COPD past, present and future

Chronic obstructive pulmonary disease past, present and future
P M A Calverley, J A Wedzicha

Progress in the understanding of COPD

Chronic obstructive pulmonary disease (COPD) is a topic of clinical concern and active research that is strongly represented at the meetings of the British Thoracic Society and in Thorax. This has not always been the case and, for rather different reasons, this disease may not be as important in future decades because the impact of COPD—at least in the developing world—should finally diminish over the next 20 years. This reflects the demographics of smoking cessation and the availability of more effective treatments to reduce the impact of this condition. The problems with COPD are not as current as is often stated. Necropsy data from the late 19th century identified the pathological features of emphysema while the clinical associations of this condition were described by René Laennec in his treatise on diseases of the chest in 1819. However, the slow pace of the illness and its lack of dramatic physical signs delayed our appreciation of its importance.

In the 20th century three partly related developments changed this. The first was the impact of warfare, specifically the use of toxic gases in World War I which stimulated research on pulmonary gas exchange. In World War II the need to fly at high altitudes without the pilots blacking out led to a renaissance of respiratory physiology which had its full impact when the relevant research was declassified at the end of hostilities. The ability to make objective measurements has transformed our understanding of COPD and coincided with a time when clinicians became aware of its importance, partly because of the accelerated death rate from respiratory causes including “bronchitis” after the 1952 London smog which linked impaired air quality very clearly with respiratory death. Additionally, Sir Richard Doll began his studies into the causes of death from lung cancer which led to the unequivocal relationship between tobacco smoking and this disease. As his studies on death in British doctors subsequently showed, the increase in deaths from lung cancer with rising tobacco consumption was paralleled by a similar increase in deaths due to chronic bronchitis and emphysema.1

Clinical terminology has proved to be a consistent barrier to progress in this field, and it was not until the late 1960s that it became clear that “British bronchitis” was clinically the same disease as “American emphysema”. Compelling scientific data on the overlap of pathology between these clinically defined conditions was provided by the work of Hogg et al2 who established a clear association between pathological changes and abnormalities in pulmonary function, specifically airflow obstruction. A major step forward in our understanding of COPD came from the longitudinal study of Fletcher et al3 in Whitehall postal workers in whom symptoms and lung function were recorded over an 8-year period. Their initial hypothesis was that patients with symptoms of chronic bronchitis would show more deterioration. This did not prove to be the case and, instead, the initial level of lung function was a stronger predictor of their subsequent performance. As a result of these careful pathological and clinical observations, the role of airflow obstruction became central to the diagnosis and understanding of COPD and the preferred method of detecting this became spirometry. However, argument has continued over what to call this obstructive disease with a range of confusing synonyms being developed. Although COPD has eventually become the most widely used name, many clinicians still revert to chronic obstructive airways disease, chronic obstructive lung disease, chronic airflow limitation and even (although mainly in The Netherlands) chronic non-specific lung disease.

By the late 1970s the physiological basis of chronic airflow obstruction in terms of abnormal lung mechanics, gas exchange and the pulmonary circulation, at rest and during exercise, had largely been established. Unfortunately, much of the data was restricted to interested academics and did not diffuse into clinical practice until nearly 25 years later. Physiological studies did slowly begin to influence the way patients were managed. The development of controlled oxygen therapy was based on knowledge of oxygen delivery to the tissues and the risk of suppressing hypoxic ventilatory responses and of potentially modifying lung ventilation-perfusion relationships when patients were exposed to high concentrations of oxygen. This is a lesson which still has to be learnt in many emergency departments in the UK. The next step was to test the benefits of correcting persistent hypoxaemia in patients with more severe COPD where this was known to be a predictive factor for increased mortality. The resulting MRC and NIH oxygen trial provided the justification for domiciliary oxygen, not just in COPD but in many other conditions associated with chronic hypoxaemia.4,5 During the 1980s we failed to build on these pioneering studies, but in the last 15 years we have seen important large-scale clinical trials addressing the effect of smokingcession in COPD,6 the role of long-acting inhaled bronchodilators and corticosteroids in changing clinical outcome potentially affecting...
mortality\(^7\) and the risks and benefits of lung volume reduction surgery.\(^6\) In each case a clinically relevant idea with an acceptable scientific rationale has been explored and large trials have provided answers which inform clinical guidance and stimulate further research.

The ability to image the lung in vivo was realised when CT scanning was first applied to COPD, an area where conventional radiographic imaging had been difficult to interpret and was not quantitative. The inflammatory nature of COPD was confirmed, not only by careful histopathological studies of resected lung but also by endobronchial biopsies of the larger airways.\(^7\) The latter approach has meant that the effectiveness of treatment on the inflammation of COPD can be evaluated. When large enough studies are undertaken, clear answers can be obtained. As was the case with physiology four decades ago, the challenge with these new methods is to develop robust methodologies to conduct and report the data that will permit them to be incorporated in routine clinical practice.

These developments are important if we are to move forward our understanding of the care of patients with COPD. Although tobacco smoking has been the major driver of COPD in the 20th century, data from the developing world together with a historical review of the causes of death in the 19th century suggest that other factors are just as important in a global perspective. Thus, indoor pollution from exposure to biomass fuel is clearly associated with significant airflow obstruction in non-smokers, especially women.\(^3\) This helps explain the high mortality from COPD in women in rural China and perhaps accounts for the fact that death from bronchitis at the end of the 19th century in England was as likely to occur in women as in men. The high background prevalence of tuberculosis is often thought to explain all respiratory deaths in this period but, as recent data from South Africa have shown, airflow obstruction also is very prevalent in communities where tuberculosis is itself common.

Exacerbations of COPD are a major cause of hospital admission and considerable healthcare costs, although recognition of their importance has only occurred relatively recently. In the classic studies of Fletcher et al.\(^6\) it was reported that exacerbations did not affect COPD disease progression, but recent research has shown that exacerbations, in addition to having an effect on the decline in forced expiratory volume in 1 s, are also a major driver of health status\(^2,4\) and mortality in COPD. Exacerbations have therefore become important outcome measures for treatment in COPD as reduction in exacerbation frequency improves quality of life. However, exacerbations are heterogeneous events and are difficult to study, so large adequately powered trials performed over at least 12 months to account for seasonal fluctuations are necessary to study the effect of treatments on exacerbation frequency.

There have also been recent developments in the understanding of the causes and mechanisms of COPD exacerbations. We now recognise that most exacerbations are associated with respiratory viral and bacterial infection and this drives the increased airflow and systemic inflammation associated with the episodes. However, we need much more research on the interactions of infection with airflow epithelium in order to understand the pathogenesis and long-term consequences of exacerbations. Current preventive treatments only reduce exacerbation frequency by about 25%,\(^7\) so novel treatments based on an understanding of the mechanisms of exacerbation are required to treat the actual exacerbation and also reduce exacerbation frequency.

As stated above, the last 15 years have been associated with huge developments in the understanding and management of COPD. National and international guidelines for the management of COPD have been written and implemented and these have led to enormous influence and publicity about the condition. However, very large numbers of patients are still not diagnosed and treated. COPD is at last on the agenda of healthcare planners in many countries and is recognised as a priority for clinical service development and research. We now need to ensure that patients with COPD of all severities have access to diagnostic services, education about their condition and smoking cessation and optimal management both in the long term and at exacerbation. In this way we will be able to curb the significant morbidity and mortality caused by this disabling condition.


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