Chronic obstructive pulmonary disease (COPD) is a new name for an old malady. The ancients included the disease under the rubric of “catarrh.” In modern times, COPD has come to signify a mixture of chronic bronchitis, asthmatic bronchitis, and emphysema (1, 2). Rarification of the lung in emphysema may progress to form bullae (Figure 1). Cigarette smoking has long been recognized as the predominant etiologic agent. Arterial hypoxemia, a frequent complication of COPD, can lead to pulmonary hypertension and cor pulmonale (Figure 2).

Michaud, Murray, and Bloom have recently underscored the enormous national and global impact of COPD (3). The disease is the fourth most common cause of death, and the harmful effects of the disease extend beyond the lungs. The disease is prevalent worldwide and in 1993, the cost of health care for COPD was estimated to be of the order of $15 billion. Arterial hypoxemia, a frequent complication of lung disease, can lead to pulmonary hypertension and cor pulmonale. Neither the prevalence of the disease nor the mortality that it causes shows signs of slackening.

NOMENCLATURE

Two inventions in the nineteenth century stimulated interest and promoted understanding of the disease: the stethoscope by Laenec in 1819 (4) and the spirometer by Hutchinson in 1842 (5). However, ambiguities about the nature of the disease and uncertainties about what to call it persisted into modern times. For example, in the mid-twentieth century, the British still referred to the disease—which in their country was widespread and disabling—as “chronic bronchitis.” In contrast to the British Hypothesis, the Americans, who were dealing with a milder form of the disease, called it “emphysema” (6). In 1944, in his Goulstonian Lecture, Christie underscored the uncertainties that were introduced into epidemiologic studies by the disparities in nomenclature (7). In 2004, Anthonisen revisited the British Hypothesis that recurrent bronchial infections are responsible for progressive airway obstruction in smokers (8).

At the close of the 1950s and in the early 1960s, several international meetings addressed uncertainties in the nomenclature of COPD: one by the Ciba Foundation, another by the American Thoracic Society, and the third by the British Medical Research Council (9–11). All three arrived at virtually the same conclusion: the essential features of so-called chronic bronchitis in England and of emphysema in the United States are the same.

In 1966, the differences in nomenclature between the British and American terminology were reconciled, and Briscoe’s suggestion that chronic bronchitis, asthmatic bronchitis, and emphysema be included under the rubric “chronic obstructive pulmonary disease” was widely adopted.

NATURAL HISTORY AND PATHOGENESIS

In 1953, Oswald described the clinical features of “chronic bronchitis” and “emphysema” based on his observations of 1,000 patients (12). Using his own extensive experience, in 1965 Stuart-Harris provided important descriptions of the clinical course of COPD (13). In the same year, the American Thoracic Society published the “Diagnostic Standards for Non-Tuberculous Respiratory Disease” (14). In the 1960s, Burrows, Fletcher, Heard, Jones, and Woolf distinguished between the emphysematous and bronchial types of chronic airways obstruction (6), and the term “chronic obstructive pulmonary disease” coined by Briscoe was adopted widely (15). In 1977, Fletcher and Peto provided a description of the natural history of the disease (16).

In his Goulstonian Lecture, Christie not only dealt with the clinical features of emphysema, but also with the pathophysiologic mechanisms responsible for the disturbances in pulmonary function associated with this disease (7). For Christie, the predominant disorder in emphysema was a decrease in lung elasticity caused by cough or respiratory obstruction. He explained the dyspnea and impaired hemo-respiratory gas exchange that accompany COPD by invoking a “wastage of ventilation” in the overdistended air sacs and bullae, i.e., a “pathological dead space.”

At the close of the 1950s, Liebow described in detail the histopathologic features of emphysema and focused predominantly on the associated vascular changes (17). In the 1960s, Hogg, Macklem, and Thurlbeck pinpointed the site and nature of the obstruction to airflow in COPD to the small airways in cigarette smokers and then described how these anatomic alterations could lead to the clinical manifestations of COPD (18). In the 1970s, Bolduc and Reid described the microscopic anatomy of the bronchial and alveolar linings of the normal rat lung thereby providing a standard of reference for the changes in COPD (19).

In 1999, Renard described the chronic inflammatory and repair process in COPD and raised the possibility that the repair process could be enhanced by the use of exogenous agents (20). In 2004, Hogg and colleagues described the nature of the obstruction in the small airways in COPD (21).

The gross pathology of emphysema was dramatically displayed in the 1950s by Gough and Heppleston using whole lung sections (22, 23) (Figures 3–6). These sections of the whole lung afforded the prospect of relating global pulmonary pathology to overall disturbances in physiologic function. Thurlbeck and Muller quantified the extent of emphysema by imaging the postmortem lung (24). The ability to visualize sagittal sections of the lung during life and to relate such images to the Gough-
Figure 1. Bullous emphysema. Large bullae throughout lung with greatest (slide) concentration at apex and in vicinity of septum.

Heppleston whole lung sections obtained postmortem became possible with the advent of computed axial tomography (CAT scanning) and magnetic resonance imaging (MRI).

Physiologic studies added functional data to the clinical–pathologic correlations. In 1954, Hickam, Blair, and Frayser described an open-circuit, helium method for assessing defects in intrapulmonary gas mixing and measuring functional residual capacity (25). In 1967, Macklem and Mead partitioned the resistance of the airways into central and peripheral components by means of a retrograde catheter (26). In the same year, Pride, Permutt, Riley, and Bromberger-Barnea described the determinants of maximal expiratory flow from the lungs (27). A decade later, Dawson and Elliott depicted the effect of wave-speed limitation on expiratory flow (28). At a subsequent Annual Aspen Conference on Research in Emphysema, Silvers and coworkers and Mitchell and colleagues related airway resistance in excised, artificially ventilated lungs to postmortem bronchography (29, 30). They showed that in the emphysematous lung, the airways collapsed early in expiration and trapped expired air. As recently as 2004, studies of dynamic hyperinflation have continued to provide additional insights into the pathophysiologic features of the emphysematous lung (31).

By the middle of the twentieth century, the maximum breathing capacity had become widely used as an objective measure of the disturbance in function caused by COPD. In 1947, Tiffeneau and Pinelli proposed that the same information could be provided by the less strenuous test of the forced expiratory volume in 1 second (FEV₁) (reviewed in Reference 32). In the 1950s, Gaensler endorsed and popularized this view (33). Since then, FEV₁ has continued to be widely used to assess pulmonary function in COPD.

In the early 1960s, Orie proposed that inherent hyperresponsiveness of the airways and atopy predisposed to COPD as well as to asthma (34, 35). This proposal, which came to be known as the “Dutch Hypothesis,” contrasted with the so-called “British Hypothesis,” which attributed airway obstruction to recurrent infections of the airways. In essence, the Dutch Hypothesis underscored the role of endogenous factors contributing to airway dysfunction as central contributors to the development of COPD, whereas the British Hypothesis focused on extrinsic factors, notably cigarette smoking (36).

Seminal observations relating to the pathogenesis of emphysema were presented in 1958 by McCluskey and Thomas (37). They demonstrated the ability of intravenous papain, a crude protease, to degrade cartilage rapidly. In turn, this demonstration prompted the investigation of the ability of other enzymes, notably elastases and collagenase, to degrade elastin, collagen, and cartilage. These findings also led to examination of the consequences of such airway processes on the mechanical properties of the lungs. The protease–antiprotease imbalance hypothesis emerged, and attributed lung destruction in emphysema to the release of in vivo proteolytic enzymes (38).

In 1963, Laurell and Ericksson reported a high prevalence of emphysema in members of families with subnormal concentrations of α₁-antitrypsin in serum (39, 40). Both males and females were affected. α₁-Antitrypsin deficiency was found to be a genetic disorder that not only increases the risk of developing pulmonary emphysema, but also can be accompanied by cirrhosis of the liver (41). The affected gene codes for the 52-kD glycoprotein α₁-antitrypsin, the major serine proteinase inhibitor (serpin), and is located on chromosome 14 of the human genome. Cigarette smokers with this deficiency developed emphysema at a much higher rate than did the usual smoking population. A recent National Heart, Lung, and Blood Institute (NHLBI) workshop suggested that a clinical trial of augmentation therapy with α₁-antitrypsin is warranted in patients with α₁-antitrypsin deficiency (42, 43).
NATIONAL AND INTERNATIONAL PROGRAMS ON COPD

In 1994 and 1997, workshops convened by the NHLBI dealt with possible national strategies for prevention, management, and research in COPD (44–46). The 1994 workshop focused on smoking intervention and the use of an inhaled bronchodilator to slow the rate of decline in FEV1. The 1997 workshop dealt with three other aspects: prevention, management, and research in COPD. Both workshops played important roles in raising physician and patient awareness about the magnitude of the problem posed by COPD, the availability of effective therapeutic measures, and the need for research into pathogenesis and management.

A “Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD)” was launched in 2001 and subsequently updated in 2004 as a combined venture of the NHLBI and the World Health Organization (47). The GOLD guidelines define COPD as “a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases.” The initiative was designed to raise awareness of COPD as a public health problem by governments, public health officials, health care workers, and the general public. The report is broad in scope and deals with the various aspects of COPD including natural history, epidemiology, risk factors, pathogenesis, management, and future research.

In 1995, The American Thoracic Society set standards for the diagnosis and care of patients with COPD, and in 2004 joined forces with the European Respiratory Society to publish position papers on the diagnosis and treatment of patients with this disorder (48, 49). This combined approach represents a major step forward in raising professional and public awareness of the latest advances in the understanding of the harmful effects of smoking and of the pathogenesis, diagnosis, monitoring, and treatment of COPD.

It is important to stress that cigarette smoking has long been recognized to be the predominant cause of COPD. The deleterious effects of smoking on the lungs, as well as systemic effects, are well known (50). However, concerted efforts to promote smoking cessation have met with only partial success. Other risk
factors for COPD have also been identified and attempts have been made to minimize them. Among these are air pollution, individual bronchial hyperreactivity, individual susceptibility to environmental allergens, a history of childhood respiratory infections, occupational inhalants, socioeconomic status, genetic factors, and alcohol consumption. However, none of these compare with cigarette smoking as a risk factor for COPD.

PHARMACOLOGIC TREATMENT OF COPD

Although COPD has a long history, effective treatment of the disease is the product of only the last two decades. In the 1960s, drug therapy was limited to potassium iodide and ephedrine. Corticosteroids were not used, and oxygen and exercise were regarded as contraindicated. In more recent times, insights into pathogenesis accompanied by a remarkable increase in the number of therapeutic options have greatly improved medical management. The newer therapies include long-acting bronchodilators, antibiotics, inhaled corticosteroids, oxygen therapy, mechanical ventilation, and lung volume reduction surgery (LVRS) (for emphysema) (51).

In a systematic review of the contemporary management of COPD, Sin and coworkers examined the impact of various therapies on the health status of patients with COPD and the natural course of the disease (51). Their review included long-acting bronchodilators, inhaled corticosteroids, nocturnal noninvasive mechanical ventilation, pulmonary rehabilitation, domiciliary oxygen therapy, and disease management programs on clinical outcomes. The review indicated that a significant body of evidence supported the use of long-acting bronchodilators and inhaled corticosteroids in reducing exacerbation in patients with moderate to severe COPD. Observational studies indicate that
the age-related decrease in pulmonary function is accelerated by smoking and that smoking cessation is associated with a slowing of the rate of decline. In 2003, prompted by the large number of physician visits caused by acute exacerbations of chronic bronchitis, the Canadian guidelines for the management of acute exacerbations of chronic bronchitis, originally written in 1993, were updated (52). This comprehensive document deals with the different effects of the disease varying from epidemiology and risk factors on the one hand to therapies on the other.

Adrenergic agents have been used for many years in the treatment of acute asthma (53). Ephedrine, a sympathomimetic agent derived from the plant Ephedra Vulgaris, was used by the Chinese in 3000 B.C. to make the drug Ma Huang for the treatment of asthma. In the late 1800s, adrenal extracts began to be used for asthma, as well as for rhinitis and conjunctivitis. Epinephrine was synthesized at the turn of the twentieth century and was used to treat individuals with asthma, first by the oral and subcutaneous routes, and as an aerosol in 1910. Isoproterenol came into use as a bronchodilator 30 years later, and isethionate was introduced for the treatment of asthma in 1951. Currently, epinephrine and its derivatives comprise the large majority of oral inhaled aerosols available as adrenergic bronchodilator drugs (53).

Attempts to promote effectiveness and to minimize or eliminate undesirable side effects of adrenergic agents have led to the development of selective β2 agents. These drugs achieve selectivity not only by inhalation into the lungs, but also by their specificity for β2 receptor subtypes. The specific β2 agonists play a key role in the treatment of asthma, but their role in treating COPD is confined to those patients in whom bronchospasm is part of the clinical manifestations (54). An important advance in the use of bronchodilators is the development of long-acting agents, which decrease the need for frequent dosing.

An alternative approach to the use of an inhaled adrenergic agent is the use of an inhaled anticholinergic bronchodilator (45). Among these is tiotropium, a long-acting anticholinergic agent that increases FEV1 in COPD (55). These agents have proved useful in chronic maintenance therapy. In a systematic review of 33 clinical trials of bronchodilators on exercise capacity in patients with COPD, Liesker and colleagues found that bronchodilator therapy improved exercise capacity in about half of the patients (56). Most effective were the short-acting anticholinergics, especially at higher doses, and the short-acting β2 mimetics. In contrast, the theophyllines were generally without effect. Short-acting β2 mimetics had a favorable effect in more than two-thirds of the studies, whereas the effects of long-acting β2 agents was less clear. In 12 randomized controlled trials of long-acting β2 agonists in stable COPD with poor reversibility, Husereau and coworkers could find no convincing evidence that salmeterol and formoterol had advantages over ipratropium, a less expensive anticholinergic drug, with respect to clinical outcomes (57). The Lung Health Study, initiated by the NHLBI, coupled the use of inhaled ipratropium bromide with a smoking cessation program. The aggressive smoking intervention program significantly slowed the age-related decline in FEV1 in middle-aged smokers with mild airways obstruction. However, the use of this anticholinergic bronchodilator elicited only small improvement in FEV1 that disappeared upon discontinuing the drug and had no influence on the long-term decline in FEV1 (45).

MECHANICAL VENTILATION IN COPD

The first use of mechanical devices has been traced to the 1700s. Usage peaked during the polio epidemic of the 1920s. Currently, interest is high in the use of mechanical devices for ventilatory support in patients with respiratory failure, including patients with COPD. Among the landmark devices have been Drinker's body respirator, the Emerson respirator, and the Cuirass respirator (63–68).

The high airway resistance in COPD promotes dynamic hyperinflation. Dynamic hyperinflation runs the risk of circulatory impairment, especially at high peak pressures. The determinants of dynamic hyperinflation have been examined in a bench model, and untoward side effects, such as barotrauma, have been explored (31).

In 1966, Emmanuel, Smith, and Briscoe compared the effects of antibiotics. Because no single individual antibiotic or class of antibiotics is ideal, the choice of antibiotics depends on the attributes of available antibiotics, including the spectrum of activity, the dominant organisms, the dosage, patient tolerance of the antibiotic, potential organ toxicity, and cost and loss effectiveness. The Canadian guidelines for the treatment of exacerbations of COPD do not recommend that all exacerbations should be treated with antibiotics. Instead, they suggest a stratification approach based on the severity of the COPD and the presence of comorbid conditions (52).

COPD entails chronic inflammation and injury of airways and parenchyma. In the review of the literature, Sin and colleagues found a significant body of evidence in support of the use of long-acting bronchodilators and inhaled corticosteroids in reducing exacerbations with moderate to severe COPD (51). The advent of inhaled corticosteroids offers the prospect of avoiding the side effects of systemic corticosteroids. Elastin degradation within alveoli is believed to play an important role in the pathogenesis of emphysema. Studies are underway to define the role of inadequate repair and to devise therapeutic interventions to remedy this deficiency (20).

THE THERAPEUTIC USE OF OXYGEN

In the early 1920s, Alvan L. Barach, M.D., a superb clinician, pioneered the use of oxygen therapy in COPD. He played a key role in establishing the rational basis for oxygen therapy by pinpointing the essential indications for its use and describing methods for the effective administration of oxygen (60, 61). He introduced into his practice and clinic a variety of interventions that were designed to improve oxygenation of the blood and popularized them by prolific lectures and writings. Among his innovations were pursed-lip breathing, an emphysema belt, exercises in diaphragmatic breathing, and manual compression of the lower chest and abdomen.

Patients with COPD and hypoxemia have a poor prognosis, despite treatment regimens directed at improving the mechanical functions of the lungs. As a result, such patients are usually treated empirically with supplementary oxygen. In 1980, the NHLBI initiated a multicenter trial which compared continuous O2 therapy with nocturnal O2 therapy in patients with hypoxemic COPD. The results, based on 203 patients with hypoxemic COPD, indicated that round-the-clock O2 therapy is associated with lower mortality than nocturnal O2 therapy. At approximately the same time, a Working Party of the Medical Research Council in Great Britain performed a controlled trial of long-term domiciliary oxygen therapy in three centers in the UK. Oxygen therapy did not slow the progress of those who died early but seemed to stop deterioration in longer-term survivors (62).
of Intermittent Positive Pressure Breathing (IPPB) and voluntary hyperventilation on oxygen saturation and CO₂ levels in COPD (67). Both exerted the same effect by improving the ventilation of the least ventilated areas of the lung, i.e., the so-called “slow space” of Hickam, Blair, and Frayser (25). Although only a small fraction of the added ventilation went to the slow space, oxygen saturation improved and the CO₂ level decreased.

There has been an exponential increase in recent years in the use of nasal positive pressure ventilation (NPPV) in various lung diseases, including COPD (69). Interest in NPPV centers around the use of NPPV to rest chronically fatigued respiratory muscles. Large retrospective analyses have examined the outcomes of patients treated with NPPV for periods of up to 5 years, averaging 2 to 3 years. The results indicate that survival among patients with COPD treated with long-term NPPV is comparable to that of patients with tracheotomies or long-term oxygen therapy. Despite an overall trend for increased survival of patients treated with NPPV, statistically significant differences have not been registered, largely because the number of patients has as yet been too small for statistical analysis. Overall, the evidence suggests that patients with COPD with severe airways obstruction and CO₂ retention, particularly those with nocturnal oxygen desaturation, are most apt to respond favorably to nocturnal NPPV (70).

PULMONARY REHABILITATION IN COPD

In principle, the practice of pulmonary rehabilitation requires specialized knowledge of both rehabilitation medicine and chest medicine. Early on, the lead was taken by individual chest physicians, notably Alvan Barach (60, 61). In 1994, a workshop sponsored by the NHLBI and the Center for Medical Rehabilitation Research reviewed the present state of research in COPD, including pulmonary rehabilitation, and pinpointed several areas for exploration and development.

Interest is high in objective markers of the outcome of pulmonary rehabilitation in COPD. Exhaled concentrations of nitric oxide are being investigated as a marker, because the concentration of nitric oxide in expired air is increased in inflammatory diseases of the lungs and decreased in COPD. A pulmonary rehabilitation program that increased exercise tolerance in patients with mild to moderate COPD was associated with an increase in the resting concentration of expiratory nitric oxide (71).

LVRS and transplantation

LVRS is an option for the palliative treatment for severe emphysema. Uncertainty about preoperative predictors of benefit, the occurrence, magnitude and duration of benefit, and about morbidity and mortality of the surgical procedure led in 2002 to a multicenter, federally sponsored, randomized clinical trial, the “National Emphysema Treatment Trial (NETT)” (72, 73). The study has provided reliable estimates of the risk and benefit of LVRS. After excluding high-risk patients, four clinically meaningful subgroups of patients were identified on the basis of post-rehabilitation CT scanning and exercise capacity. Although there was no survival benefit after LVRS, patients with predominantly upper lobe emphysema and a low maximal workload had lower mortality and greater probability for improvement in symptoms and exercise capacity after LVRS than did patients who received medical therapy alone. A study after 3 years of follow-up indicates that although LVRS is relatively costly as compared with medical therapy, LVRS may prove to be cost effective if benefits are maintained over a longer period of time (74, 75). Another milestone in the history of the surgical treatment of emphysema is represented by lung transplantation. This is clearly a measure of last resort and its application is handicapped by the postoperative development of bronchiolitis obliterans (76).

CONCLUSIONS

The past century has witnessed dramatic improvements in the prevention, diagnosis, and treatment of “chronic obstructive pulmonary disease,” formerly called “chronic bronchitis and emphysema.” Cigarette smoking has been identified as the leading cause of the disease (COPD) and public awareness has been raised about its etiologic role and dire consequences. The medical management of COPD now includes a wide array of therapies for the medical management of acute exacerbations and chronic maintenance therapy of the more enduring symptoms. In 1997, Petty and Weinmann presented a national strategy for prevention, management, and research on COPD based on a workshop sponsored by the NHLBI (46).

A few years ago, the medical management of COPD was supplemented by rekindled interest in surgically removing overdistended and nonfunctioning lung in patients with emphysema. A federally sponsored, multicenter trial, “The National Emphysema Treatment Trial,” undertook to define the population of patients with COPD who would most likely benefit from surgical removal of emphysematous, nonfunctioning segments of the lungs. Currently, this surgical approach marks the end of a spectrum of therapeutic options for COPD that depend on the severity and incapacity produced by the COPD.

Past experience has shown that the key component of any program to deal with COPD is the avoidance or cessation of cigarette smoking. Information about the harmful effects of smoking is widespread and well known. Nonetheless, although public awareness of cigarette smoking as the predominant cause of COPD is at an all-time high, a large segment of the population continues to indulge in cigarette smoking without due regard for the morbidity and mortality that this habit can produce.

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