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CHRONIC OBSTRUCTIVE PULMONARY DISEASE - A DISEASE OUT OF CONTROL*

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Classical descriptions of chronic bronchitis and emphysema were made in the early nineteenth century in western Europe by Badham[1] and Laennec[2] respectively. A British medical textbook of the 1860s describes the clinically familiar picture of chronic bronchitis advancing via repeated bronchial infection to end in oedematous heart failure, causing more than 5% of all deaths in middle and old age;[3] the condition was commonest among the poor and was attributed to 'bad living'. Despite the recognition of its high prevalence and mortality in Britain, 'chronic bronchitis and emphysema' attracted little attention from medical investigators until the 1950s when many sufferers died in the London smog disasters, prompting research into the condition and Parliament to pass the Clean Air Acts. During the same period spirometry was becoming widely used and airflow obstruction was recognised as a key factor in determining disability; pathological methods were developed for assessing emphysema. These developments led to the Ciba symposium of 1958[4] which suggested definitions of chronic bronchitis and emphysema, and new terminology incorporating the concept of airflow obstruction. Subsequent attempts to develop simple means to separate the contributory roles of alveolar destruction ('emphysema') and airway disease in the genesis of airflow obstruction failed, and many synonyms were proposed to describe 'obstructive lung disease'. The term 'chronic obstructive pulmonary disease' (COPD) has proved the winner and was coined as recently as 1964, although it has never completely displaced the older terminology or been adopted by patients.

AIRFLOW OBSTRUCTION

The original description of COPD emphasised the obstruction to airflow especially on expiration, its large irreversible component and tendency to progress. Surprisingly it did not clarify whether or not it included chronic asthma with impaired airway function, but in subsequent years most groups, such as the American Thoracic Society in 1987, and the European Respiratory Society in 1995, specifically excluded asthma, at least in concept.[5,6] Most textbooks have separate chapters for asthma and COPD, and these days separate clinical treatment guidelines have been developed suggesting this remains the conventional view, whatever overlap there may be between the two conditions. However, the 1995 American Thoracic Society guidelines specifically included asthma with an irreversible component within COPD.[7] The overlap with asthma remains an everyday clinical problem; 'limited' reversibility of airflow obstruction is present in almost all subjects with COPD but an acceptable boundary has not been defined. Those who support the distinction argue that the aetiology, natural history and prognosis of COPD and asthma are radically different, and that the present tendency to use similar treatments may not persist indefinitely. Obviously COPD is a remarkably vague concept; currently, abnormal airway function is the only requirement for inclusion

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and the diagnosis is one of exclusion - by convention, supracarinal airway obstruction is always excluded, and specific, better-defined causes of diffuse intrapulmonary airway obstruction such as cystic fibrosis, obstructive bronchiolitis due to chemicals, connective tissue disease, or reaction to lung or bone marrow transplant are usually not included.

PATHOGENESIS

The broad categories of established risk factors for COPD fall into the usual genetic and environmental categories, but because of the slow accumulation of pathological change in the lungs, increasing age is a very important factor. Inherited homozygous alpha$_1$-antitrypsin deficiency is the strongest single risk factor but accounts for less than 2% of severe COPD; the search for other genetic factors (other than milder forms of α_1-antitrypsin deficiency and cystic fibrosis) has hardly begun.[8] But environmental factors, related to air pollution, occupation or cigarette smoking play a very large part; currently, in the UK, active cigarette smoking is calculated to account for 78% of attributable risk in doctors, an economically favoured group.[9] Unlike lung cancer, the incidence of which clearly lagged behind the uptake of smoking by about 30 years, COPD predates cigarette smoking. Christie, one of the few investigators into emphysema in the 1930s and 1940s, did not mention the role of cigarette smoking in its pathogenesis.[10]

A fascinating analysis of long-term trends in mortality from COPD has been made by Marks and Burney (Figure 1).[11]

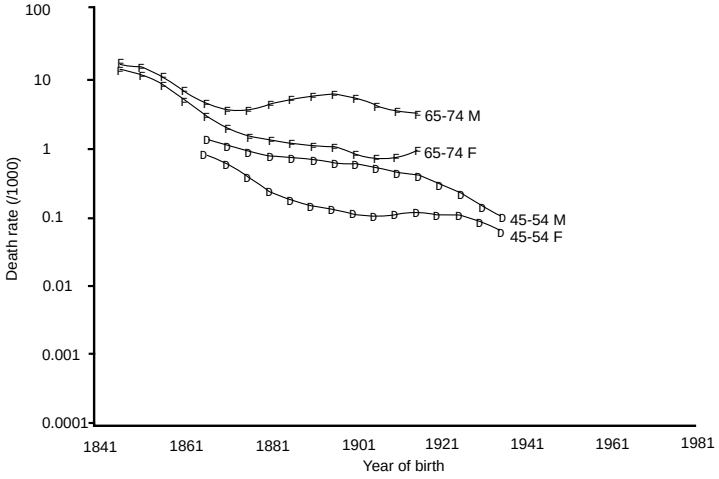

FIGURE 1

Reported deaths from COPD in Britain in men and women according to year of birth.[11] Figure taken from *Health of Adult Britain: 1841 to 1994 Part II* Office of National Statistics © Crown copyright 1998.

These show extremely high attributed death rates which are similar in men and women born 150 years ago. Mortality rates between men and women diverge at a time consistent with the taking up of cigarette smoking by men; declines in mortality in older women have slowed or even converted to a small rise more recently, consistent with the later adoption of cigarette smoking in women. Inevitably the data are imperfect, and in the days before routine chest radiography the diagnosis may have included patients with other lung diseases, notably bronchiectasis, tuberculosis and dust diseases, but the implication is clear and a warning against assuming the current dominant

influence of smoking in westernised countries applies worldwide. As already mentioned, COPD has always had a strong socio-economic bias and this persisted even in the years when cigarette smoking was relatively evenly distributed across economic strata. It is striking how many of the other known risk factors for COPD are related to poor socio-economic status (Table 1).

TABLE 1
Socio-economic factors increasing the risk of COPD.

Low birthweight[12]
Frequent childhood infections[12]
Damp housing
Diet low in dark fish,[13] fruit and antioxidants[14]
Cigarette smoking[15]
Dusty occupation[16]
Environmental pollution

In 1976 Fletcher published his pioneering study of the natural history of airflow obstruction in COPD,[17,18] which provided the conceptual basis for attempts to alter the prognosis (Figure 2).

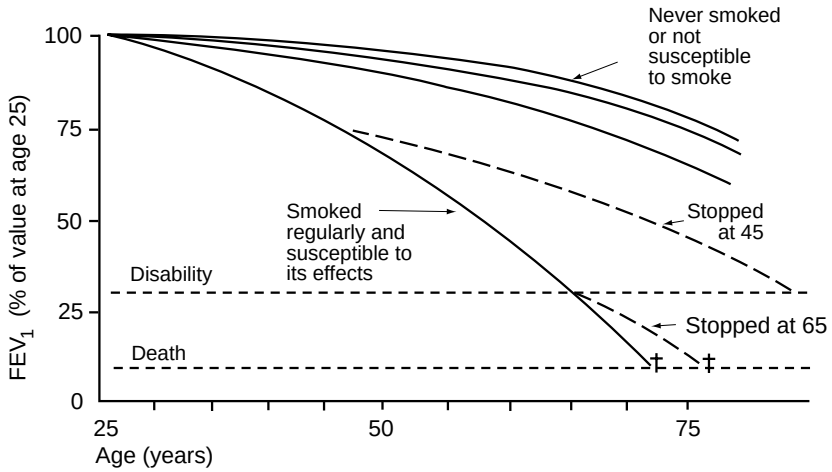

FIGURE 2
Natural history of COPD as proposed by Fletcher and Peto.[18] FEV_1 = forced expiratory volume in one second. (This figure was first published in the BMJ: Fletcher C, Peto R. The natural history of chronic airflow obstruction. BMJ 1977; 1:1645-8, and is reproduced by permission of the BMJ.)

The key features were the very slow progression of airflow obstruction even in susceptible individuals, the wide differences in susceptibility to developing obstruction between smokers, and the effects of quitting smoking in slowing the annual decline in FEV_1. All these features have been confirmed over the last 20 years. Commentators frequently deduce from Fletcher's study that only 15-20% of smokers are susceptible. In fact, as shown in the original study,[17] and confirmed and elaborated since,[19] there is

a wide and continuous distribution of FEV_1 among smokers. With increasing 'pack years', the decrease in FEV_1 below expected values increases progressively with a tail of fast decliners (Figure 3), so that the percentage of 'susceptible' smokers depends on where the boundary is chosen.

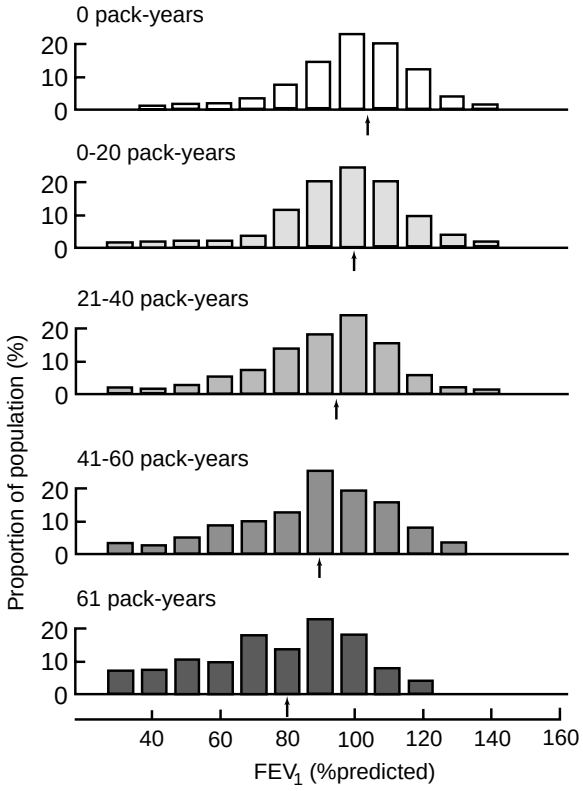

FIGURE 3

Effects of individual susceptibility and cumulative smoking history (expressed as packs/day years of smoking, pack-years) on FEV_1 expressed as a % of value for a healthy never smoker of same age. Although median FEV_1 (solid arrow) falls as cigarette consumption increases and a tail of low values develops, FEV_1 can be normal despite heavy cigarette consumption.[19] (Reproduced with permission from Burrows B, Knudson RJ, Cline MG, Lebowitz MD. Quantitative relationships between cigarette smoking and ventilatory function. *American Review of Respiratory Disease* 1977; 115:195-205.)

A major aim of current research is to identify the factors responsible for an individual smoker's susceptibility to developing airflow obstruction. Fletcher's study also attempted to study the role of three factors in progression: recurrent bronchopulmonary infections ('British hypothesis'), pre-existing atopy and airway hyper-responsiveness ('Dutch hypothesis')[20] and the presence of emphysema. To their surprise they could not show an effect of recurrent infections in accelerating decline in the relatively healthy smokers in their study. Indeed, they also showed that the presence of chronic mucus hyper-secretion had no effect even though this predisposed to recurrent infections. The latter finding was confirmed by subsequent UK studies,[21,22] but recently has been challenged by studies from Copenhagen.[23]

I suspect, but have no backing evidence, that recurrent infection may have been important historically but was declining in importance by the time their studies

commenced in the 1960s. Fletcher was also unable to confirm the 'Dutch' hypothesis although their investigations of this were much less comprehensive. Subsequently it was shown that increased responsiveness to inhaled histamine or methacholine is common in smokers with mild airflow obstruction,[24,25] but the suspicion developed that this was often an acquired responsiveness different from that associated with asthma and atopy, and it was uncertain whether it was a predictor of accelerated decline in FEV_1 or merely a consequence of airway narrowing. The large Lung Health Study (LHS) in North America, however, has clearly shown that the intensity of responsiveness to methacholine is related to the subsequent decline in FEV_1 in smokers[26] (Figure 4). Whether this fully confirms the 'Dutch hypothesis' is less clear. More than two-thirds of the smokers recruited responded to inhaled methacholine $\leq 25.mg.ml^{-1}$, but it is not known how much of the hyper-responsiveness predated smoking and was related to atopy and asthma, and how much was acquired following the development of smoking-related changes in the airways.

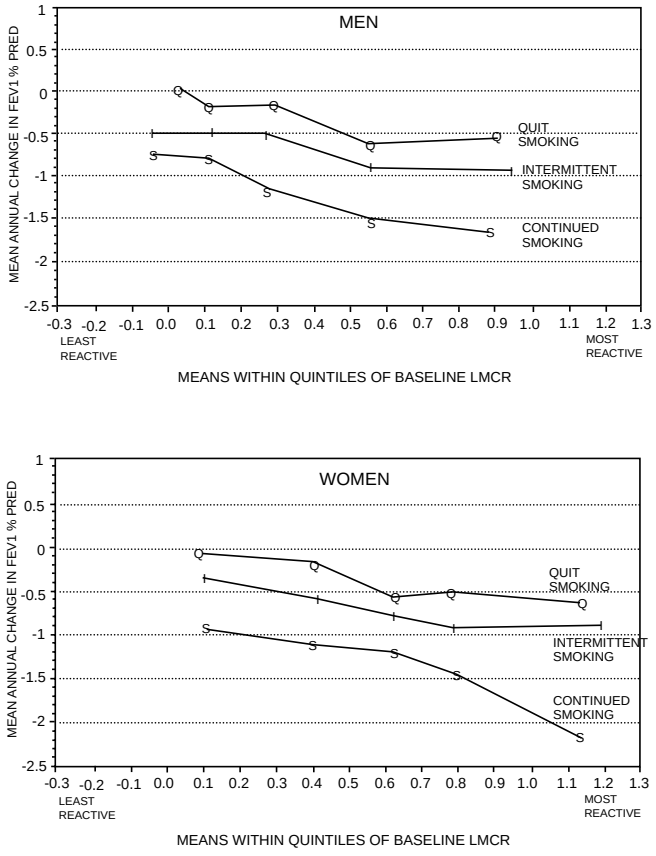

FIGURE 4

Interactions between methacholine reactivity (LMCR), annual decline in FEV_1 (% predicted) according to gender and smoking habit during four year follow-up. Subjects with the most reactive airways showed the fastest decline in FEV_1 if they continued to smoke.[26] (Reproduced with permission from Tashkin DP, Altose MD, Connett JE *et al*., for the Lung Health Study Research Group. Methacholine reactivity predicts changes in lung function over time in smokers with early chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1996; 153:1802-11.)

Before the use of spirometry became routine, when breathlessness developed in COPD it was attributed to the development of emphysema.[10] Research in Edinburgh - originally led by the late Professor David Flenley - has generally continued to support an important role for parenchymal destruction, although emphasis has shifted from the gross areas of macroscopic destruction - which in general are not ventilated or perfused - to the more subtle accompanying microscopic changes in lung parenchyma which is still functional.[27] The importance of emphysema in determining disability is confirmed by the natural history of α_1-antitrypsin deficiency. Therefore, it may seem surprising that there is still considerable controversy about emphysema[28,29] with sophisticated proponents of the opinion (based on morphology in smokers submitted to lung resection for lung cancer) that it is of little importance in determining the impairment of FEV_1. The problem has been to identify the subtler forms of emphysema in life. While imaging by CT scans is a great improvement on radiography, current techniques resemble the visual scoring systems of pathologists, in emphasising the grossly abnormal, non-functioning areas.

We studied two small groups of male smokers who were first seen with moderate airflow obstruction and then followed for a mean of 19 years, sufficient to establish reliable rates of decline in FEV_1 in each individual. The men were divided into two groups with similar initial FEV_1 (mean 56% predicted) according to whether the CO transfer coefficient (TLco/VA), which is an established surrogate for microscopic emphysema, was normal or abnormal. The men with abnormal CO transfer coefficient showed a subsequent decline in FEV_1 of 1.8% of the predicted value per year; the men who started with a normal CO transfer coefficient showed a smaller decline of 1.1% of predicted FEV_1 per year (Figure 5).

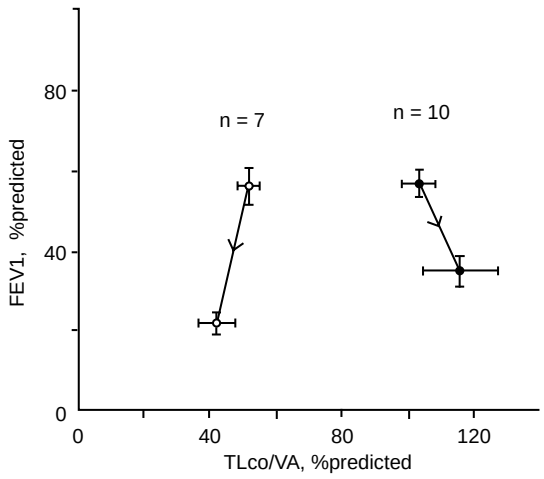

FIGURE 5

Influence of carbon monoxide transfer coefficient (T_{LCO}/V_A) on mean decline in FEV_1 (% predicted) over a mean of 19 years in middle-aged male smokers with COPD. At start of follow-up, men with reduced and with normal (>80% predicted) values of T_{LCO}/V_A had similar reduction in FEV_1. Loss of FEV_1 during follow-up was greater in the men with initially reduced T_{LCO}/V_A (p0.007). During follow-up, T_{LCO}/V_A remained normal in the men with initially normal T_{LCO}/V_A.

INTERVENTION STRATEGY

Given the natural history and the limited reversibility of airflow obstruction in COPD it is surprising that large-scale, long-term intervention studies on the lines of those for hypertension have only been developed in the 1990s. Clearly the most important treatment is cessation of cigarette smoking; only this, if achieved in middle life, can restore a normal life prognosis;[9] whereas treatments directed at COPD itself leave the increased risk of lung cancer and vascular disease untouched. The Lung Health Study (LHS) provides the largest and most encouraging results;[30] the group targeted for smoking cessation, which used nicotine-gum replacement together with extensive and expensive counselling, had a 22% sustained quit rate after five years compared to 5% in those given 'usual care'. The long-term effect on FEV_1 was dramatic (Figure 6), with a small improvement in the first year after quitting (mean +57ml) and thereafter an annual decline in FEV_1, in the range of 34-43 ml/year, which approaches values in those who have never smoked, confirming the Fletcher model of natural history.[18] There is undue pessimism about the role of health professionals in encouraging smoking cessation even although it is true that the 40% of smokers who have quit by the age of 60 years in the UK have largely achieved this without medical assistance. Perhaps, despite recognition of the addictiveness of nicotine, there has been some reluctance to treat this with nicotine replacement (gum, patches or sprays) on the model of methadone for opiate addiction, although there is no doubt that replacement works.[31] So it is

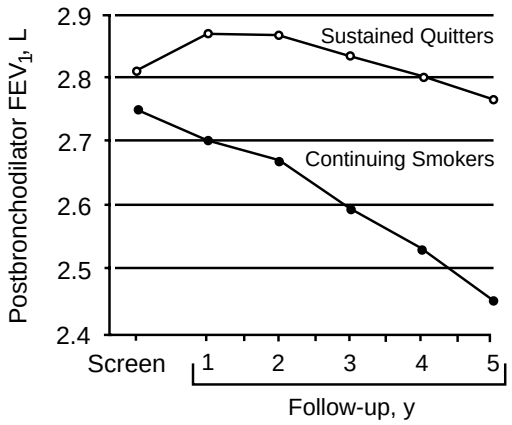

FIGURE 6

Effect of quitting smoking on post-bronchodilator FEV_1 in the Lung Health Study. There is a small rise in FEV_1 in the first year after quitting, but the important change is the subsequent slowing of decline in FEV_1.[30] (Reproduced with permission from Anthonisen NR, Connett JE, Kiley JP *et al.* Effects of smoking intervention and the use of an inhaled anti-cholinergic bronchodilator on the rate of decline of FEV_1. The Lung Health Study. *Journal of the American Medical Association* 1994; 272:1497-505.)

encouraging that a 23% quit-rate at one year (compared to 12% on placebo) has been obtained with the anti-depressant bupropion[32] (in smokers who show no sign of depression); this should stimulate much more work on other pharmacological aids to breaking nicotine addiction. The downside of the overall trend to reduce smoking in the UK is that this has been achieved largely by reductions among the more prosperous; in the most deprived members of the population the same high proportion (about 75%) smoked in 1973 and 1992 (Figure 7).[15]

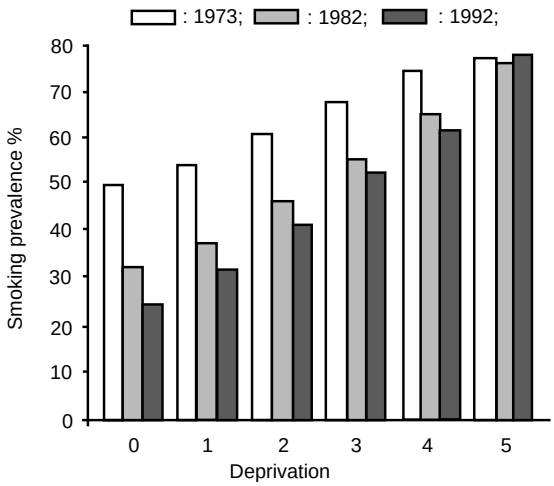

FIGURE 7
Changes in the prevalence of cigarette smoking 1973-1992 in UK males according to a six-point scale of socio-economic deprivation (0 affluent, 5 most deprived). While cigarette-smoking prevalence has halved in the affluent, it remains near 75% in the most deprived. OPCS data analysed by Jarvis.[15] (Reproduced with permission from Jarvis MJ. Smoking cessation. *European Respiratory Review* 1997; 7(45):230-4.)

Two other preventive treatments have been studied in large-scale trials: inhaled muscarinic antagonists and inhaled corticosteroids (ICS). Ipratropium, a muscarinic antagonist, was used in one arm of the LHS;[30] it produced a small immediate benefit but no additional long-term benefit. Ipratropium has a rather small effect in attenuating the enhanced airway responsiveness of smokers and conceivably a ß-adrenergic agonist might have been more effective in this regard; so far the longest trials of a long-acting ß-agonist in COPD are for six months. The use of corticosteroids is also based on their success in asthma. Assessment is bedevilled by the clinical overlap with asthma which may account for some of the responses observed in meta-analysis.[33] There have been only two published controlled studies of the treatment of acute exacerbations of COPD, one of intravenous,[34] and the second of oral, corticosteroids.[35] Both studies show that improvement is faster when steroids are used. Despite the widespread use of ICS in many westernised countries, there is insufficient evidence to support their long-term use in COPD, although several studies with differing limitations all suggest some benefit.[36] Perhaps the most familiar is the study of Dompeling[37] but this showed most improvement in pre-bronchodilator rather than post-bronchodilator FEV_1.

Because of this lack, there are now four long-term (3-4.5 years) studies of ICS due to be completed by the year 2000 (Table 2). The first of these to be completed, Euroscop, has recently reported an initial analysis. In this trial, 1,277 middle-aged smokers (mean age 52.5 years with a 39 'pack-year' history and mean current smoking of 22 cigarettes a day) with mild airflow obstruction (mean FEV_1 77% predicted, FEV_1/VC 62%) were randomised to receive either budesonide 400 mcg twice a day or placebo over three years. The primary end-point was annual decline in post-bronchodilator FEV_1 over the treatment period. Smokers with a history of asthma or a greater than 10% of predicted FEV_1 improvement after an inhaled ß-agonist were excluded. In men there was a small initial improvement in FEV_1 on ICS in the first

three months but no significant effect on decline in the subsequent 33 months (annual decline -60 ml/yr on ICS, -68 ml/yr on placebo). These are fast rates of decline. In women, who comprised 28% of the total sample and had similar impairment of baseline FEV_1, there was a larger slowing of annual decline in FEV_1 on ICS (-56 ml/yr) compared to placebo (-71 ml/yr). The differences between men and women were not anticipated and are unexplained; evidence of atopy was considerably less frequent in women than in the men in the study. Clearly these results do not provide definitive guidance for long-term treatment with ICS in COPD and it is fortunate that further studies in similar groups (from Copenhagen and North America) and in a more severely obstructed group (Isolde trial in Britain) will be available shortly.

TABLE 2
Long-term treatment of COPD.

Medical	Outcome
Long-term home O_2 for 15 or more hours per day (North American,[42] British MRC,[43] Swedish[44] and Polish[45] studies)	Limited survival benefit (see text)
Inhaled muscarinic antagonists (Lung Health Study North America):[30] 5-year follow-up	No long-term improvement in annual decline in FEV_1
Inhaled corticosteroids (Euroscop, Isolde, Copenhagen, Lung Health Study - Part 2): 3-year follow-up	Results expected 1998-9
Surgical	
Bullectomy	No formal studies
Lung transplant (single or double)	USA survival registry[46]
Lung volume reduction surgery	North American trial, results in 2002

Both bronchodilator and ICS treatment are based on their success in asthma where airway inflammation is the target. There are differences between the airway inflammation in asthma and smokers - although it is proving an over-simplification to characterise them solely as eosinophilic and neutrophilic respectively[38,39] - and perhaps different types of anti-inflammatory agents are required in COPD. Although emphysema is itself the end-result of an inflammatory process, there is no speculation that this may be attenuated by ICS. The only current medical treatment aimed specifically at the alveolar component of disease is intravenous α_1-antitrypsin deficiency replacement therapy in patients with this severe deficiency;[40] uncontrolled studies are taking place in North America but the results of a controlled trial in Denmark and the Netherlands should be available before 2000. In the future we can expect trials of antioxidant and anti-neutrophil elastase therapy, and perhaps manipulation of cytokines.

I have deliberately concentrated on attempts to modify the natural history of COPD before gross disability is reached; but the supportive role of rehabilitation, nutritional support and indeed bronchodilator treatment is certainly very important in advanced disease. As graphically pointed out in the recent British Thoracic Society guidelines for COPD,[41] the worse the disability, the more types of treatment are applied. For advanced disease there are medical and surgical options which may genuinely improve prognosis, and perhaps also quality of life (Table 2).

The first long-term trials (Table 2) in COPD were of home O_2 by the National Institute of Health in North America[42] and by the Medical Research Council in the UK[43] given to patients whose steady-state arterial Po_2 was less than 8kPa (60mm Hg). The extension of life shown by these studies has been confirmed by a Swedish study.[44] Giving long-term O_2 to a slightly less hypoxic group in Poland[45] provided no benefit so that on present evidence there is no role for introduction of this treatment earlier in the natural history. Surgical treatment of large bullae has played a small part in the management of COPD for many years, while the introduction of lung transplantation,[46] initially of both lungs, but now typically of single lungs, has had some success in younger patients, including those with α_1-antitrypsin deficiency. Lung volume reduction surgery (LVRS) potentially offers a more widely applicable procedure for producing a remission in the natural history, without the complications of immunosuppression or the constraints of donor organ supply. The short-term results in the best hands are similar to single lung transplantation with a very useful improvement in FEV_1;[47] if these results can be replicated by others and are sustained for three to five years a useful advance will have been achieved in a relatively unexpected way.

Perhaps we are unimaginative in assuming alveolar destruction can only be treated by transplantation or by removing the most abnormal areas (LVRS) and allowing the remaining lung to expand and function better. A remarkable experiment has been reported recently by Massaro from George Washington University[48] in which emphysema was induced in adult rats by a single application of intratracheal elastase. A month later, a course of intraperitoneal retinoic acid, a growth factor known to regulate alveolisation in growing rats, was given and this resulted in the apparent restoration of nearly normal alveolar numbers, size and surface area. While there is an enormous gap between this experiment and its application to human disease, the idea that alveolar remodelling may be possible far overshadows the current interest in minor 'remodelling' of airway structure that may be possible in asthma.

CHANGES IN MORTALITY

A further cause for optimism in the UK is that incidence of deaths from COPD, at least in males, has been slowly dropping for the last 20 years; in women there is a slow rise so that it is now about one third of the male mortality, probably due, as already discussed, to the drastic increases in cigarette smoking in women following the Second World War. A very recent report suggests that death rates from COPD in the USA have stabilised in men, although they continue to rise in women.[49] According to WHO, in 1984, the British Isles and Eastern Europe had the highest recorded death rates from COPD, while low rates were reported from Norway, France, Greece and Japan. Indeed the countries with high and low mortality rates with COPD show rather similar trends in ischaemic heart disease, with strikingly low mortality in Greece, Spain, France and Japan. In ischaemic heart disease, where the role of cigarette smoking is relatively smaller, this has led to great interest in the role of diet and alcohol. There has been little research in these areas in COPD, yet, as emphasised above, factors other than smoking were paramount in COPD in the UK a century or more ago. Of course speculation has to be restrained, because death rates may be artificially low due to diagnostic habit and fashion, as they probably were in the USA until the last 25 years, and a lack of correspondence with current smoking habits may reflect less 'maturity' of the smoking epidemic. Thus Japan and Greece, where current smoking is very high yet reported COPD deaths are low, had very low estimated smoking rates in 1945 (Figure 8).[50]

Recently there has been enormous growth in cigarette consumption worldwide fuelled by its adoption in China, Indonesia, Brazil, India and other centres of enormous populations where there are few data on causes of mortality. Murray and Lopez have estimated that in 1990 there were over two million deaths worldwide from COPD;[51,52] that is about 6% of all deaths which is similar to Britain in the 1860s, and about the same number as were due to tuberculosis. They predict that COPD deaths will double over the next 30 years. Some of the increase occurs because reductions in childhood mortality due to infections and other causes allow more persons to survive into middle age, and some also reflects the population explosion over recent decades. The proportion of the current high mortality in these heavily-populated countries related to cigarette smoking is uncertain, because the smoking epidemic there has not matured. In China, which now accounts for about one third of all cigarette consumption worldwide, daily

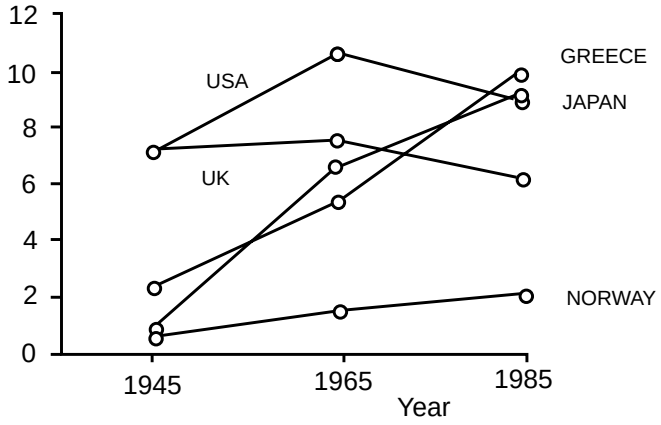

FIGURE 8
Cigarettes/day per adult (male and female) 1945-1985 in UK and USA with high COPD mortality in 1984 and in three countries, Norway, Greece and Japan with low reported COPD mortality in 1984.[53] (Reproduced with permission. Data from Wald NJ, Hackshaw AK. Cigarette smoking: an epidemiological overview. *Br Med Bull* 1996; 52:3-11.)

consumption was estimated to be only about two cigarettes per adult as recently as 1970, while the estimate is 5.5 cigarettes/day in 1990-1992[53] (compare Figure 8). The current aetiology of COPD in these countries probably has similarities to that in Britain before cigarette smoking became dominant, with a strong component from the adverse socio-economic factors listed in Table 1 and perhaps from bronchiectasis, together with such local factors as exposure, in confined quarters, to fumes from domestic cooking and heating. Simple data on mortality rates according to age, gender, occupation and residence would provide important clues to aetiology.

The recent addition of cigarette smoking to the risk factors for COPD within the less prosperous communities in the world is alarming, given our knowledge of how long it takes for improved social conditions, clean air and decreased smoking to be manifest in reduced COPD mortality. Fortunately there are signs that the recent period of relative inattention to the prevention and treatment of COPD is coming to an end; but while awareness of the problem is the first essential, remedies for early or established disease still have to be found, while the worldwide adoption of cigarette smoking proceeds at a much faster pace.

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