CURRENT PULMONOLOGY

VOLUME 2

Edited by Daniel H. Simmons, MD, PhD

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Preface

I introduce the second volume of *Current Pulmonology* with particular pleasure because I feel that it has accomplished the goal of this annual series. The "birth pains" of Volume 1 have led to "growing pains" with this volume, which is more extensive and more consistent with our original intent in publishing this series. It has had the benefit of helpful comments from many readers, including published reviews of Volume 1.

There appear to be two camps among both our readers and our reviewers. Some—usually those not having a major subspecialty interest in pulmonology—feel we should provide more background in each area covered, which implies they would prefer "state-of-the-art" reviews. Others—usually more experienced and more interested in clinical pulmonology—prefer chapters that present important recent developments in detail and have objective and critical evaluations of this information rather than broader, less detailed and less critically evaluated reviews. We have attempted to meet both needs in this second volume and are likely to continue to do so in future volumes.

Our main purpose in creating this publication has not changed. We felt, and still feel, that an annual volume that critically evaluates the previous year's literature by quoting the most important recent articles as well as by including the author's own judgments concerning the conclusions to be drawn from them is a unique and valuable contribution to the literature.

Most of the chapters in Volume 2 provide continuing coverage of subjects covered in Volume 1, focusing on literature published after that quoted in Volume 1. The other chapters have more of a "special topics" approach, providing background information as well as interspersed references to clinical problems, current and past.

Certain areas in pulmonology will be reviewed in chapters every year because of their importance and because of the amount of published information requiring critical evaluation and synthesis by an expert in the field. These include chapters on chronic obstructive pulmonary disease, asthma, respiratory distress syndrome, tuberculosis, nontuberculous infections, fungal diseases, and lung cancer. Of the other chapters in this volume, that on alpha$_1$-antitrypsin deficiency both updates a major field in pulmonology and provides considerable background information about its implications in nonpulmonary diseases. This approach to this clinical entity should be of interest to both pulmonologists and nonpulmonologists and should improve their appreciation of the abnormality and enable them to treat both the patient and his or her family better.

Other "special topics" chapters provide extensive background information as well as comments evaluating recent developments. These include chapters on respiratory failure, flexible fiberoptic bronchoscopy, lung immunology, and mucociliary clearance. These were judged to be topics of such particular interest that the reader would benefit from an expert's careful compilation and review.

Some material in the "special topics" chapters obviously crosses over into the "annual" chapters. In fact, overlap between chapters has not been discouraged, since it often presents two different and useful views of a topic. Even disagreement has not been discouraged, because different expert opinions should all be given serious attention. Also, disagreement often gives the reader a better "feel" for the state of knowledge in a field. For example, the chapter on flexible fiberoptic bronchoscopy contains much important information on lung cancer, tuberculosis, nontuberculous infections, fungal disease, and asthma. The authors' orientations to this information are often different, making apparent the fact that there are different approaches to clinical problems and differences of opinion in management.

Once again, I would like to thank Peggy Wilson of the Medical Division of Houghton Mifflin for her continued advice and support. I would also like to thank Rosalyn Palmer and Maureen Van Dell for the many tedious hours they have spent to help me organize and carry out the monumental tasks of correspondence and telephoning involved in producing this volume.

Finally, it is with deep regret that I report that the intended first chapter on occupational lung disease—now a field of great interest in pulmonology—is not included in this volume because of the tragic and sudden death of Dr Morton Ziskind. I appreciated Dr Ziskind's gentleness and his willingness to initiate this topic for the series. I regret that he was not given the time to do so.

Daniel H. Simmons

Contents

1

Chronic Obstructive Pulmonary Disease

RICHARD E. BRASHEAR

Chronic obstructive pulmonary (lung) disease, a major health problem, is probably underdiagnosed on death certificates, and its vital statistics death rates probably reflect an underestimate of the true mortality rate (1). In a British general practice of 3137 patients, respiratory illness was the most common diagnosis, accounting for 29% of illness episodes and 25% of total consultations. The next most common problem was psychiatric illness, which accounted for 12% of the illness episodes (2).

In the United States from January 1975 through December 1976, an estimated 163.4 million visits to office-based physicians were attributed to diseases of the respiratory system. These 163.4 million visits comprised approximately 14% of all office visits for any condition during that period. Asthma, emphysema, and bronchitis (chronic or unqualified) accounted for 19.5%; emphysema, with an average office visit of 17 minutes' duration, accounted for 3.2% of the 163.4 million visits (3).

In 1977, a Task Force Report by the US Public Health Service found 1,540,000 newly diagnosed cases of chronic obstructive lung disease, with an overall prevalence of 38 per 1000 population (4). From 1970 to 1975, the mortality from chronic obstructive lung disease increased from a conservative estimate of 16 per 100,000 population to 19 per 100,000. Morbidity from chronic obstructive lung disease possibly resulted in 34 days of restricted activity per 100 persons per year. Additionally, the economic impact is staggering, with an estimated $803 million expended in 1972 for direct costs of hospital treatment, physician service, and prescribed drugs. Lost earnings were estimated at $3.05 billion for disability payments and $645 million for death benefits (4). These costs have increased significantly since 1972.

Chronic obstructive pulmonary disease was not included in the first volume of this series (5). Because adequate discussion of all aspects of this disease would be difficult in the space provided, and because the result would be superficial, I have instead elected to discuss only the terminology and the etiology of chronic obstructive pulmonary disease.

Most of the references can be used as background material. The treatment of chronic obstructive lung disease has been thoroughly covered in a recent text (6), and new information about therapy will be discussed in a subsequent volume of this series.

DEFINITIONS AND TERMINOLOGY

Concept of Disease

It is customary to discuss the diagnosis, prognosis, and treatment of a disease. However, no agreement has been reached regarding the definition of this basic concept of medical practice. The word *disease* seems to be in general use without formal definition, and the majority of users allow themselves the comfortable delusion that everyone knows what "disease" means. Scadding has discussed this difficulty for many years, especially regarding chronic bronchitis and emphysema (7–10). A formal definition of disease should be based on observable phenomena. Further, a precise definition should not deviate so far from common usage that it generates additional confusion. Scadding's definition of disease, after a series of revisions and refinements, is: "A disease is the sum of the abnormal phenomena displayed by a group of living organisms in association with a specified common characteristic by which they differ from the norm for their species in such a way as to place them at a biological disadvantage" (10).

The common characteristic that defines the group in the preceding definition can be of four different types. First, the common characteristic can be clinical-descriptive (syndromic) in nature. This is no more than a combination of signs and symptoms occurring together so frequently as to present a recognizable clinical picture. Second, the characteristic can be based on morbid anatomy, either macroscopic or microscopic. Third, a disease can be defined on the basis of measurable disorders of function, biochemical abnormalities, or specific deficiencies. Fourth, a disease can be defined in terms of etiology when it has been demonstrated to be attributable to a specific noxious agent, whether chemical, physical, or microbiologic (9).

With the passage of time and the acquisition of additional information, the common characteristic that defines the group tends to progress from a clinical-descriptive to an etiologic feature. Tuberculosis illustrates this evolution of the common characteristic. At first, various manifestations of tuberculosis could only be defined descriptively, and the manifestations were given names such as pulmonary consumption. Later, when it was recognized that the pathologic lesion (tubercle) was a common characteristic, the illness was considered in relation to morbid anatomy. With the discovery of the tubercle bacillus, it was possible to define the illness on an etiologic basis.

This very important change of the common characteristic with time creates difficulties. Chronic bronchitis was defined 20 years ago as a condition of chronic or recurrent excessive mucus secretion in the bronchial tree (11). This descriptive definition essentially means cough and expectoration. Efforts are now being made to define bronchitis on an etiologic basis (infectious or noninfectious irritation) (12). However, a recent editorial still refers to chronic bronchitis as "cough and spit" (13). It should be remembered that the relative importance of similar symptoms may be interpreted differently at various historic times, and that diseases, especially those based on descriptive terms, may be identified with certain historic periods. As research and technology continue to clarify illness, diseases will be redefined. Small-airways disease was not a diagnosis (or recog-

nized disease) of several decades ago; its recognition resulted from the availability of improved pathology and advanced technology (14). In essence, "diagnosis is relative to the historical era in which the diagnosticians perform their task" (15).

Chronology of Specific Definitions

In 1958, a group of scholars (mostly British) met to clarify the terminology of pulmonary emphysema and related conditions (11). Confusion and misunderstanding existed between investigators in different medical centers and in different branches of medicine. The purpose of the meeting was to provide some provisional definitions, classifications, and terminology that might clarify the chaos and confusion.

Emphysema was defined as a condition of the lung characterized by an increase beyond normal in the size of air spaces distal to the terminal bronchiole either from dilation or from destruction of their walls (11). Destruction of the alveolar walls was not a requirement of this definition. Because the definition was based on morbid anatomy, it was suggested that clinical use of the word *emphysema* be regarded as presumptive and used only when the defined morbid anatomic changes could reasonably be expected to be present. Emphysema could only be consistently diagnosed from an examination of lungs that were distended and fixed before slicing.

Emphysema, asthma, and chronic bronchitis were all included under the term *chronic nonspecific lung disease*, which was defined as the condition of chronic cough with expectoration and/or paroxysmal or persistent breathlessness (11). Also, the cough or breathlessness could not be attributed solely to localized lung disease of any kind (infective lung disease, etc). Subsequent definitions were based on the association of clinical terms with respiratory disorders such as chronic bronchitis (chronic or recurrent excessive secretion of bronchial mucus), asthma (intermittent obstruction to bronchial air flow), and emphysema (persistent obstruction to bronchial air flow).

Two large subdivisions of *chronic nonspecific lung disease* were defined: chronic bronchitis and generalized obstructive lung disease. *Chronic bronchitis*, the condition of chronic or recurrent excessive mucus secretion in the bronchial tree, was a very descriptive clinical definition based on cough and expectoration. *Generalized obstructive lung disease* referred to widespread narrowing of the airways causing an increase in resistance to air flow. Generalized obstructive lung disease included intermittent or reversible obstructive lung disease (asthma) and irreversible or persistent obstructive lung disease (emphysema) (11).

The American scholars introduced their terminology in 1962 (16). They also were concerned that workers in various disciplines were defining the diseases differently by using personally selected criteria. Chronic bronchitis was again defined as a clinical disorder characterized by excessive mucus secretion in the bronchial tree. Chronic bronchitis was manifested by a chronic or recurrent productive cough present on most days for a minimum of three months in the year and for not less than two successive years. Other diseases with similar manifestations were excluded from the definition, such as abscess and tuberculosis. Asthma was defined as increased responsiveness of the airways, manifested by narrowing of the airways, that changed in severity either spontaneously or as a result of treatment. Emphysema was defined as an anatomic alteration of the lung characterized by an abnormal enlargement of the air spaces distal to the terminal, nonrespiratory bronchiole, and accompanied by destructive changes of the alveolar walls.

By 1965, the British decided to subdivide chronic bronchitis (bronchial hypersecretion usually manifested as cough) into simple chronic bronchitis (sufficient mucoid bronchial secretion to cause expectoration either chronically or recurrently), chronic or recurrent mucopurulent bronchitis (sputum persistently or intermittently mucopurulent), and chronic obstructive bronchitis (persistent and widespread narrowing of the intrapulmonary airways causing an increased resistance to air flow) (17).

In 1968, Poirier proposed that the forced expiratory volume expelled in one second (FEV_1) be adopted as the critical defining measurement for chronic obstructive lung disease, as its major component was an obstructive defect (18).

Chronic obstructive lung (pulmonary or airways) *disease* currently is defined as chronic obstruction to air flow within the lungs. The common causes are emphysema, chronic bronchitis, asthma; sometimes bronchiectasis is included under this umbrella term.

Bronchiectasis, defined as permanent and abnormal dilation of bronchi, commonly exists in patients with bronchitis and emphysema (19), and is usually manifested as diffuse bronchial obstruction and uneven distribution of ventilation and perfusion (20). The mechanism of airways obstruction in bronchiectasis is not understood but current thinking holds that bronchospasm, airway collapse during expiration, mucosal edema, and glandular hyperplasia may all be contributory. Although a prior investigation demonstrated no significant change in FEV_1 after isoproterenol administration (20), a recent study has shown significant reversibility of airway obstruction after salbutamol in patients with radiologic evidence of bronchiectasis (21). However, the presence or absence of other causes of airway obstruction could not be excluded. The reversibility was related to the baseline severity of airway obstruction and in this aspect was similar to the reversibility of airway obstruction in patients with asthma.

In 1975, the World Health Organization defined CNSRD (chronic nonspecific respiratory diseases) as conditions of the lungs and airways characterized by disorders of function, structure, or both (22). The conditions included in CNSRD were emphysema, chronic bronchitis, and generalized airway obstruction. These conditions could be present alone or in combination in the same individual. Emphysema was again defined as an enlargement of the air spaces distal to the terminal bronchiole that was associated with destructive changes of the alveolar walls. Although various criteria have been proposed for the detection of emphysema during life, the final verdict depends on the demonstration of emphysematous changes on pathologic examination of the lung. Chronic bronchitis was defined as a nonneoplastic disorder of structure or function of the bronchi usually resulting from prolonged or recurrent exposure to infectious or noninfectious irritation. This definition is now based on an etiology rather than on the clinical description of cough and expectoration. Generalized airway obstruction (slowing of forced expiration that may be acute or chronic) was subdivided into chronic obstructive bronchitis, small-airway obstruction, asthma, and bronchospasm.

A combined statement by the American College of Chest Physicians and the American Thoracic Society also appeared in 1975 (12). Under the term *diseases associated with airways abnormality*, they included bronchitis, pulmonary emphysema, bronchiolitis, asthma, and chronic obstructive pulmonary disease (COPD). Bronchitis was again defined on an etiologic basis as a nonneoplastic disorder of structure or function of the bronchi resulting from infectious or noninfec-

tious irritation. The definitions of asthma and emphysema were unchanged from those used in 1962 (16). Chronic obstructive pulmonary disease referred to "diseases of uncertain etiology characterized by persistent slowing of air flow during forced expiration." It was suggested that specific terms (e.g., chronic bronchitis) be used whenever possible.

Thurlbeck discussed and dissected the terminology issue in 1977; the reader is encouraged to read the original article (23). He discussed the deficiencies of terms such as chronic airway obstruction (CAO), chronic obstructive pulmonary disease (COPD), and chronic obstructive lung disease (COLD) and suggested that these expressions be replaced with *chronic air flow obstruction*. Because expiratory air flow obstruction could be caused by obstruction and narrowing of airways or by loss of elastic recoil, the term *air flow obstruction* is preferred, as no organic airway obstruction may be present when decreased air flow is due to loss of elastic recoil. The author suggested that the term *chronic mucus hypersecretion* replace *chronic bronchitis*. Mucus hypersecretion is probably a relatively benign condition. The prognosis of patients with chronic air flow obstruction is determined by the degree of expiratory air flow obstruction and not the amount of mucus secreted or expectorated by the patient. Also, since the pulmonary architecture in emphysema is distorted and abnormal, Thurlbeck suggested we alter our concept of emphysema from lung tissue being destroyed to tissue being disarranged (23).

Conclusion

The discussions continue unabated. We are exhorted to distinguish among the various disorders designated by the anachronistic acronyms COPD, COLD, CAO, CNSLD, and CNSRD (24). Petty prefers "cough and spit" for chronic bronchitis and correctly places more importance on defining etiologies and mechanisms and designing therapy to reverse disease manifestations than continuing idle chit-chat (13).

Dr C. M. Fletcher was a prime mover of the Ciba Symposium in 1958 that attempted to define and clarify the nature of pulmonary emphysema and related conditions (11). In 1978, Dr Fletcher continued to uncover new and old difficulties regarding the terminology of chronic obstructive lung disease (14). We can be confident that editorials and debates will continue, generated by new data, knowledge, and our propensity for thought and self-expression.

ETIOLOGY AND PATHOGENESIS

Environmental Factors

Environmental agents significantly affect the lung and respiratory tract. These factors have access to the lung via the vascular bed or the airways. Regardless of the access route, these agents interfere with biochemical processes. Witschi (25) and Dannenberg (26) have investigated blood-borne causative agents of acute and chronic lung lesions; this topic will not, therefore, be discussed here.

Occupational factors

Industrial Bronchitis. The term *industrial bronchitis* includes chronic obstructive bronchitis caused by occupational inhalants. Lack of a close temporal relationship between symptoms and exposure and the absence of a distinctive chest roentgenogram have slowed the recognition of industrial bronchitis. Cigarette smoking is the major confounding variable. Attempts to relate bronchitis to foundry and gold mine dusts, irritant gases and vapors, coal dusts, solvents, and isocyanates have yielded equivocal or

disputed results. Eventually, a high incidence of bronchitis may be firmly substantiated in many occupations (27).

Grain Dust. Recently concern has been increasing over the relationship between grain dust exposure and chronic obstructive lung disease (28–30). Grain dust is composed of various types of grain and their disintegration products, silica, fungi, insects and mites, hairs and excreta of rodents and pigeons, and chemicals (30). The pulmonary manifestations of grain dust exposure include chronic cough with sputum production, wheezing, and shortness of breath. Chronic bronchitis is probably the most common respiratory condition resulting from grain dust exposure. Between one-third and one-half of grain handlers have a chronic productive cough. There seems to be general agreement that grain workers who smoke have more symptoms of chronic respiratory disease than do smokers not exposed to grain. Inconclusive evidence indicates a relation between air flow obstruction and grain exposure (29). Cigarette smoking may play an important role in the chronic obstructive lung disease of grain handlers; the effects of cigarette smoking and grain dust exposure may be synergistic and not simply additive. Grain workers who smoke may have more air flow obstruction than would be predicted from the degree of air flow obstruction due to smoking alone and exposure to grain dust alone (28, 29). Grain dust exposure of sufficient concentration and duration, with or without cigarette smoking, may be an important occupational cause of chronic obstructive lung disease.

Cadmium Dust. In the past, occupational exposure to cadmium dust had been thought to have a role in the cause of emphysema. These older reports were generally accepted without criticism or regard for the patient's history of cigarette smoking. Stanescu and coworkers recently evaluated 18 workers exposed to cadmium dust and fumes for an average of 32 years, and 20 nonexposed control workers (31). The two groups were comparable with regard to cigarette smoking, age, height, and weight. No evidence of pulmonary emphysema was found in the cadmium workers.

Air pollution

A vast amount of literature has been published about air pollution and the lung (32). The reader is encouraged to read the excellent and comprehensive Health Effects of Air Pollution, an American Thoracic Society Statement (33). The three major types of air pollution recognized are the sulfur oxide and particulate complex, photochemical oxidants, and a miscellaneous category.

The sulfur oxide/particulate complex and photochemical oxidants are ubiquitous and occur in increased concentrations in large metropolitan areas (33). These pollutants are produced by combustion of sulfur-containing fossil fuels. The sulfur oxide component includes sulfur dioxide, sulfuric acid, and sulfate aerosols; the particulate component consists of soot, fly ash, silicates, nitrates, metallic oxides, and other compounds.

Photochemical oxidants are formed in the atmosphere from a complex chemical reaction between solar radiation and hydrocarbons and nitrogen oxides. Most of the hydrocarbons are produced by motor vehicles. The major characteristics of photochemical oxidants are: *(a)* formation of ozone, *(b)* acute eye and respiratory tract irritation, *(c)* damage to plants, and *(d)* the formation of a visible atmospheric aerosol (smog).

The third large class of air pollutants is composed of the variable emissions from factories, mills, etc. These pollutants exist as gases or particles (33).

Identifying the contribution of air pollution to the development of chronic

obstructive lung disease is difficult, because one must isolate the effects of air pollution from previous infections, cigarette smoking, occupational exposures, and other contributing factors. In addition, a lack of uniform criteria has made comparison of studies from various parts of the world unreliable, although this problem has been rectified to some degree by standardized questionnaires. Most studies of chronic lung disease suggest a relationship between the prevalence of chronic respiratory symptoms and the sulfur oxide and particulate complex (33). Regardless of prevalence, it is even more difficult to determine what degree of air pollution exposure is related to increased risk of chronic lung disease. At present, we have not arrived at a consensus on a pollutant concentration that increases the risk of chronic lung disease. In all probability, cigarette smoking is a dominant risk factor for chronic lung disease; air pollution probably adds only a small part to the overall hazard (33). Bouhuys and coworkers recently emphasized the relative unimportance of air pollution to respiratory health as compared to the effects of cigarette smoking and certain occupational exposure hazards (34).

Cigarette smoking

The Surgeon General's report, *The Health Consequences of Smoking: 1979*, was summarized succinctly in the *Morbidity and Mortality Weekly Report* (35). Overall, current cigarette smokers have an approximately 70% greater chance of dying from disease than do nonsmokers. Both female and male cigarette smokers have an increased chance of dying from emphysema and chronic bronchitis, and demonstrate a significantly higher prevalence of these diseases. Pulmonary function abnormalities can be detected among smokers in young age groups and pulmonary function abnormalities are greater among smokers than nonsmokers. Autopsy data have demonstrated dose-related abnormalities in microscopic and macroscopic lung sections from smokers.

This brief discussion will not recapitulate all that has been reviewed in the 10 US Public Health Service publications (*The Health Consequences of Smoking*, etc) and elsewhere (36, 37) regarding smoking and chronic obstructive lung disease. However, several more recent reports deserve mention. The concern about the effects of passive smoking continues (38). Passive smoking is the breathing of smoke-containing air composed of mainstream smoke exhaled by smokers and of sidestream smoke, which leaves the burning end of the tobacco product. Indoor particulate exposures are significantly higher among children who live with one or more cigarette smokers. The presence or absence of a smoker in the indoor environment does not seem to affect some basic spirometric tests of pulmonary function (39). While smoke-filled spaces may increase the carboxyhemoglobin levels in nonsmokers, the level may not be sufficient to adversely affect healthy individuals (40, 41). In patients with exercise-induced angina, the angina can be aggravated by passive smoking (42). No evidence exists that passive smoking causes chronic obstructive lung disease in healthy persons.

The extensive work summarized by Fletcher and Peto deserves particular mention (43). Of an initial sample of 1136 men, 792 were examined regularly enough over eight years to provide adequate data for drawing several conclusions about cigarette smoking and chronic air flow obstruction. Nonsmokers lose FEV_1 slowly and almost never develop clinically significant air flow obstruction. Many smokers lose FEV_1 almost as slowly as nonsmokers and also never develop clinically severe air flow obstruction. However, some smokers, who are more susceptible to the effects of

smoke, develop various degrees of air flow obstruction that may become disabling or fatal. In addition, a susceptible smoker who stops smoking will not recover lost FEV_1, but the subsequent rate of loss of FEV_1 will revert toward normal (Fig. 1). Severely affected patients derive little benefit from stopping smoking since the damage already done to their lungs is severe.

Peripheral pooling of contrast material has recently been demonstrated in bronchograms of smokers (44). Thirty-three of 66 smokers had some degree (11 had a marked degree) of bronchographic pooling, but no pooling was seen in any of 10 nonsmokers. Smokers with marked pooling had greater impairment of pulmonary function. This study suggests that a causal relationship may exist between peripheral pooling and panacinar emphysema.

In general, the prevalence of respiratory symptoms is significantly greater in smokers than in nonsmokers. Respiratory symptoms increase with the number of cigarettes smoked and the younger the age at which one starts to smoke. Even schoolchildren (ages 11–17 years) who smoke regularly have a higher incidence of respiratory symptoms than do nonsmokers (45, 46). In essence, the data show that cigarette smoking is the prime cause of chronic obstructive lung disease.

Respiratory Tract Infections

The role of infection as a cause of chronic obstructive lung disease is uncertain. *Streptococcus pneumoniae* and *Hemophilus influenzae* can easily be recovered from the lower airways of patients with chronic bronchitis regardless of the presence or absence of an exacerbation (47–50). There is little question that bacteria and viruses play a very important role in exacerbations.

Two separate elements can be identified in the relationship of acute respi-

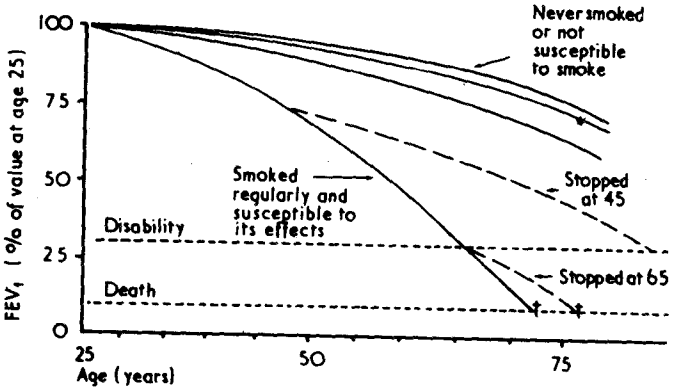

FIG. 1. Risks for various men if they smoke. Differences among these lines illustrate the effects that smoking, and stopping smoking, can have on the FEV_1 of men who are likely to develop chronic obstructive lung disease if they smoke. † = Death, the underlying cause of which is irreversible chronic obstructive lung disease, whether the immediate cause of death is respiratory failure, pneumonia, cor pulmonale, or aggravation of other heart disease by respiratory insufficiency. This figure shows the rate of loss of FEV_1 for one particular susceptible smoker; other susceptible smokers will have different rates of loss and will reach the disability line at different ages. (Reprinted with permission from Fletcher C, Peto R: The natural history of chronic airflow obstruction. Br Med J 1:1645–1648, 1977.)

ratory infection to chronic lung disease. One is the question of specific agents in exacerbations; the other is differential susceptibility to infection. Differential susceptibility implies that an individual with chronic respiratory disease becomes infected more frequently than a comparable healthy person, and implies a role of infection in the pathogenesis of chronic lung disease. The Tecumseh Study confirmed in large part that susceptibility does exist in individuals with minor evidence of chronic respiratory illness or impairment of lung function, and that the relationship of infection to chronic lung disease may be independent of smoking (51). However, a long-term study of large numbers of asymptomatic persons still is required to document the presence of increased infection before the appearance of lung abnormalities. Fletcher and Peto strongly believe that infections are not an important cause of irreversible air flow obstruction (43).

Childhood respiratory illness

Clinicians have long suspected that adults with chronic obstructive lung disease had histories of more frequent respiratory difficulties in childhood than did adults without lung disease. Leeder, in an excellent review, has summarized the information regarding infection as a cause of chronic obstructive lung disease (52). He presented the epidemiologic and physiologic evidence that repeated respiratory tract infections cause permanent damage to airways and eventually result in chronic obstructive lung disease. However, the evidence was complicated by cigarette smoking, poor living conditions, air pollution, family size, and so forth. Overall, the physiologic and epidemiologic observations implied an association between respiratory tract infection during childhood and chronic obstructive lung disease in adulthood.

Burrows and coworkers reviewed the evidence more recently (53, 54). They reported a large series of persons at least 20 years of age who provided histories concerning the presence or absence of childhood respiratory difficulties (54). A comparison was made between 415 persons with childhood respiratory trouble and 2211 persons who denied such a history. Mean values of three measures of ventilatory function (FEV_1%, FEV_1/FVC%, $Vmax_{25}$%) were all significantly lower in persons with a history of childhood respiratory problems. Additionally, almost all respiratory abnormalities occurred with greater frequency in individuals with a history of childhood respiratory trouble. The high prevalence of chronic cough and chronic sputum production in subjects with childhood respiratory trouble, as compared to those without childhood respiratory problems, was independent of the cigarette-smoking history (Fig. 2).

These studies further establish the suspected relationship between pediatric respiratory illness and the subsequent development of airway disease in adulthood (53, 54). A greater rate of decline in ventilatory function occurred with increasing cigarette consumption in subjects with childhood respiratory trouble (Fig. 3). The ever-smokers (exsmokers or present smokers) had a greater rate of decline than did never-smokers with or without a history of childhood respiratory trouble. Of particular interest was the tendency for ventilatory function to decline excessively in persons who never smoked but had a history of childhood respiratory trouble. Twenty-four nonsmoking children and adolescents 8–17 years of age with a past history of croup, bronchiolitis, or both in infancy were studied recently for the presence of respiratory dysfunction (55). The forced expiratory flow after exhalation of 75% of the vital capacity ($\dot{V}max_{25}$%) was abnormal in 14 of this group. Also, those

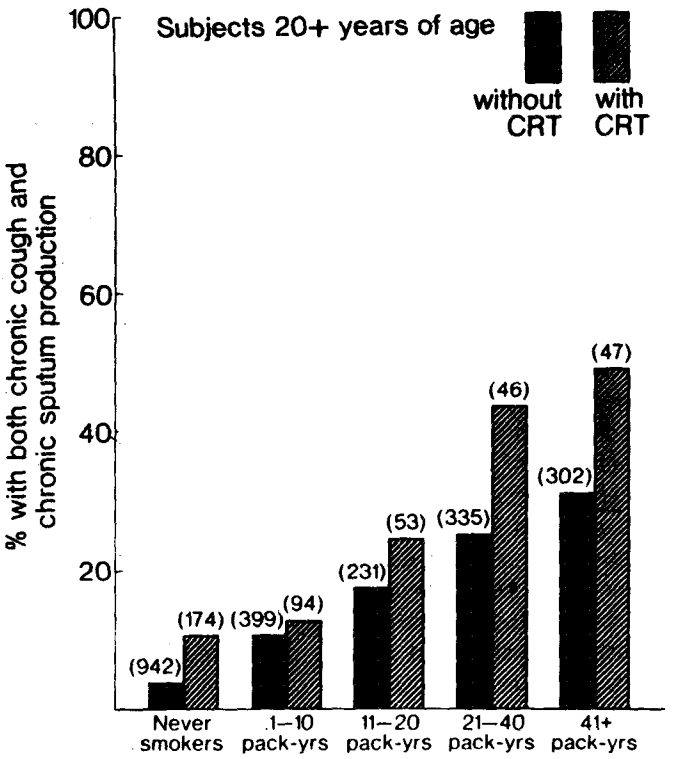

FIG. 2. Percentage prevalence of chronic cough and chronic phlegm (present on most days for three or more months per year) in subjects with and without a history of childhood respiratory trouble (CRT) according to pack-years of cigarette consumption. (Reprinted with permission from Burrows B, Knudson RJ, Lebowitz MD: The relationship of childhood respiratory illness to adult obstructive airway disease. Am Rev Respir Dis 115:751–760, 1977.)

individuals with a history of croup or bronchiolitis demonstrated exercise-induced bronchospasm.

These studies suggest that children and adults with a history of respiratory troubles have an increased prevalence of respiratory symptoms and abnormalities in lung function (54, 55). This relationship could be due to some inherent susceptibility of the airways of such persons, or the childhood/infancy respiratory trouble could enhance the subsequent adverse effects of smoking, air pollution, and recurrent infections. These studies also suggest that pediatric illness may be another very significant risk factor for adult cigarette smokers. Childhood/infancy respiratory trouble may explain a number of airway problems noted in adults who have never smoked cigarettes. It must be remembered that parental recall, preferential recall of childhood illnesses by adults with respiratory symptoms or disease, and population peculiarities are among some of the limitations of these studies.

Longitudinal studies will be necessary to assess more fully the effect of childhood respiratory trouble on the subsequent development of chronic obstructive lung disease. Early results of a long-term longitudinal study of infants admitted to the hospital for croup, pneumonia, or bronchiolitis indicate that only those

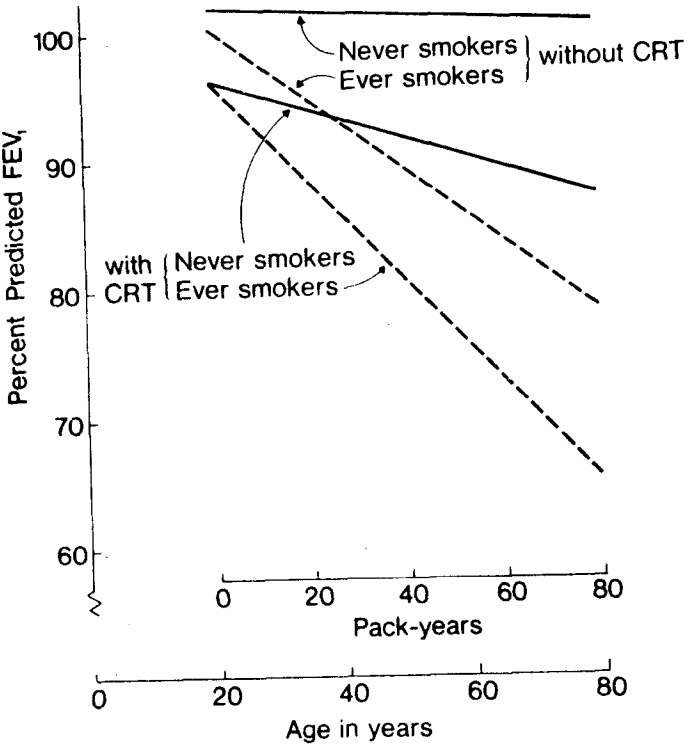

FIG. 3. Regressions of percentage predicted FEV_1 against age for never-smokers (solid lines) and against pack-years of cigarette use for ever-smokers (broken lines) in subjects with and without childhood respiratory trouble (CRT). The arrangement of the scales assumes that subjects reached their usual level of cigarette consumption at 20 years of age. As drawn, the age scale applies to a person who smoked an average of 26 to 27 cigarettes per day. The decline with age among never-smokers without CRT was totally insignificant, and the P value for the regression among never-smokers without CRT was only 0.07. Actual values of FEV_1 % were lower in never-smokers with CRT than in those without this history at a highly significant level ($P < 0.001$). (Reprinted with permission from Burrows B, Knudson RJ, Lebowitz MD: The relationship of childhood respiratory illness to adult obstructive airway disease. Am Rev Respir Dis 115:751–760, 1977.)

infants with bronchiolitis have continuing symptoms or abnormal pulmonary function tests (55).

A 9-year longitudinal study in England tends to substantiate a later excess of respiratory symptoms in children with a history of bronchitis, pneumonia, or asthma in the first 5 years of life (56). After 9 years, 28% of the original 4704 children first examined at age 5 years were still available for examination. The relative risk of children having respiratory symptoms at ages 11 and 14 was especially significant in those 273 persons with a history of bronchitis before the age of 5. Attrition of the original sample was a problem in this longitudinal study, and the group remaining after 9 years was not representative of the original sample. Additionally, the original diagnosis of bronchitis was that perceived by the parents and was not a physician's diagnosis.