Chronic Obstructive Pulmonary Disease

CRITICAL DEBATES

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Preface

COPD is a challenge to health systems across the world. As cigarette smoking increased during the 20th century so the prevalence of COPD increased in its wake. Acute exacerbations of COPD are the second most common cause of admission to UK hospitals. Over 5% of people aged over 60 in the UK are affected and seeking help to relieve their symptoms. Not all countries are as severely affected as the UK but in most countries across the world cigarette smoking is increasing and with it so is the prevalence of COPD. The World Health Organization predicts that by the year 2020, COPD will be the fourth most common cause of death worldwide.

Until quite recently there was little medical interest in COPD but a surge of interest has been stimulated by the development of simple measurements, and by inhaled drugs that relieve the symptoms at least in part. Although the damage caused by smoking cannot be reversed, the COPD patient's life quality can be significantly improved and in some cases their life expectancy improved too.

The research world has woken up to these possibilities and the burgeoning number of sessions at international meetings allocated to COPD is testament to the amount of new effort devoted to the disease. Now the pharmaceutical industry has developed a range of products of proven benefit; and more are on the way.

This book has an unusual format. It is not intended to be a textbook for the expert, and makes no attempt to be comprehensive in its coverage. Instead our contributors were asked to discuss COPD topics that the average clinician (doctors, nurses and allied health professionals) would be able to read easily and find interest in. The questioning format has allowed our contributors to select from the many issues that could be discussed and so inevitably some subjects have not been covered (so apologies if your pet concern is not described). Nevertheless we hope that there is plenty to interest all those who manage patients with COPD in primary and secondary care and they will be stimulated to want to know more about this all too common disorder. This is

a rapidly developing field with many exciting and interesting developments that are being translated into direct patient care.

We hope that those who read this book are left with an enthusiasm that COPD is not a 'no-hope' disorder and will want to do more for their patients. Much can and should be done that will benefit not only the patients directly but also their families and thus society. But if we are to succeed we need not only to recognize what can be done, we also have to put into place systems that ensure it really is done.

Mike Pearson
Wisia Wedzicha

1: The aetiology and epidemiology of chronic obstructive pulmonary disease

John Corless

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality throughout the world. It is the fourth commonest cause of death in the United States after ischaemic heart disease (IHD), cancer and cerebrovascular disease. Unlike IHD and cancer, however, COPD suffers from an 'image problem'. Surely no other disease of similar impact can have as many different names—chronic obstructive airways disease, chronic obstructive lung disease, chronic bronchitis and emphysema, to name a few. Similarly, personal experience suggests that only a minority of patients know the name of the disease from which they suffer. The precise definitions used to diagnose the condition are open to contention and debate, based on assessment of symptoms and interpretation of spirometry. As the most important aetiological factor is smoking, the disease is often regarded as self- inflicted—and in turn, patients are at times viewed less sympathetically than those with malignancy, for example.

Despite the difficulties that arise from varying nomenclature and definitions, there is no doubt that COPD has a major impact on global health, particularly in the developed world. This chapter seeks to address the following issues:

- Does all COPD result from smoking?
- Other aetiological factors in the pathogenesis of COPD
- The global impact of COPD
- The natural history of COPD
- The future of COPD.

The aetiology of COPD

Does all COPD result from smoking?

The evidence that cigarette smoking is a major cause of lung cancer and COPD

Table 1.1 Annual mortality per 100 000 men. Adapted from [1].

	Never smokers	Current cigarette smokers	Ex-cigarette smokers	Current cigar/pipe smokers	Ex-cigar/pipe smokers
COPD	10	127	57	51	40
Lung cancer	14	209	58	112	59
IHD	572	892	678	653	676

COPD, chronic obstructive pulmonary disease; IHD, ischaemic heart disease.

has been derived from a series of very different studies over many years. Although none of these have used the randomized controlled trial design that provides the 'gold standard' for evidence in most Cochrane reviews, it is widely accepted that cigarette smoking is the single most important risk factor for the development of COPD, even though a precise model of the mechanism has yet to be constructed. It is worth reviewing the strength of the evidence.

As late as 1948, there were experts prepared to argue that smoking was not harmful, but by 1950 the link to lung cancer seemed probable. Richard Doll and colleagues decided to commence a prospective longitudinal study to find out what other diseases might or might not be smoking-related. In 1951, all doctors in Britain were asked about their smoking habits, and 40 000 replied. These doctors were followed up for 40 years, with interim reports at 10 and 20 years that confirmed the link to cancer and showed that other conditions were also linked to smoking. The 40-year report [1] concentrated on the 34 439 males in the study, and at this time it was possible to establish the vital status of 99.7% of the 1951 cohort. A cause of death was obtained for 99% of the deaths, and of those who were alive, 94% completed a further questionnaire. Longitudinal studies are usually marred by a significant loss to follow-up, and the completeness of this study is remarkable. Although it was not a randomized, controlled trial, it is probably one of the most complete and devastatingly strong observational studies ever mounted.

Positive associations with smoking were confirmed for death from cancers of the mouth, oesophagus, pharynx, larynx, lung, pancreas and bladder. Details of mortality for COPD, lung cancer and ischaemic heart disease (IHD) are outlined in Table 1.1. Cigarette smoking increased the risk of death from COPD, lung cancer and from ischaemic heart disease. In each case, those who had ceased smoking had values that were intermediate between those of non-smokers and continuing smokers. Because ischaemic heart disease is so much more common, the total effects of cigarette smoking on the heart were similar to those on the lung. Thus, when expressed in terms of the population

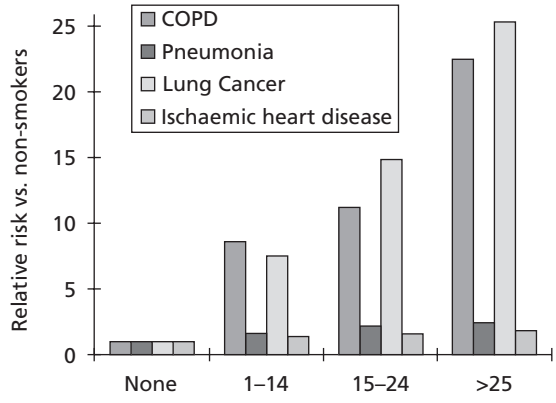

Fig. 1.1 Relative risks of current smoking—the risk in non-smokers for each condition has been set at 1, and values displayed for different intensities of smoking.

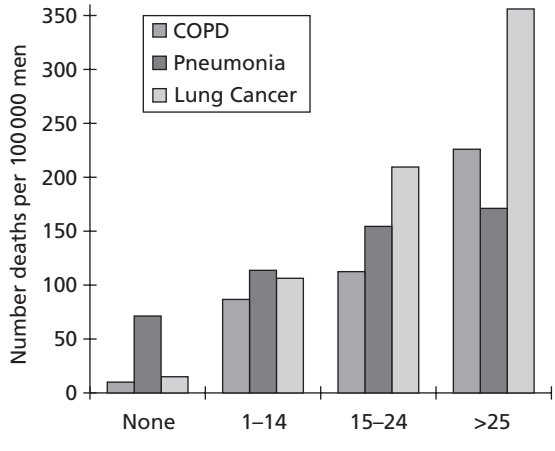

Fig. 1.2 Mortality of current smokers by amount smoked [1].

affected, there are an extra 320 deaths per 100 000 from ischaemic heart disease and 312 from COPD and lung cancer together.

The crude relative increase in ischaemic heart disease from these figures is 1.55 compared to 12.7 for COPD and 14.9 for lung cancer, and the much higher relative risk suggests a much closer and more complete causal link to pulmonary disease (Fig. 1.1). For heart disease, it is recognized that smoking is only one factor amongst several involved in the causation of disease. Genetic susceptibility (as shown by the strong influence of a history of heart disease amongst close relatives) and lipid control are two other strong predictors that may be as important as smoking.

The increased risks attributable to smoking are dose-dependent (Fig. 1.2). Not only is the number of deaths per 100 000 much increased for COPD and lung cancer, but there is also a significant increase in deaths from pneumonia, and many of the patients concerned could well have had COPD too. The

COPD effect may therefore be underestimated. This leaves approximately 5–10% of cases of COPD that are not directly attributable to smoking.

The authors were able to go further in their estimations of risk to show that for the average smoker, there was a loss of 7.5 years of life, increasing to 10 years for a smoker of more than 25 cigarettes per day. Another way of describing the data is to state that only 21% of smokers will attain the age of 85 years, compared to 41% of non-smokers. If a person ceases smoking, then the risks of death are reduced and there are discernible benefits even for those quitting when over 65 years of age.

As was noted above, this was an observational study and there were a number of potential confounding factors. Death certification could have been wrong—it is known that the reliability of death certificates is not good, and there were many changes in the lifestyle, wealth and personality of the population over the period studied. While it is possible that some of these factors could have affected survival, it is unlikely that they could have altered the huge relative risks observed.

These data were derived from a relatively privileged sector of the population; while this has an advantage in that there was no social class disease gradient to be taken into account, it also raises the possibility that the relative risks could be different in other parts of society. More recent data for the UK based on survival data from life-insurance work [2] show a very similar effect on loss of life expectancy—7 years between the ages of 30 and 70—suggesting that the Doll and Peto data can probably be extrapolated to the general population.

The size, completeness and length of this study make the links between smoking and both lung cancer and COPD irrefutable, and indeed many other studies since have confirmed and supported these conclusions.

How many non-smokers develop COPD? From the Doll and Peto figures, it would seem that of 285 deaths per 100 000 due to COPD, there were 10 individuals, or about 3%, who had never smoked and were labelled as having COPD. Similar figures are reported from cross-sectional studies of living patients, e.g. that 5–7% of their cohort were non-smokers [3]. Assuming that these cases of COPD do not result from incorrect recording of diagnosis or smoking status, other aetiological factors may exist. This is discussed later in the chapter.

Many other examples from other countries have confirmed the dose-related relationship between the risk of developing COPD and cigarette smoking [4]. They also confirm the lower incidence of COPD in those who smoke a pipe or cigars rather than cigarettes [5]. The incidence of COPD is consistently reported to be significantly lower in women, reflecting the lower prevalence of cigarette smoking amongst females, but the pattern is changing. In the UK, death rates from COPD in men have fallen, reflecting a change from a 65% rate of current smokers in 1970 to less than 30% in 2000, but the death rate in

women is still rising [6] following the surge in female smoking after the second world war. In Denmark, where a high proportion of women have been smokers for many years, the percentage of deaths in women attributable to tobacco already approaches that of men [7]. This trend is likely to be seen in other European countries in the coming years.

Other aetiological factors in the pathogenesis of COPD

Asthma

A proportion of asthma patients develop an irreversible component that is usually attributed to airway remodelling. It is not known why some asthmatics progress to fixed airflow obstruction—but once they have, it is very difficult to differentiate them from patients with COPD on clinical or physiological grounds. Approximately 2% of asthmatics have a forced expiratory volume in 1 s (FEV_1) below 60% predicted. As asthma is so common, even this small percentage may explain many of those who are labelled as having COPD despite not having any history of exposure to cigarette smoke. In comparison, 10% of moderate smokers (21–40 pack-years) and over 22% of heavy smokers (>60 pack-years) will develop this severity of airway obstruction [8].

Bronchiolitis

An alternative mislabelling can occur with bronchiolitis. Bronchiolitis and bronchiolitis obliterans are general terms used to describe a non-specific inflammatory injury that primarily affects the small airways, often sparing the interstitium. This disorder is currently poorly understood. It is likely that a small proportion of patients with a diagnosis of COPD have a progressive, constrictive bronchiolitis that has not been recognized—hardly surprising, as there is no test other than histology with which to differentiate the cause of the airflow limitation.

Occupation

The precise role of occupation in the pathogenesis of COPD remains unclear. Epidemiological studies assessing the role of occupation in the development of COPD are difficult both to conduct and interpret [9]. Most of the evidence is derived from cross-sectional studies, in which it has been difficult to record dust exposure, or indeed cigarette exposure, reliably. There is no doubt that exposure to heavy dust loads leads to a productive cough, but this can be a normal physiological response to the particular burden that has to be cleared. There are cross-sectional studies of populations [10,11] that have described

more COPD amongst those working in dusty jobs. But while cross-sectional studies can indicate associations, they cannot differentiate causality between the dust and other factors. Those in dustier jobs tend to be of lower social class and have a higher smoking prevalence, poorer nutrition and worse general health. Most data are available on coal miners, but even here the data are not conclusive. A UK legal ruling concluded that on the balance of probabilities, coal dust could cause emphysema and airway obstruction and thus miners are to receive compensation even with a smoking history [12]. There remains no mechanism to explain how coal dust (generally a remarkably inert substance) should compare with cigarette smoke (containing 10^{17} free radicals per puff), but legal cases are not science and conclude on a 'balance of probabilities'. Other studies have claimed similar effects from gold mining and for underground tunnel workers [13], although in the legal case which considered coal dust, the other rock dusts were excluded as likely causes.

Atmospheric pollution

If occupational dust can cause airway obstruction, then it is logical to examine the effects of pollution. A small additional contribution to COPD severity has been reported in patients who live in cities. However, these effects are small and remain contentious. High exposures to very small particles of less than 10 μm (PM_{10}) have also been associated with an increase in both cardiac and respiratory deaths in cross-sectional population studies [14]. These exposures are many times less than the occupational exposures experienced by miners, and thus the question arises as to whether other components of pollution may be additive in causing these apparent effects. Ozone and diesel have also been associated with the development of COPD, but the latter claim must be balanced by the studies of miners in diesel pits (i.e. pits in which the underground trains that transported men and coal along the shafts were diesel-powered). Despite heavy exposures in quite enclosed environments, no adverse effects have been observed in these coal mines [15]. Indoor exposure to wood smoke and fumes from biomass fuels has also been implicated [16,17]. Paradoxically, while concerns in the popular press about the effect of outdoor pollutants on the lung have escalated in recent times, the levels of sulphur dioxide and black smoke have been dramatically reduced in most developed countries over the last 30 years. The situation regarding environmental pollution and COPD can best be described as confused—and of an order of magnitude less than any effect of smoking cigarettes.

Socio-economic status

Low socio-economic status correlates strongly with the development of

COPD. Men of social classes IV and V aged between 20 and 64 in the UK are 14 times more likely to die of COPD than men with professional occupations [18]. This seems to occur even when different smoking rates are taken into account. It is unclear whether this is due to nutrition, different patterns of respiratory infection exposure in early life, or environmental exposures.

Premature birth is more common amongst mothers of lower socioeconomic group and in mothers who smoke. Smoking mothers produce smaller babies [19]. Prematurity is associated with early-life infections [20], and early-life infections are associated with COPD deaths 50 years later [21]. Precise mechanisms, or even a clear sequence of events that might cause this, are unknown, but it does seem increasingly likely that some of the later lung morbidity is due to failure to grow and develop properly both *in utero* and shortly thereafter.

In the Copenhagen City Heart Study, men in the lowest income/least education group had a forced vital capacity (FVC) that was 400 mL less than those in the highest group [22]. Even after control for smoking duration and quantity, the difference was still 363 mL. In females, the differences were smaller, at 259 mL (220 mL adjusted), but of similar pattern. The lowest socioeconomic groups were more likely to have had an admission for COPD even after adjustment for smoking, so these differences would seem to be of clinical importance to patients.

Some of these changes may be due to effects of poor nutrition either precipitating or accelerating the development of COPD. Harik-Khan *et al.* [23] studied 458 men without COPD and followed them for a mean of 10.2 years. An inverse relationship between body mass index (BMI) and the risk of developing COPD was demonstrated. The relative risk of developing COPD was 2.76 times greater (95% confidence interval 1.15–6.59) in the lowest BMI tertile compared to the highest tertile. In rats, starvation has been shown to induce emphysematous changes within the lungs [24]. While this association has not been proven in humans, poor nutrition has been associated with pneumothorax [25] and pneumomediastinum [26].

Infections

Latent infection with viruses has been cited as a factor that may predispose to COPD. Double-stranded DNA viruses have the ability to persist in airway epithelial cells long after the acute infection has cleared. Expression of adenoviral genes produces a trans-activating protein that has been demonstrated to amplify the inflammatory response to cigarette smoke [27]. Thus far this remains speculation only.

The global impact of COPD

Any data on the prevalence of COPD must depend on the definition that is adopted. Early stages of COPD are not associated with symptoms, or only with 'smoker's cough' that is accepted as 'inevitable'. These individuals are unknown to the medical profession. Once symptoms develop, the COPD has typically become fairly advanced, with an FEV_1 that has already fallen to less than 60% of the predicted value or worse. Most studies will therefore underestimate the true prevalence and potential impact of the disease.

Historical variations in the terminology and International Classification of Diseases (ICD) codes used for COPD also create difficulties in compiling data on COPD. Until the late 1960s, the terms 'chronic bronchitis' and 'emphysema' were commonly used. Following the eighth revision of ICD codes, 'COPD' was used increasingly frequently in the United States, but often not in other countries, making comparison difficult. The current tenth revision of the ICD recognizes a broad band of 'COPD and allied conditions' (ICD-10 codes J42-46).

Morbidity

The World Bank and World Health Organization (WHO) predict that by 2020, COPD will be ranked fifth in terms of the worldwide burden of disease [27]. The WHO also estimates that 1.1 billion people currently smoke. Assuming that 14% of smokers develop COPD, one could estimate that 150 million either have or will develop COPD—a number equivalent to the entire population of Russia.

In the United Kingdom during 1999/2000, there were 28 million days of certified incapacity due to diseases of the respiratory system [30]. Over 10% of all acute medical admissions to hospital are due to exacerbations of COPD, and with an average length of stay of 10 days, these represent some 2.8 million hospital-bed days annually in the UK.

Morbidity from COPD is not confined to wealthy countries. Smoking prevalence is high and rising in many poorer regions, with China in particular likely to see huge death rates from smoking-related disease in the coming decades. Many of the statistics available in the UK or in the US are not collated in such countries, so that the effect of COPD can only be estimated. Some estimates of the global incidence of COPD in such countries are detailed in Table 1.2 [28,29].

But morbidity is not the only concern. Airflow limitation is associated with premature death, and the World Health Organization statistics attribute 2.74 million deaths worldwide to COPD in the year 2000. It is the fourth commonest cause of death in the USA, China and United Kingdom. In the United States,

Table 1.2 Prevalence of chronic obstructive pulmonary disease in poorer countries in 1990. Adapted from [28].

	Male/ 1000	Female/ 1000
China	26.20	23.70
Former socialist economies	7.35	3.45
Established market economies	6.98	3.79
Sub-Saharan Africa	4.41	2.49
India	4.38	3.44
Latin America and Caribbean	3.36	2.72
Other Asian countries and islands	2.89	1.79
Middle Eastern crescent	2.69	2.83
World	9.34	7.33

112 000 people died of COPD in 1998, and in the United Kingdom 32 000 people died of COPD in 1999 [30]. The latter figure represents 5% of all deaths in the country.

Health expenditure

The financial cost of COPD is very large. In 1993, it was calculated that it created annual costs of US$ 23.9 billion to the US economy. This included US$ 14.7 billion for direct medical costs, with the remainder representing costs resulting from morbidity and premature mortality [31]. The direct health costs of COPD in the UK have been estimated at £846 million (US$ 1.4 billion), accounting for 11% of all expenditure on prescription medications [32]. Typically, the expenditure on COPD is disproportionately distributed, with approximately 10% of patients accounting for 75% of expenditure.

In the UK (figures adapted from [33]), a typical primary-care group caring for a population of 100 000 will have:

- 1000 diagnosed cases of COPD
- 238 annual admissions due to COPD
- 55 deaths from COPD annually (25% below aged 65)
- General practitioner consultations costing £44 000 annually
- Drug therapy costing £718 per patient per year (asthma £198).

The natural history of COPD

The studies discussed above show that death from COPD is most commonly the result of smoking—but what of the processes that lead to these deaths? It is clear that a healthy individual has to pass through mild, then moderate and then severe stages of COPD to reach the stage at which COPD may cause

death. But the processes by which this happens and the rate at which it develops require a different sort of study.

It is unclear what distinguishes individuals who develop clinically significant COPD from those who do not, despite a similar smoking history. In 1970, Thurlbeck showed that almost all smokers of more than 20 pack-years will have some emphysema detectable at post-mortem, although only about 15–20% had had any loss of lung function in life [34]. However, while an autopsy-based study can suggest likely causal factors and can add detail to information from longitudinal death certificate studies, it cannot detemine how the disease developed.

Cross-sectional studies of large populations can examine the manifestation of disease at stages of development in large numbers of people. The National Health and Nutrition Examination Survey (NHANES 3) [35] in the US questioned 34 000 people between 1988 and 1994. It reported that up to 24% of current smokers reported chronic cough. Airflow limitation (defined as $FEV_1/FVC < 70\%$) among white males was present in 14.2% of current smokers, 6.9% of ex-smokers and 3.3% of those who had never smoked. Similar proportions were found in white females, while the incidence of airflow obstruction was lower in the black population. Other studies have also suggested ethnic variations in COPD incidence, with 15% of active white cigarette smokers and 5% of active Asian cigarette smokers developing clinically significant COPD [36]. Because the disease develops over many years, it is inevitable that the majority of the most severe disease cases are seen in the elderly, but the statistics from North America indicate that 50% are below age 65 and 22% are below 55, with a mean age at diagnosis of 53 years.

The heterogeneity of the disease is illustrated by the fact than even 'light' smokers can develop severe emphysema. Thus, deaths before the age of 50 in individuals claiming to only have smoked five cigarettes daily (equating to approximately nine pack-years) do occur, although such cases are unusual. Clearly, factors other than cigarette smoke alone must be involved (see below), whether acting through a separate mechanism or in synergy with cigarette smoke. More than 40 years ago, the 'Dutch hypothesis' [37] suggested that the risks of developing COPD were related to environmental exposures in combination with the genetic make-up of the individual. This concept may still be true today.

Rate of decline in lung function

Typically, FEV_1 reaches a peak at around age 20–25 and then gradually declines with age by approximately 20–30 mL/year. Little, however, is known about the lung function of existing individuals with COPD in the decades be-

fore the disease becomes apparent. It seems logical that patients with COPD may have reached their low FEV_1 by one of the following three routes.

1 An accelerated decline in lung function. In their classic paper that followed 800 London office staff with serial measures of FEV_1 over 8 years, Fletcher *et al.* [38] demonstrated that there is a range of FEV_1 decline per year from almost nil to over 100 mL per year. They suggested that those with a rapid decline were susceptible smokers. The average decline was 18 mL greater in a smoker than in a non-smoker, i.e. 54 mL vs. 36 mL/year. Some non-smokers showed a rapid decline in function, indicating that there are factors other than smoking to be considered, but there were many more rapid decliners amongst the smokers and it is only those with very rapid declines (i.e. of 70–100 mL per year) who can lose the 3 L or more of lung function that places them in the FEV_1 1-litre category that is seen with hospital admissions of patients in their sixties.

The rate of decline is not linear over a lifetime. In the young, FEV_1 may rise between 20 and 25, followed by a relative plateau, before falling at an initially slow but accelerating rate over the years. Thus, the average rate of fall in FEV_1 described in a cohort may be describing an average between small gains in the youngest and large falls in older subjects. This makes it difficult to compare different studies. There are few longitudinal studies to compare with that of Fletcher *et al.*

The US Lung Health Study [39] observed 4000 patients with mild COPD over 5 years with and without an anticholinergic bronchodilator. While the drug had no effect on rate of loss of FEV_1, the authors did note as a secondary end point that the rate of loss of FEV_1 was significantly less in those who quit smoking compared to those who continued. They also observed that those with bronchial hyperreactivity had an increased rate of loss compared to those without. Thus, both exogenous and endogenous factors may affect the rate of decline. As a generalization, the average fall in FEV_1 in susceptible smokers seems to be in the order of 60 mL per year (i.e. twice that of non-smokers) [40].

The cross-sectional studies of smokers and non-smokers have also found a greater loss of lung function amongst smokers. Many have applied linear regression analysis to the data in an attempt to determine the additional aetiological factors responsible. This must be viewed with caution—firstly because the rate of loss is not uniform, and secondly because the starting point for different cohorts is unknown. An analysis of decline in a Dutch community study [41] reported that there was a significant effect depending on when a person was born. Men born a generation later tended to be 2 cm taller and to have 360 mL more FEV_1—presumably a reflection of better socio-economic condi-

tions and better conditions in childhood. Few studies include year of birth as a variable, and thus the cross-sectional analysis performed on the raw FEV_1 data would wrongly attribute this loss to another cause.

2 Premature decline in lung function. All parts of the human body deteriorate with increasing age, and the lung is no exception. Humans also age at different biological speeds, and perhaps one of the most promising areas for future research is the genetic basis of COPD. Accelerated loss of lung function in smokers with α1-antiprotease deficiency was first recognized by Laurell and Eriksson in 1963 [42]. This autosomal-recessive condition (ZZ phenotype) is found in 0.03% of the UK population. The lung is rendered susceptible to damage from neutrophil elastase, typically causing rapidly progressive emphysema in homozygotes who smoke. The heterozygotic state MZ is found in 3.9–14.2% of COPD patients, compared with 1.2–5.3% of controls (odds ratio 1.2–5.0). Other genetic predispositions are very likely to exist. Silverman *et al.* have reported a three-fold increased risk of developing COPD among first-degree relatives that is unrelated to α1-antiprotease status [43]. A family history of chronic bronchitis was shown by Carrozzi *et al.* to be associated with impaired FEV_1 in smokers [44]. Other postulated genetic mechanisms include polymorphisms in the tumour necrosis factor-α gene, the microsomal epoxide hydrolase gene and the glutathione S-transferase P1 gene.

3 Impaired lung growth and therefore a decrease in the peak lung function attained. Insults to the developing lung during childhood, including premature birth and infection, may have a role. In a study of 700 people with a mean age of 70, Shaheen *et al.* [45] reported that pneumonia before the age of two was associated with a mean reduction in FEV1 of 0.65 L in men, compared with controls. In women, the reduction was smaller and non-significant. In South Wales, children who had admissions for infections as children had an increased risk of dying 60 years later of COPD. Whether it is the infections themselves that are to blame or problems in utero is not known, but there is one study that suggests that poor nutrition in utero is a factor. Barker *et al.* noted that low birthweight was predictive of an increased risk of dying of COPD 60 years later [46].

It is of great concern therefore that women who smoke are known to have smaller babies with an increased incidence of prematurity—this may be placing their children at risk of COPD long before the children have a chance to make decisions for themselves.

The future of COPD

Despite the now well-documented health risks posed by smoking, the cigarette

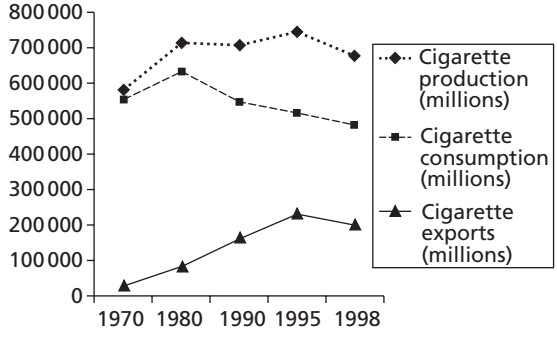

Fig. 1.3 Cigarette production and consumption in the USA, 1970–98. Source: World Health Organization.

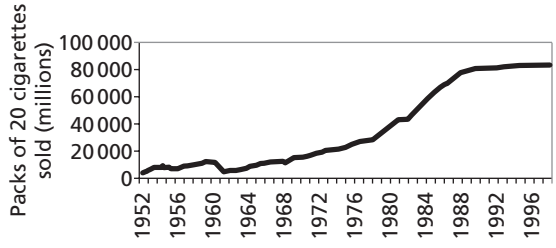

Fig. 1.4 Cigarette sales in China, 1952–98. Source: *China Statistical Year Book*, 1993, 1998; USDA, *China Tobacco Report*, 1999.

industry remains alive and well. Figure 1.3 outlines the current state of the industry in the United States. We are still surrounded by cigarette advertising. Governments have difficulty in reconciling the huge tax revenues they receive from cigarette sales and the outlay on health care that results from these sales. High-profile sports such as Formula One racing could not exist without cigarette advertising. The World Health Organization recently launched a counter-campaign with large posters in the style of 'Marlboro Man' proclaiming 'Bob—I've got emphysema'.

Even if the health message is beginning to have an impact in wealthy countries, cigarettes are heavily promoted in the Third World. The numbers of cigarette exports from the USA has doubled in the last 20 years. The WHO estimates that the number of smokers worldwide will increase from current numbers of 1.1 billion to 1.6 billion by 2025. Much of this growth will be in poorer countries. China in particular appears to have a grim future. Total cigarette consumption there has risen almost 10-fold in the last 50 years (Fig. 1.4), and the country will be reaping the whirlwind of subsequent respiratory disease for years to come.

The mortality figures discussed above describe a lower incidence of COPD in women than men. Recent large cross-sectional population-based studies in the US confirm this, but show a changing pattern emerging, with the prevalence of COPD almost equal in men and women [31,35]. This probably re-

flects the changing pattern of exposure to the most important risk factor, tobacco smoke.

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