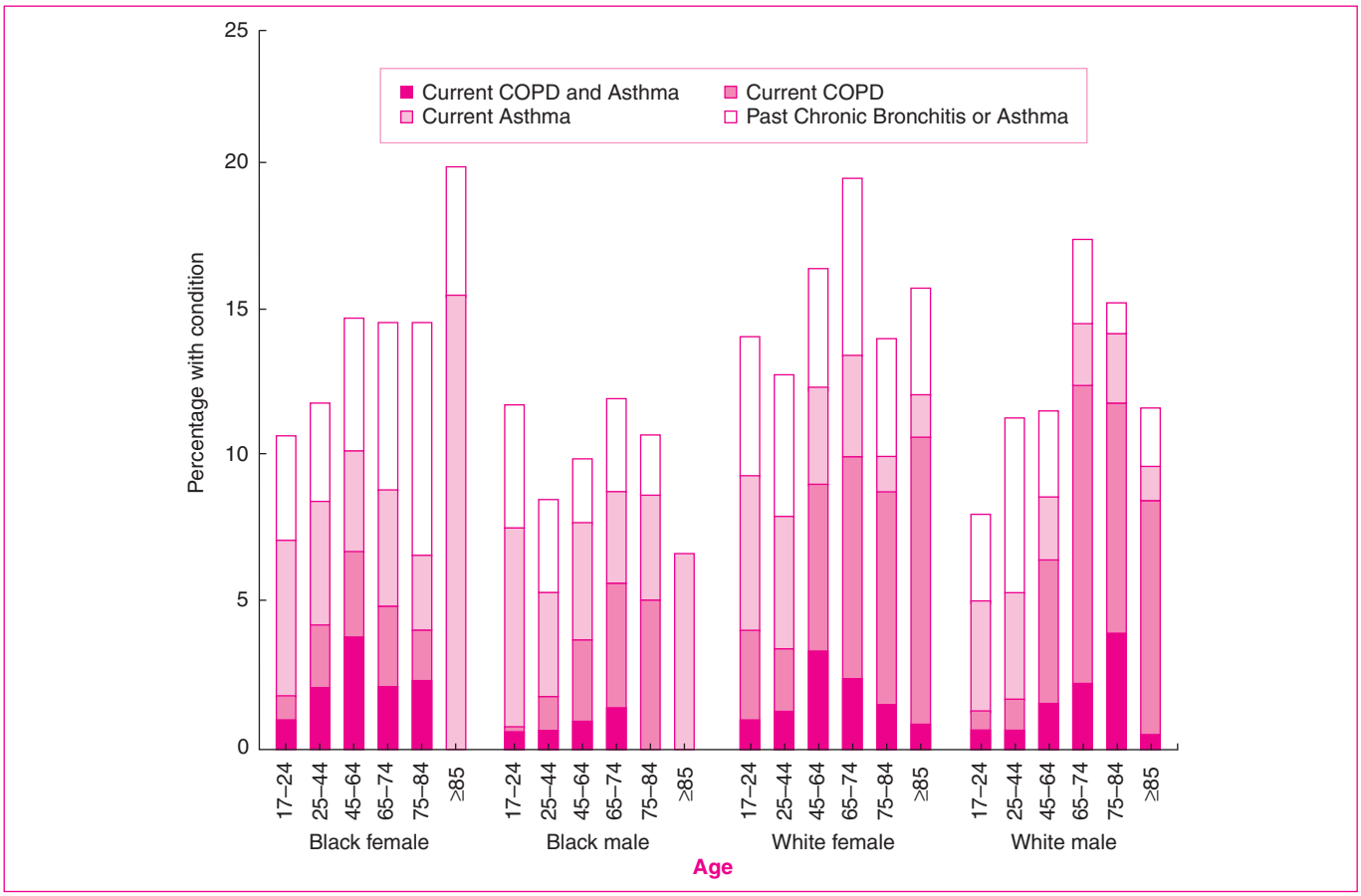

Fig. 2.1. Age-specific percentage of individuals, stratified by race and sex, with chronic obstructive pulmonary disease and asthma, current COPD, current asthma, and past chronic bronchitis or asthma. Reproduced from National Center for Health Statistics, *Plan and Operation of the Third National Health and Nutrition Examination Survey, 1988–94*, US Dept of Health and Human Services publication PHS 94-1308, 1994, with permission.

Importantly, 63.3% of those with documented low lung function had no current or prior doctor diagnosis of obstructive lung disease. In addition to prevalence information regarding low lung function, data from NHANES suggests that there is still a significant proportion of disease that goes undiagnosed in the mild stages, thus leading to an underestimation of the true prevalence of obstructive lung disease.

Asthma

Data from the United States suggest an increase in prevalence of asthma in children as well as in older adults. During the last several decades studies have suggested an increase in prevalence worldwide of 5–6% per year. Data from the National Health Interview Survey reveal an increase of 75% in self-reported asthma rates from 1980 to 1994 (**Fig. 2.2**). This trend was demonstrated in all age and race strata as well as in both genders. The most significant increase was among:

- children 0–4 years of age (increase of 160%);
- persons 5–14 years of age (increase 74%).[15]

The prevalence among inner-city children is much higher.[15–17] It has been suggested that a doctor's diagnosis of asthma is made less frequently than asthma symptom reporting, raising concern that despite increasing prevalence there is still a tendency to underdiagnose asthma, and consequently underestimate true prevalence values.[18]

The increasing prevalence of asthma has been recapitulated in international data. The International Study of Asthma and Allergies in Children (ISAAC) has as its aim to describe, across 155 centers, the prevalence and severity of asthma in children in 56 countries.[4] Phase 1 of this trial has demonstrated a large variation in the prevalence of asthma symptoms in children throughout the world, with the highest prevalence in centers from Australia, New Zealand, the United Kingdom, and Ireland[18–21] (**Fig. 2.3**). While the prevalence of allergic rhinitis has been noted to be scattered in the groups with the highest prevalence of asthma, the lowest prevalence for rhinitis has been found in countries where the asthma prevalence was lowest, such as in Eastern Europe, Indonesia, Greece, and India. In addition to defining prevalence rates, the ISAAC study represents an effort to establish an international standard to facilitate comparability of data from epidemiological studies of asthma.

COPD

Susceptibility to cigarette smoke is not uniform. However, COPD is best understood by understanding first the trends for smoking in populations. Although projected smoking rates throughout the world have increased, smoking prevalence in the United States between 1983 and 1995 declined overall:

- from 30% to 24% in white women;
- from 32% to 23% in African American women;
- from 34% to 26% in white men;
- from 41% to 29% in African American men.

Stang et al.[22] utilized smoking rates to create a mathematical model for estimating current COPD prevalence. Using their model, they estimated that 15.3 million people in the United States aged 40 years or more have COPD; this was a reasonable estimate compared to the spirometric prevalence of 17.1 million as estimated by the Third National Health and Nutrition Examination Survey. Using this model, they also predicted the prevalence of COPD in Germany (2.7 million), the United Kingdom (3.0 million), Spain (1.5 million), Italy (2.6 million), and France (2.6 million), and suggested smoking rates as a useful surrogate for estimating COPD prevalence.

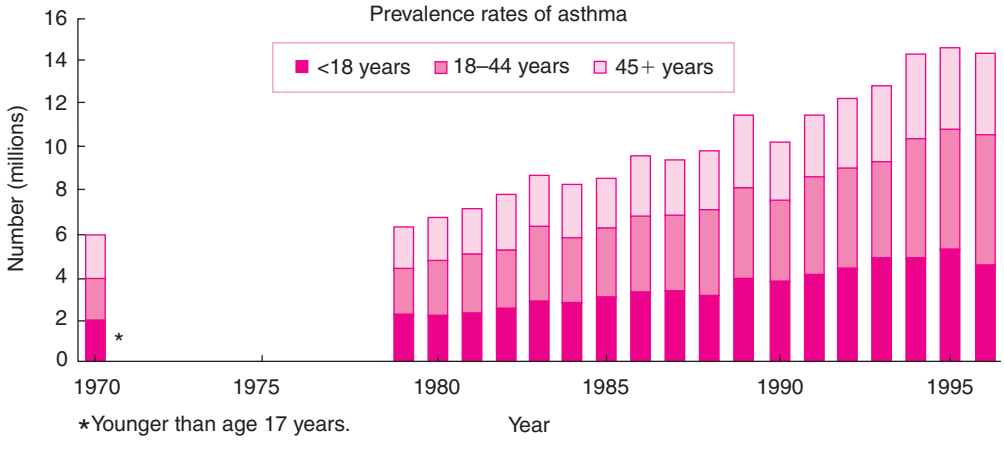

Fig. 2.2. Prevalence of asthma in individuals less than age 18, aged 18–44, and greater than age 45. Between 1979 and 1994 the prevalence of asthma increased in all three age groups. Reproduced from *NHLBI Morbidity and Mortality Chartbook*, 2000, p. 61, with permission. http://www.nhlbi.nih.gov/resources/docs/cht-book.htm

Fig. 2.3. Prevalence of wheeze measured in the last 12 months prior to survey in the International Study of Asthma and Allergy in Children. Only 28 of 56 of the participating countries are highlighted here. Reproduced from reference 102, with permission.

The World Health Organization prediction is that by 2020 COPD will rise from being the twelfth to the fifth most prevalent disease worldwide, and from being the sixth most common cause of death to the third most common.[23] Recent prevalence estimates of COPD in the United States suggest that approximately 15 million people have COPD: 14.1 million with chronic bronchitis and 1.8 with emphysema in 1996 (**Fig. 2.4**). There was no change in the prevalence of emphysema from 1982 to 1996, although from 1983 to 1995 the prevalence of chronic bronchitis continued to increase. In a study of the Canadian population, prevalence rates of COPD were 4.6% in the 55–64 age group, 5.0% in the 65–74 age group, and 6.8% in the greater than 75 age group.[24] These data may be an underestimation, as there is a suggestion that COPD prevalence rates are underestimated in the elderly, especially in those with lower incomes.[25]

COPD is thought to be underdiagnosed in both North American and European populations. The IBERPOC Project (Estudio Epidemiologico de la EPOC en España)

Fig. 2.4. Prevalence measures for chronic bronchitis and emphysema. **(a)** From 1983 to 1995 the prevalence of chronic bronchitis increased steadily, with most of the increase in those older than age 18 years. **(b)** Despite fluctuations from year to year there was no overall change in the prevalence rate of emphysema from 1982 to 1996; most of the burden of the disease has been in older individuals. Reproduced from *NHLBI Morbidity and Mortality Chartbook,* 2000, p. 56, with permission.
http://www.nhlbi.nih.gov/resources/docs/cht-book.htm

was a population-based study of prevalence of COPD in Spain.[26] The prevalence of COPD in this population (26% current smokers, 24% ex-smokers, 76% men), defined according to European Respiratory Society criteria, was 9.1%. Only 22% of those diagnosed had a prior diagnosis, while 48% had prior respiratory symptoms. The WHO and the National Institute of Heart, Lung and Blood Diseases have collaborated in an effort to broach the increasing present and projected future burdens of COPD by implementing a Global Initiative for Obstructive Lung Disease (GOLD). GOLD aims to promote studies to understand the increasing prevalence of COPD worldwide, as well as to standardize the collection of data for international comparison[27] (**Fig. 2.5**).

Summary

- The prevalences of both asthma and COPD are increasing in Western developed countries.
- If both asthma and COPD are underdiagnosed, the prevalence estimates underestimate the true burden of these diseases.
- Variability in definitions of both asthma and COPD contribute to inexact prevalence estimates and problems with comparisons of prevalence data.
- ISAAC (for asthma) and GOLD (for COPD) represent efforts underway to standardize the definitions used in studies to enhance international comparisons of incidence, prevalence, and burden of disease.

UTILIZATION AND HOSPITALIZATION TRENDS

In the United States, the estimated cost for year 2000 for asthma was projected to be 12.7 billion dollars (8.1 for

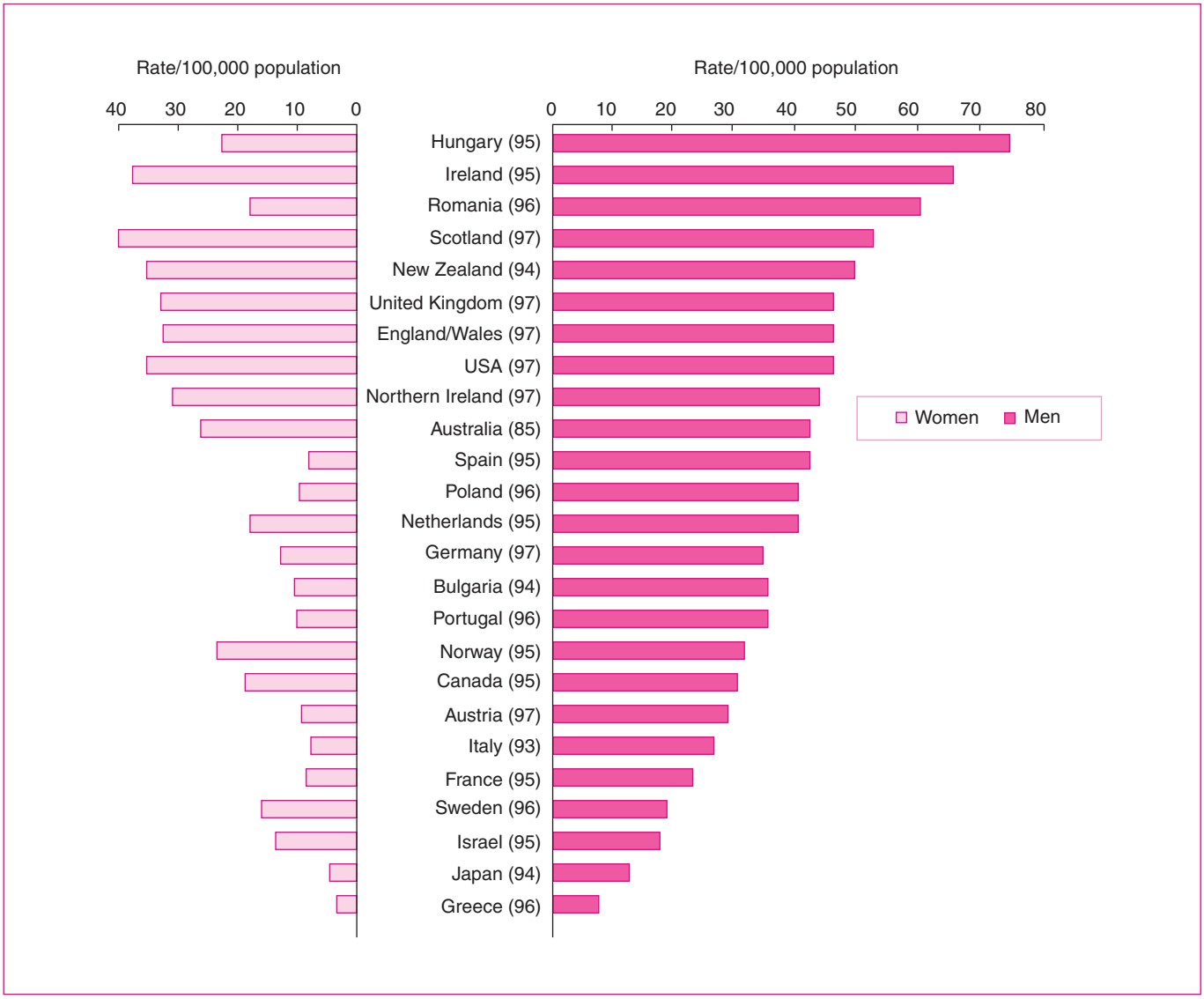

Fig. 2.5. Age-adjusted death rates for chronic obstructive pulmonary disease by country and sex, for individuals aged 35 to 77. The year of data is shown in parentheses. Reproduced from reference 27, with permission.

direct cost, 2.6 related to morbidity, 2.0 related to mortality) and 30.4 billion dollars for chronic obstructive pulmonary disease (14.7 for direct cost, 6.5 related to morbidity, 9.2 related to mortality). Utilization of health services continues to increase for both diseases. An increase in health service use has been documented in many countries, including the United Kingdom, Canada, and the United States; the utilization increase has been concomitant with the documented increase in asthma prevalence.[28–30]

Increased hospital visits have been documented worldwide, including in England, New Zealand, the United States, Greece, Australia, and Canada.[31–38] From 1971 to 1997, hospitalizations for asthma in the United States increased for children less than age 15, remained stable for people aged 15–44, and decreased for those greater than 45 years of age. Overall, hospitalizations with asthma as a primary diagnosis increased in the 1970s until the mid 1980s and then remained constant; this is in contrast to asthma as a secondary diagnosis which increased until 1997. From 1975 to 1995, office visits for asthma more than doubled, from 4.6 to 10.4 million.[15]

Based on the National Ambulatory Medical Care Survey, in 1995 more than 16 million visits were made to physicians for diagnoses related to COPD, increased from 9.3 million reported in 1985; 10 million were accounted for by chronic bronchitis and 4 million for chronic airways obstruction. This same survey noted nine million office visits coded for asthma in 1995. In 1995, there were 553,000 discharges coded as COPD or allied conditions. Again this may be a definitional problem; more than half of the discharge diagnoses were nonspecifically coded as COPD or allied conditions.

In summary, increased health service utilization for asthma and COPD occurred in the last decade. Overall, hospital admissions and discharges increased for asthma and COPD.

MORBIDITY AND MORTALITY

Asthma

The New Zealand epidemic of asthma in the 1970s prompted a review of asthma deaths in Western countries; there was a notable increase of 1.5–2 fold in the asthma mortality rates between the mid-1970s and the mid-1980s.[39] The highest mortality rates in the United States have been in the inner-city regions, with particularly high-risk populations studied in East Harlem, New York City, and Cook County, Chicago.[17,40] One study found that socioeconomic and racial disparities were attributable to higher incidence of asthma exacerbations among inner-city children, with no excess utilization of medical resources.[41]

International comparisons of mortality rates have been limited by differences in recording statistics of cause of death.[42] Comparison of mortality rates are difficult also because of the lack of standardized definitions for the disease, and because of environmental, genetic, socioeconomic, and occupational influences unique to a given population.

COPD

Since 1960 there has been an increased mortality associated with COPD, and in 1998 COPD mortality in the United States increased with age for all racial and gender groups. COPD mortality rates in white men in the United States are the highest, but have remained stable since 1980. During this time period, rates have increased in African American men and have doubled in white and African American women.

International mortality trends demonstrate high rates of deaths for COPD in many countries. These differences may be accounted for in part by different smoking behaviors including tobacco type, environment, infectious, and genetic factors. Differences among these death rates are striking, but again lack of standardization in coding practices and death certification as well as practice differences and quality of care are relevant when comparing estimates.[27]

Although overall asthma mortality remains low compared with COPD, mortality rates for both asthma and COPD have increased in the last decade. Differences in death rates for asthma and COPD between countries are multifactorial (genetic, environmental, occupational, socioeconomic), but differential coding of cause-of-death statistics hinders accuracy of estimates for both diseases.

SMOKING

Burrows et al.[43] have demonstrated that, for a given level of tobacco smoke exposure, FEV_1 varies substantially (**Fig. 2.6**). In addition, the dose–effect relationship between cigarette smoking and FEV_1 decline depends on when an individual is exposed. Dose and timing of tobacco smoke exposure have a differential effect on FEV_1 depending on the stage of the life cycle (**Table 2.1**). Cunningham et al.[44] observed that maternal smoking during pregnancy resulted in a 1.3% reduction in FEV_1 when children were 8–12 years old. Tager et al.[45] found that adolescents who smoke when aged 15–20 have an estimated 8% reduction in FEV_1. The Vlagtwedde/Vlaardingen study[46] demonstrated a large effect of cigarette smoking in decreasing maximal lung function in individuals less than age 20; this effect exceeded the effect of cigarette smoking on lung function decline seen in older subjects.

Smoking is a notable risk factor for both asthma and COPD in children and adults. Overall, smoking is associated with an increase in asthma incidence.[47,48] Passive exposure to cigarette smoke increases the risk for the development of asthma and allergic sensitization.[49–51] There has also been a suggestion that nonspecific airways responsiveness is increased by environmental and personal smoke exposure.[52]

Maternal smoking is a risk factor for the development of asthma in children up to one year of age.[53] In a case–control study of children whose mothers were heavy smokers, one group demonstrated an odds ratio of 2.15 among 3–4 year olds for the development of asthma; these data were

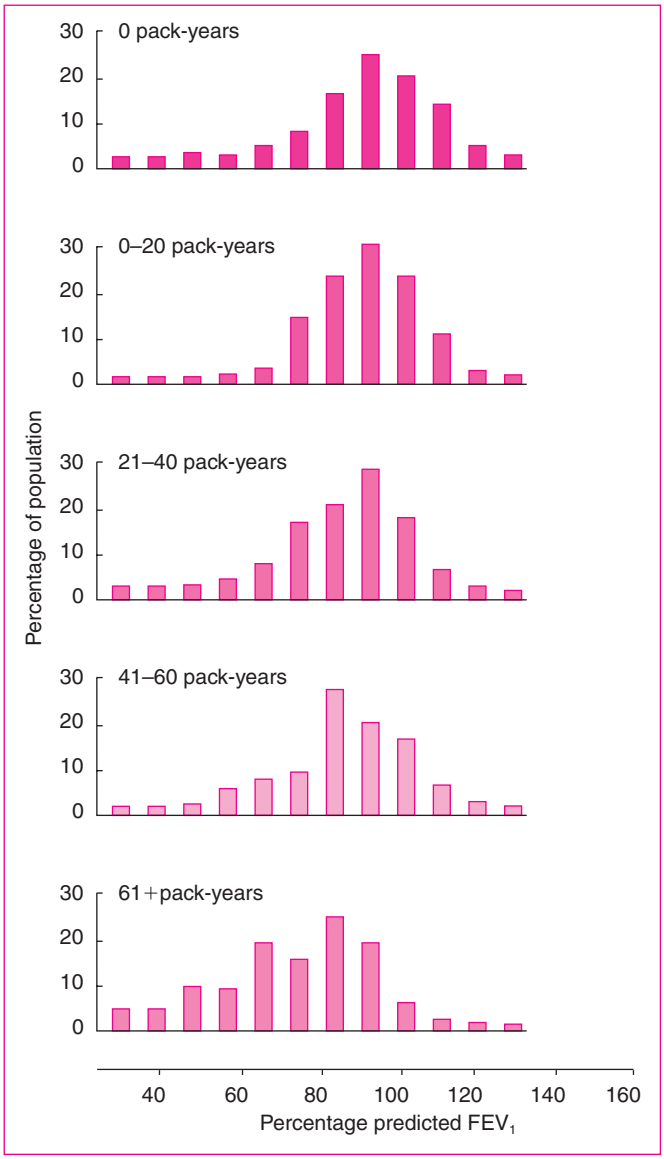

Fig. 2.6. Distribution of percentage predicted forced expiratory volume in one second (FEV_1) in adults with varying smoking histories as measured in pack-years. The proportion of smokers with normal flow decreased with increasing pack-year histories. Yet, many have near-normal FEV_1 with extensive smoking history. Subjects with "respiratory trouble" before age 16 were excluded. Medians and means ± 1 SD are shown for each group in the abscissae. Note that among the 425 persons with 20+ pack-years, only 15% have an FEV_1 of 60% of predicted or less. Reproduced from reference 43, with permission.

controlled for family history, past infections, gender, and other demographic variables.[54] In a six-year follow-up, the odds ratio for asthma among those exposed to maternal smoking was 3.8.[55]

As noted above, the single most important risk for COPD is tobacco smoking, although only 10–15% of smokers actually go on to develop obstructive lung disease. Among those smokers already with a decreased FEV_1, lung injury and subsequent decrements in lung function secondary to cigarette smoking are more dramatic. In the Lung Health Study, middle-aged smokers (with FEV_1 between 55% and 90%) who continued smoking for 5 years had further losses of several hundred milliliters of FEV_1.[56] However, chronic obstructive pulmonary disease has been identified in nonsmokers as well, with 4% of men and 5% of women reporting physician-diagnosed obstructive lung disease. Prevalence has been noted to increase with age, to be higher in women than in men, to be particularly high in Hispanic individuals, and to be higher in low-income versus affluent individuals.[57]

Summary

- For asthma and COPD, smoking has a lifetime influence, starting *in utero* and continuing into older age.
- Smoking is associated with increase airway responsiveness, both in asthma and COPD.
- Smoking is sufficient but not necessary for the development of COPD.
- Smoking is only one of several risk factors for asthma.

INTERMEDIATE PHENOTYPES

Allergy

Allergy represents immediate hypersensitivity to an antigen and is associated with an increased production of a specific immunoglobulin by sensitized lymphocytes. Elevations in specific IgE and/or total IgE, total eosinophil counts, and skin test reactivity to specific allergens have been used clinically to detect allergic individuals. As measured by skin test reactivity, allergy increases with age until about age 15, at which point it is maximal. The decline in skin test reactivity after age 35 confounds the measurement of this phenotype in older individuals susceptible to both asthma and COPD. This reported association between skin test reactivity and decline in FEV_1 is not consistent in the literature. In retrospective studies, Taylor et al.[58] and Frew et al.[59] demonstrated no relation of skin test positivity to decline in FEV_1. However, Gottlieb et al.[60] investigated this prospectively in the Normative Aging Study and found that skin test positivity predicted increased annual rates of decline in both FEV_1 and FEV_1/FVC ratios.

Allergic inflammation is characteristic of asthma; 80–90% of childhood asthmatics are atopic, and the degree of atopy appears to be associated with prognosis in childhood asthma.[61] Studies have demonstrated that the asthmatic phenotype is associated with elevated serum IgE levels more so than skin test positivity,[62] and that increased airways responsiveness is related to total serum IgE levels.[63]

Weiss has suggested that immediate type I hypersensitivity is a risk factor for the development of chronic obstructive lung disease, and suggests that atopy may influence childhood asthma and limit maximal lung function, accelerate FEV_1 decline, and potentially enhance interaction with cigarette smoking to progress to the development of COPD.[64] Hargreave and Leigh[65] demonstrated, in a subset of COPD patients, that eosinophilic inflammation is important in COPD exacerbations, and potentially leads to a

Table 2.1. Effects of cigarette smoking at different stages of the life cycle

Life phase (gender)	Cigarette dose	Total FEV_1 reduction	FEV_1 reduction (mL/year per packs/day)
In utero (M & F)	? Intensity for 9 mo	27.3 mL[a]	36
Adolescence (M)	15 cigs/day for 5 yr[b]	390 mL	104
Adolescence (F)	10 cigs/day for 5 yr[b]	340 mL	136
Adult (M)	Variable	N/A	13[c]
Adult (F)	Variable	N/A	7[c]

M = male, F = female
[a]Adjusted for gender and maternal smoking in the past year; based on 1.3% reduction and mean FEV_1 = 2.1 liters, 1 pack/day in smoking mothers during pregnancy is assumed for relative FEV_1 reduction (ref. 44).
[b]Median values for cigarette smoking (ref. 45).
[c]Estimated values (ref. 46).

Adapted from Weiss ST, Silverman EK. Risk factors for the development of chronic obstructive pulmonary disease. In: *Severe Asthma*, New York: Marcel Dekker, 2000.

decline in lung function. These data indicate that, in both asthma and COPD, allergen sensitization may represent an intermediate phenotype which needs to be considered in understanding disease onset and progression.

Airways responsiveness

Airways responsiveness to methacholine and histamine has been used in population-based studies to help define individuals susceptible to the development of obstructive lung disease. This intermediate phenotype is a feature of both asthma and a subset of patients with COPD. Baseline levels of lung function, allergy, age, and cigarette smoking history all influence airways responsiveness.

Airways hyperresponsiveness has been demonstrated to predict accelerated decline in lung function and the development of COPD.[66] More recently, airways responsiveness has been demonstrated to predict COPD mortality.[67]

Airways responsiveness has been demonstrated to predict the development of asthma.[68] The prevalence of airway hyperresponsiveness exceeds the prevalence of asthma; the former is about 20% in the general population. Data from the Childhood Respiratory Disease Study demonstrate that increased airway responsiveness predicts the development of asthma in children and young adults with a 2–3-fold risk.[69] Some have found risk increased as much as 5-fold.[70]

Airways hyperresponsiveness in COPD patients may be demonstrated in 64–100% in situations where it is actually measured.[71] Some individuals who develop COPD have an allergic asthma phenotype, as suggested by the Dutch hypothesis.[72] Alternatively the hyperresponsiveness may be a consequence of COPD. Results from a 25-year longitudinal study in the Netherlands revealed that increased airways responsiveness is an independent risk factor for FEV_1 decline.[73] Among those with early-onset COPD, the degree of baseline airways responsiveness determines the response to cigarette smoking; those with early-onset COPD who have increased airways responsiveness appear more sensitive to the effects of cigarette smoke and have an accelerated decline in FEV_1.[74]

Gender-related influences

The epidemiology of asthma is characterized by gender differences that vary with age. Asthma and wheezing have been demonstrated to be more prevalent in young boys than young girls.[10] This trend disappears during puberty.[75] A recent analysis of the European Respiratory Health Survey[76] found that, during childhood, girls had a lower risk of developing asthma than did boys; about the time of puberty the risk was equal. After puberty the risk in women was higher than in men and was a consistent finding in the 16 countries included in this study.

Women older than 20 years have higher prevalence and morbidity rates from asthma, and women are more like to present to the emergency department and be admitted with asthma.[77] In the multicenter Asthma Collaboration Study,[78] women were more likely to be admitted to the hospital and report ongoing symptoms at follow-up, although overall men had less outpatient care and lower pulmonary function.

Men have been noted to have an increased risk for the development of chronic obstructive lung disease,[79] and cigarette consumption clearly has a role in this gender difference. Yet, Prescott et al.[80] have suggested that women are more susceptible to the development of COPD, and observed that smoking was associated with a greater decrement in FEV_1 per pack-years of cigarette smoked when compared to male smokers. Mannino et al.[81] analyzed data for deaths from obstructive lung disease from 1979 until 1993 and found that the mortality rates for men with COPD have started to stabilize but were continuing to increase among women, reflecting smoking trends. These gender differences most likely represent influences of both dose of tobacco exposure and underlying genetic and hormonal susceptibilities.

Summary

- In the adult years women have a higher prevalence of asthma.
- The prevalence of COPD in women is increasing, with the prospect that it may equal that of men in the future, in keeping with the parallel trends of cigarette smoking and disease.
- The gender differences between asthma and COPD raise speculation as to the nature of hormonal or genetic influences relevant to disease expression in each sex.

DEMOGRAPHICS

In the United States, morbidity from asthma has been demonstrated in multiple studies to be greater in children of African American descent. In the United States, physician-diagnosed asthma has been reported in 13.4% of African American children and 9.7% of white children.[82] African American children have also been reported to have greater limitation on activity due to asthma, with more hospital admissions and fewer doctors' visits when compared with white children.[83] Mortality from asthma has been higher for African American children when compared with children of other races since the mid-1980s.[29,84–88]

Studies in Chicago have demonstrated socioeconomic gradients and differing outcomes by race. In 1996, asthma hospitalization rates were more than twice as high as the United States' rates overall. Age-adjusted mortality was 4.7 times higher in non-Hispanic blacks than in non-Hispanic whites.[89] An association with poverty has been suggested,[90] and it has also been suggested that severe asthma may occur more frequently in poorer communities.[91,92] The association of lower socioeconomic status with increased asthma prevalence is most likely multifactorial: the effects of indoor air pollution, passive cigarette smoke exposure, allergen exposure, and reduced access to medical care may all be relevant.

Using education as a surrogate for lower socioeconomic status, some have suggested an association with the development of obstructive lung disease. Bakke et al.[93] demonstrated that completion of only primary schooling was associated with a 2.9 odds ratio for the development of obstructive lung disease when compared with those who achieved university level education. Exposure to smoking and occupational hazards decreased with increasing educational status.

Overall in both asthma and COPD, there are substantial demographic differences between the prevalence, morbidity, and mortality outcomes.

AGE

Infants born prematurely have a risk for asthma that is increased approximately 4-fold.[94] There are data that breastfeeding is protective against asthma and, as noted, the risk for asthma increases in children exposed to cigarette smoke *in utero* and in childhood. Asthma that begins after age 50 is thought to be more severe and less reversible than asthma that is incident in childhood.[95] In childhood, the remission of asthma has been suggested to be about 50%.[47,96,97] Less information is available on the epidemiology of asthma in the middle-aged or elderly, yet some suggest that older patients are more severely affected than younger patients.[98]

Some data support the proposition that adults may outgrow their asthma (with remission rates decreasing with increasing age).[99] Other data suggest that remission of asthma and respiratory symptoms are uncommon.[100] Aging has been associated with increased airway obstruction overall.[101] The association of aging with the development of COPD most likely represents the cumulative insult of a lifetime of smoking and environmental exposure interacting with a susceptible host.

CONCLUSION

Ninety percent of all childhood asthma is diagnosed before the age of 6 years. Since there is a crude inverse relationship between respiratory symptoms and level of lung function, it is not surprising that as lung function increases in childhood, respiratory symptoms decrease and often disappear. Thus, a large number of children are left with the intermediate phenotypes of increased airways responsiveness and/or allergy at the time that they reach their maximally attained level of lung function between the ages of 15 and 30.

These intermediate phenotypes represent definable host characteristics that confer increased susceptibility to a variety of environmental exposures encountered in adult life, such as viral respiratory illness, occupation, allergen exposure, and perhaps most importantly, cigarette smoking (**Table 2.2**). Only 10–15% of cigarette smokers subsequently go on to develop fixed airflow obstruction. This is likely to be due to two factors: premature mortality as a result of a variety of fatal illnesses associated with cigarette smoking, and the fact that genetic susceptibility to cigarette smoking is only present in a minority of subjects.

The most clearly defined susceptibility factors for premature or early-onset COPD are childhood asthma, increased airways responsiveness, and allergy. It is now absolutely clear that most airways hyperresponsiveness in

Table 2.2. Risk factors

	COPD	Asthma
Smoking	+++	++
Gender	Male > female	Female > male
Age	Old	Young
Airway responsiveness	+	+
Allergy	++	++++