

Occupation and chronic obstructive pulmonary disease (COPD)

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Historical background and current controversies

Chronic obstructive pulmonary disease (COPD) is defined by the presence of a diffuse reduction in airway calibre relative to the degree of lung inflation which cannot be reversed by treatment. The "fixed" nature of this obstruction is the cardinal feature of COPD. Obstruction which responds partially but not fully to treatment implies that there may be an asthmatic (or acute bronchitic) component to the disorder, of which the fixed component alone should be identified as COPD. Its importance lies with its tendency to progress and to cause a disabling, even life threatening, loss of lung function.

EXPERIENCE WITH COTTON DUST

That COPD might arise as a consequence of the occupational environment is a matter of evolving interest and importance, and not a little controversy. The possibility of COPD of occupational origin, unassociated with complicated pneumoconiosis, first gained widespread acceptance as recently as the 1960s as a result of a series of publications of investigations in cotton workers by Schilling and Bouhuys and their colleagues.^{1,2} They suggested that byssinosis could be usefully classified into three distinct clinical grades. Workers who developed chest tightness and breathing difficulty only on the first working day of each week were said to have byssinosis grade 1; those who had similar symptoms on additional working days of the week, but who recovered fully away from the workplace, were said to have byssinosis grade 2; and those who had symptoms of persisting respiratory disability were said to have byssinosis grade 3. Physiological studies indicated that byssinosis grades 1 and 2 were associated with reversible airways obstruction, while byssinosis grade 3 was associated with fixed airways obstruction. It was assumed that affected workers followed an orderly progression through these escalating grades. Cotton dust was consequently a potential cause of COPD, and byssinosis grade 3 was occupational COPD.

These were landmark publications, and they provide a convenient and highly relevant historical focus from which to review the

claims and controversies which have followed. Particular attention may be drawn to three evolving issues.

The first is that many (perhaps most) authorities would now regard byssinosis grades 1 and 2 as occupational asthma attributable to cotton dust. The physiological correlates (acute but reversible episodes of airway obstruction) are diagnostic of asthma, and the curious work-related periodicity of the symptoms (which had been considered particularly characteristic of byssinosis) has since been observed with many other types of occupational asthma. As with active asthma of any aetiology, airway hyperresponsiveness can be demonstrated to a variety of bronchoconstrictor agents at times when byssinosis grade 1 or grade 2 is active. If, then, byssinosis grades 1 and 2 are examples of occupational asthma, is occupational COPD (byssinosis grade 3) a consequence of occupational asthma?

The relation of byssinosis grade 3 to byssinosis grades 1 and 2 may be looked at from a different viewpoint, and this constitutes the second issue. The investigations which led to the Schilling grading classification were cross sectional not longitudinal in structure, and this may pose problems over assumptions of causality. Grade 1 byssinosis was not, in fact, observed to progress to grade 3 byssinosis, and so it is entirely conceivable that byssinosis grade 3 could be a fundamentally different disorder from byssinosis grades 1 and 2, albeit one which is also induced by occupational exposure to cotton dust. Could byssinosis grade 3 after all be the prototype for occupational COPD, even in the absence of occupational asthma? If so, is it likely that cotton dust alone among occupational agents would have this effect on the airways?

The third issue highlights the most important problem in assessing occupational COPD in the 1990s. Most of the cotton workers of the 1960s had been heavy cigarette smokers for many years, and there are now doubts whether the confounding effect of this on the development of COPD (which was barely recognised in the 1960s) was adequately taken into account.³ Thus, the conclusion that occupational exposure to cotton dust causes COPD appears less secure, and the confounding role

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of cigarette smoking has come to lie at the centre of current controversies.

ROLE OF CIGARETTE SMOKING

The relative effects of smoking and occupation on COPD can only be assessed from meticulous epidemiological investigations where study populations include smokers and non-smokers, and workers with and without the relevant occupational exposure. There may be great difficulty in finding such a balanced population, and there may be great difficulty in avoiding bias in the exposure histories which are obtained. Most investigations of occupationally induced disease lead eventually to anxiety, anger, and claims for compensation in at least some of the study population; and once these arise memory tends to become unduly stimulated for the noxious nature of former workplace environments but paradoxically suppressed for estimates of former smoking consumption. An important additional tendency is for those who are best able to tolerate the heaviest consumption levels of tobacco to take on jobs with the most noxious occupational exposures, and vice versa. Conversely, workers may leave employment causing survival bias if they are less able to tolerate such exposures, or if the work is physically too demanding and they develop coincidentally smoking-induced COPD. These influences on worker selection make it particularly difficult to conduct epidemiological studies among occupational populations, and to allow fully for the contributory effects to COPD from smoking.

The greatest risk for the development of COPD in the population at large is undoubtedly posed by cigarette smoking, and cigarette smoking remains disproportionately common among the very working populations most suspected of developing COPD from occupational exposures. Cigarette smoking therefore provides a major potential source of confounding in investigations which seek to identify excessive longitudinal losses in ventilatory function in working populations. Thus investigators, regulating bodies, employers, and employees may be hard pressed to recognise when "excessive" loss is truly excessive once the idiosyncratic effect of cigarette smoking is taken into account. Full smoking histories are consequently essential in research, and should include a quantitative measure of cumulative consumption.

The issue is unduly complicated because only a minority of smokers (15–20%) actually develop COPD (hence the idiosyncrasy), and because COPD in never smokers is extremely rare even in working populations with regular exposure to noxious occupational agents. This assumes the workers do not suffer from asthma. There is evidence, however, that when smokers additionally work with noxious respirable agents, COPD occurs with unusual frequency and/or severity. This implies an adverse interaction between smoking and the working environment. Recognising such an interaction – that is, the occurrence of COPD in smokers in excess of that to be expected

through smoking alone and through the occupational environment alone – poses great difficulty for the investigator, largely because doubts over the accuracy of past smoking histories may invalidate, or at least weaken, the statistical analyses involved. There may be strong justification for such doubts. One study concluded that up to 7% of smokers and former smokers had described themselves incorrectly as never smokers.⁴

ROLE OF ASTHMA

There are two further sources of confusion. Firstly, there is the realisation that fixed airflow limitation may also arise as a consequence of long standing asthma, and secondly there is the knowledge that regular occupational exposure to respirable irritants commonly leads to mucus hypersecretion and to chronic productive cough (that is, chronic bronchitis) which, in an occupational setting, is often termed "industrial bronchitis".⁵ When chronic bronchitis develops coincidentally alongside asthma, the emergence of obstructive symptoms (wheeze, chest tightness, undue shortness of breath) is often attributed, not unreasonably, to COPD and to the cause of the productive cough. Chronic bronchitis does not itself cause airway obstruction, however, and so obstruction when it does occur with chronic bronchitis has to be attributed to other pathophysiological processes – that is, to asthma when obstruction is reversible, to COPD when obstruction is fixed, or to both when there are both reversible and fixed components.⁶

The possible presence of coincidental "cryptogenic" asthma (an increasingly common disease at all ages in the population at large) may consequently simulate occupational COPD, just as asthma in smokers in a chest clinic setting may simulate smoking induced COPD. This is particularly likely if "industrial bronchitis" (or "smokers' bronchitis") coexists. Cryptogenic asthma may also simulate occupational asthma because it is likely to worsen transiently in the workplace if there are respirable irritants, and in some occupational settings such as cotton mills the development of occupational asthma is as plausible as the development of occupational COPD. If it is true that there are substantial differences in the prevalence of cryptogenic asthma from region to region, from population to population, and from birth cohort to birth cohort, as is now suggested, formidable difficulties must be expected in allowing for this if a given working population appears to show an excess of COPD.

CURRENT CONTROVERSIES

The experience with the cotton industry consequently provides invaluable lessons for the assessment of occupational COPD, and for evaluating today's inevitable controversies. In essence they centre on whether an excess of COPD in a given working population can be attributed to smoking or cryptogenic asthma rather than to the working environment; and whether, if the workplace is responsible,

COPD arises independently of occupational asthma or as a direct consequence of it – or both.

Pathophysiology

Fixed airway obstruction may be a consequence of either intrinsic inflammatory/fibrotic disease of the intrathoracic airways, or of destructive disease of the parenchyma and interstitium of the lung (emphysema). With emphysema, airway obstruction and air trapping are associated additionally with impairment of gas transfer and loss of elastic recoil. It is this loss of elastic support to the smaller airways, whose walls are not supported by cartilage, which leads to airway collapse and obstruction. This mechanism is seen in occupational COPD attributable to complicated pneumoconiosis. With the exception of cadmium induced emphysema, it appears to be an unusual mechanism for other types of COPD attributed to occupation, though it should be said that histological research into the matter is very limited.

With most types of COPD attributed to occupation lung function tests reveal no significant impairment of gas transfer compared with control data, implying that intrinsic disease of the airways is a more probable mechanism than emphysema. Extensive work with COPD attributable to smoking has suggested that the smaller unsupported airways again provide the most probable primary site for the obstruction to airflow, there being a mixed pathological picture of inflammation and fibrosis chiefly in and around the bronchioles. The disorder is more accurately described as a bronchiolitis or bronchiolitis obliterans than as a chronic obstructive bronchitis. However, bronchial inflammation is often seen, especially when there is chronic productive cough. This is best regarded as an independent phenomenon, unrelated to airflow limitation.⁶ The mechanism and primary site underlying COPD attributable to chronic asthma remain to be clarified, and so there is much to be said for using the diagnostic term COPD in a purely functional sense – that is, to indicate fixed airway obstruction attributable to a variety of possible pathological processes.

Recognition of excessive longitudinal decline in ventilatory function

An epidemiological approach to estimate the rate of decline in ventilatory function offers the only practical means of identifying occupational causes of COPD in living populations. If the occupational contribution to COPD in a given workforce is relatively small, and if COPD itself is uncommon (often the case in populations subjected to “healthy worker” and “survivor” biases), the investigation of large numbers of subjects will be necessary if an occupational effect is to be shown convincingly. Such investigations are necessarily time consuming and expensive. They must also be complex if modern statistical analyses using multiple regression techniques are to take adequate account of all the various factors which may independently influence the measured end point – that is, the level of ventilatory

function – or interact with environmental exposures of relevance. Otherwise there is the risk that these factors – for example, age, height, race, sex, changing body mass, smoking, viral infections, atopy, airway responsiveness – might be distributed unevenly between subgroups of the study population which differ also in the levels of exposure to the agent suspected of inducing COPD. If such unevenness occurs, it might explain or exaggerate significant differences which appear otherwise to be a consequence of the occupational agent. Conversely, it might mask a true occupational effect in investigations which appear to give “negative” results. The potential for such confounding is critical to the planning and analysis of investigations of this type.

From a series of pioneering epidemiological investigations of COPD attributable to cigarette smoking, Fletcher and colleagues showed during the 1960s that the majority of smokers experienced no adverse effect on ventilatory function.⁷ In the minority who were adversely affected, a steady excess annual decline in forced expiratory volume in one second (FEV_1) was noted from study year to study year, the magnitude of which (FEV_1 slope) was related to the level of smoking consumption. The mean annual decline among symptomatic smokers was approximately twice that of the non-smokers. The excess decline could be detected after as little as five years of regular smoking, and its cumulative dose related effect was readily quantified by the degree of fixed airway obstruction evident at the time of the initial measurement of ventilatory function. The excess rate of decline ceased when smokers gave up the habit, but the damage already sustained was permanent. A similar natural history is to be expected from any cause of COPD, though there will be much variability from individual to individual, and in some of those affected many exposure years will pass before the disease becomes evident.

A cohort of the men investigated by Fletcher and colleagues (male transport workers in London) were followed longitudinally so that the actual annual changes in FEV_1 could be measured. The mean decline in FEV_1 (when standardised for height) was about 30 ml/year. The actual rates of decline were related to height, smoking, and symptoms and appeared to increase a little with increasing age.

DISCREPANCY BETWEEN CROSS SECTIONAL AND LONGITUDINAL DATA

When data from the transport workers were analysed from the initial cross sectional study, regression of FEV_1 on age suggested a rather greater mean annual decline of 45 ml/year. That is to say, the differences in FEV_1 between the youngest and oldest participants suggested that the mean annual decline in FEV_1 , after allowing for differences in height, was about 1.5 times the rate actually measured during the subsequent longitudinal phase of the investigation. The discrepancy was not readily explained at the time, but has since been recognised by a number of investigators. Those from Tulane University, New Orleans pro-

Table 1 Age related changes in ventilatory function

Cross sectional regressions of mean FEV ₁ against age:	
1974	- 42.6 ml/year
1975	- 47.2
1976	- 44.9
1977	- 50.5
1979	- 44.6
Mean of longitudinal regressions of FEV ₁ against time:	
1974-9 (5 years)	- 12.4 ml/year
1975-9 (4 years)	- 17.4

The investigation involved a 'normal' population of 52 adult caucasian men aged 30-58 years of whom nine were current smokers, 16 former smokers, and 27 never smokers. There were no relevant occupational exposures. Three subjects reported chronic cough, and seven undue breathlessness. The initial 1974 measurements were slightly less than those of 1975, possibly reflecting inexperience with spirometric manoeuvres, and so the period 1975-9 may provide a more accurate estimate of longitudinal change than 1974-9. Reproduced from Glindmeyer *et al*⁶ with permission.

duced similar mean figures for FEV₁ from a five year longitudinal study of a normal population of men aged 30-58 years.⁸ The cross sectional data from each survey year indicated a mean decline of 40-50 ml/year with increasing age, once the effect of height was taken into account, while the mean of the actual longitudinal declines measured in each participant was of the order of 15-20 ml/year (table 1).

Thus, cross sectional data cannot be extrapolated to predict longitudinal change with any precision, and should not be compared directly with longitudinal data from other investigations. The discrepancy probably arises because subjects at the younger end of an age spectrum of, say, 20-60 years from a current cross sectional investigation do not necessarily have the same mean FEV₁ as did those at the older end of the spectrum some 40 years earlier when they were of a similar young age. In fact, the currently young subjects are likely to have higher values of FEV₁ at a standardised young age, partly because they have larger lungs and partly because they are less likely to have sustained respiratory diseases such as tuberculosis and bronchiectasis which impair ventilatory function. The difference in FEV₁ between younger and older subjects at the time of a cross sectional study therefore exaggerates the true declines which were experienced by the older subjects during the preceding years. Furthermore, the currently young subjects are likely to encounter less lung damaging insults as they age to 60 years than those already aged 60. Thus, mean longitudinal decline in lung function in populations is not wholly a consequence of increasing age, but depends also on the cumulative burden of damaging pulmonary insults during the ageing period. This is illustrated in fig 1, which offers an explanation for the discrepant results from cross sectional investigation.

By using study subjects as their own "controls" and avoiding the problems which arise from mismatching in cross sectional studies - that is, by eliminating between worker variability - longitudinal studies are inherently more robust.⁹ They may be unduly vulnerable to diminishing participation rates, however, and this may introduce new risks of bias.

OTHER FACTORS OF POSSIBLE RELEVANCE

The study of London transport workers usefully showed that, although intercurrent episodes of respiratory tract viral infection - that is, episodes of acute bronchitis and exacerbations of COPD - caused significant reductions in ventilatory function, the effect was only temporary. Full recovery to former levels of ventilatory function were noted within a few weeks, after which the rate of longitudinal decline returned to its usual level. Repeated viral infections do not therefore influence the assessment of occupational COPD from either cross sectional or longitudinal studies, provided there are no acute infections at the time of study. Whether intercurrent episodes of acute bronchitis following brief exposure to toxic chemicals at work, such as gassing accidents, will prove to be equally benign is currently a matter of much speculation, concern, and ongoing investigation. Major accidents which produce life threatening pulmonary toxicity are recognised to cause bronchiolitis obliterans in a small proportion of survivors, though most appear to recover fully. A few develop asthma which may persist indefinitely and so pose a further pathway for the emergence of COPD. This complication of acute pulmonary toxicity has been termed "reactive airways dysfunction syndrome" (RADS) in North America.¹⁰ The designation is possibly unhelpful since it suggests incorrectly that RADS is a disorder which is distinct from asthma.

Age, height, race and sex, however, all exert important influences on the measurement of ventilatory function, and it has recently been suggested that air pollution and increasing body mass during the course of a longitudinal investigation may also exert a potentially important (adverse) effect. The wide range of apparent individual susceptibility to COPD suggests the possible dependence on genetic factors, and there is supportive evidence for this especially from twin studies.^{11 12} Genetically determined atopy has not generally been found to influence COPD, but this depends on how COPD is defined and how vigorously an asthmatic contribution is excluded.

A preliminary analysis of the American multicentre Lung Health Study suggests that

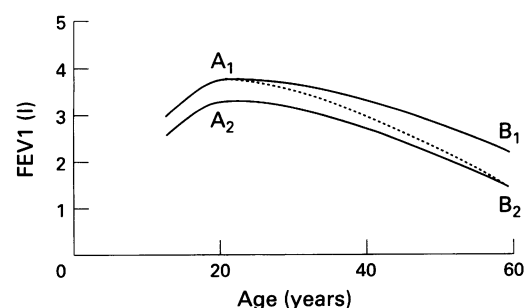


Figure 1 Discrepant mean declines in FEV₁ from cross sectional and longitudinal data as workers age from 20 to 60 years. A₁-B₁ = true (future) longitudinal decline in subjects currently aged 20 years; A₂-B₂ = true (completed) longitudinal decline in subjects currently aged 60 years; A₁-B₂ = apparent (current) longitudinal decline using cross sectional data from subjects currently aged 20-60 years.

airway responsiveness (to methacholine) may prove to be almost as important as cigarette smoking in exerting an adverse influence on the rate of decline in ventilatory function. If it is confirmed that a measure of asthmatic activity is relevant to predicting the development of COPD (a relationship enshrined in what became known as the "Dutch hypothesis" of the 1970s and 1980s but was disputed thereafter), then factors of aetiological relevance to asthma may also need to be taken into account when studying COPD.^{13 14} It may be useful therefore to consider the occupational agents which have been associated with COPD in two categories – those which are also believed to cause asthma and those which appear to have no asthmagenic properties.

COPD attributable to agents known to induce occupational asthma

NATURALLY OCCURRING INDUCERS OF OCCUPATIONAL ASTHMA

Respiratory disease in grain workers has been widely recorded since the 18th century and the time of Ramazzini. Grain dust has become a particularly well recognised cause of occupational asthma, though the precise causative agent (or agents) remains unclear. Storage mites, microbial contaminants, pesticides and fungicides, and even rodent urinary proteins have all been incriminated, together with allergenic material derived from the grain itself. A number of investigators have produced impressive evidence that occupational exposure to grain dust may also lead to COPD, though none have suggested that this is a direct consequence of occupational asthma and most have found some inconsistencies among their data.^{15 16}

The experience of Chan-Yeung and her colleagues in the port of Vancouver provides a useful illustrative example.¹⁷ They followed port grain workers and control subjects working in civic centre posts between 1978 and 1990. After six years the annual rates for the decline in FEV₁ were significantly greater among the grain workers (–31 ml/year) than the controls (+4 ml/year), but when the smokers alone were compared little difference was noted between grain workers and controls (–36 ml/year versus –31 ml/year). In this particular investigation, therefore, the "grain COPD effect" was seen largely in the non-smokers (in whom asthma was not satisfactorily excluded though atopy proved to be irrelevant), and it appeared to be of similar magnitude to the "smoking COPD effect" in the control workers. Furthermore, its demonstration depended on there being an unusually small annual decline in FEV₁ (in fact there was a trivial increase) among the controls. After 12 years significant differences between grain workers and controls were no longer evident, but this may have been a consequence of survivor bias or of greatly reduced exposure levels. Not all investigators have found this COPD effect, and when it was observed it was generally more clear among the smokers than non-smokers.

With wood dust, a further common cause of occupational asthma, evidence for a COPD effect is less strong, but again smokers appear unduly susceptible to it. This is noteworthy in view of the curious "protective" effect of smoking observed with occupational asthma attributable to western red cedar.¹⁸ A similar protective effect in smokers, for which there are plausible immunological explanations, has been observed with extrinsic allergic alveolitis and sarcoidosis, and so should not be dismissed too hastily.^{19 20}

CHEMICAL INDUCERS OF OCCUPATIONAL ASTHMA

In Britain at present isocyanates seem to be the most common cause of occupational asthma, and isocyanate asthma continues to provide a typical example of asthma attributable to occupational chemicals. Not unnaturally, isocyanate workers have provided a focus for investigations, of which there have been many, of possible occupational COPD. The results have been conflicting and have stimulated much controversy. A major multicentre surveillance programme in Britain revealed no hint of a COPD effect, while the study of a single isocyanate producing plant in the USA suggested a crippling occupationally induced mean annual decline in FEV₁ exceeding 100 ml/year.^{21 22} Both investigations may have been flawed – the one because there was an implausibly low prevalence of occupational asthma (probably a consequence of survivor bias), the other because the levels of ventilatory function observed initially were too well preserved for an excessive decline of such a degree to have been occurring before the investigation commenced.

Not surprisingly, reports of these investigations stimulated many others, and these have produced a spectrum of conclusions which is almost as wide. The five year investigation of Diem and colleagues of workers in a new toluene diisocyanate manufacturing plant included an extensive series of isocyanate exposure measurements, from which the workforce was usefully separated into categories of low to average cumulative exposure (≤ 68.2 ppb-months) and high cumulative exposure (> 68.2 ppb-months).²³ The high exposure group did show a significantly greater annual decline in FEV₁ (–37 ml/year) than the non-smokers of the low exposure group (+1 ml/year), but it was not influenced by smoking. Smoking did, however, lead to a similar excessive decline in those with low levels of exposure to isocyanate. Thus, the investigation suggested a modest excessive decline in FEV₁ as a consequence of either isocyanate exposure or smoking, without there being any additive or multiplicative effects. These conclusions differ from the general consensus, which favours an interaction between smoking and the occupational environment, but they mirror those derived from the grain workers in the port of Vancouver. Interestingly, Diem and colleagues did attempt to identify asthmatic subjects from their study population and showed no weakening of the COPD effect when these workers were excluded from the analysis.

COPD attributable to agents not known to induce asthma

CADMIUM

Cadmium occupies an unusual place among occupational agents reported to cause COPD in that it appears to do so by causing emphysema. Occupational COPD attributable to non-focal emphysema seems otherwise to be confined to complicated pneumoconiosis. Cadmium induced emphysema has not been without controversy, however, from the time of its first description in 1952.²⁴ For some years doubts persisted as to whether smoking alone was responsible for the apparently excess prevalences of COPD noted among some, but not all, cadmium exposed working populations.²⁵ More recent investigations involving long term surveillance have provided more convincing evidence in support.²⁶ Although cadmium is a trace component of cigarette smoke, cumulative exposures from smoking alone are not likely to approach those sustained occupationally. It seems improbable therefore that smoking-induced emphysema could be attributed to cadmium.

MINERAL DUSTS

The mineral dusts have provided perhaps the greatest opportunity for COPD controversy, even conflict.²⁷ Although airway obstruction was quickly recognised to be a feature of complicated pneumoconiosis and of its accompanying emphysema, COPD in the absence of complicated pneumoconiosis has generally been attributed to other coincidental disorders. High mortality rates from respiratory disease in some groups of miners led to early and intensive investigations of large numbers in many countries.²⁸⁻³¹ The outcome was the recognition that, although complicated pneumoconiosis and occupational tuberculosis were associated with excess respiratory mortality and morbidity, the pattern of respiratory disease in miners was otherwise closely duplicated in their families and in suitably matched control populations.³²⁻³⁴ It appeared to be related more to social circumstances (and particularly to smoking) than to the working environment.³⁵

The largest investigations have involved coal miners, principally because of the enormous populations employed over the years in the coal mining industry and partly because of political influence. In general, mean losses in ventilatory function attributable to coal dust exposure (rather than cigarette smoking) have been small or trivial in the absence of complicated pneumoconiosis, and because of the large numbers in many of these investigations these essentially negative findings have attracted high levels of confidence. Some investigations, however, have suggested that the COPD effect from coal dust might approach that of cigarette smoke.

The controversy has arisen because disabling levels of airway obstruction have been noted in a small minority of miners who claimed never to have smoked and who did not show evidence of complicated pneumoconiosis. They were found more prominently among

retired miners, and protagonists have argued that this is to be expected in a job that did not readily tolerate any loss of physical fitness. Thus, earlier reassuring epidemiological investigations of working coal miners were flawed by the industry's unusual susceptibility to the "survivor effect". Furthermore, a small mean loss in ventilatory function, which has not attracted much dispute, might be a consequence of large and disabling effects in a few miners rather than of small and clinically inconsequential losses in many. Antagonists have responded that smoking histories are notoriously unreliable in coal mining communities (in one study 20% of miners who described themselves as light smokers were after death described by their relatives as heavy smokers³⁶), and that if disabling losses of ventilatory function do occur, they are more likely to be due to smoking (active or passive) or other non-occupational factors such as asthma or the miners' penchant for breeding pigeons.

The most recent detailed analysis of longitudinal data from British coal mines did, like earlier investigations, provide evidence for a small excess longitudinal decline in FEV₁, independent of pneumoconiosis, which was closely related to measured levels of exposure to coal dust.³⁷⁻³⁹ The risk of a disabling loss of ventilatory function (defined by the mean loss in FEV₁ of 942 ml shown by the miners with disabling symptoms) was less than 5% among non-smoking miners with low cumulative levels of coal dust exposure (≤ 100 g.hour/m³) who had worked to the age of 55 years, but the confidence intervals were wide. The risk increased exponentially to about 20% in those with unduly heavy levels of cumulative exposure (500 g.hour/m³). Most interestingly, it was not only greater in smokers, but the smokers showed a significantly steeper slope relating increasing exposure level to increasing risk. This study therefore supports the notion of an adverse interactive effect between smoking and occupational exposure on the development of COPD. The magnitude of the adverse effect of smoking was, however, some three times that of coal dust, and may have been influenced (underestimated) more than the coal dust effect by survivor bias. The accumulating evidence for COPD attributable to coal dust has recently led to it becoming a compensatory disease in Britain, providing the claimant has worked underground for at least 20 years, there is radiographic evidence of dust deposition (that is, pneumoconiosis category 1 or more), and the severity is sufficient to reduce the FEV₁ by one litre from its predicted value.

A similar situation has arisen in South Africa, though strengthening evidence that respirable silica in gold mines might cause COPD was not published until after the introduction of state compensation in 1952.^{9 40 41} Again there has been controversy, some later investigations failing to provide clear confirmatory evidence of a silica-related loss of ventilatory function.^{42 43} Other recent investigations (cross sectional and longitudinal) have shown an excess of COPD in workers exposed to silica which could not be attributed to smoking, but

there was no clear relationship with intensity of exposure.⁴⁴⁻⁴⁶ In one of these investigations silica and smoking appeared to exert effects of similar magnitude, while in another the influence of smoking on the decline in FEV₁ was approximately twice that of silica exposure. In the severe cases which led to death, an interaction between the two environmental factors seemed likely.

WELDING FUME

Welding fume is conveniently considered separately from other mineral dusts, partly because the circumstances of exposure are rather different, partly because a possible COPD effect in welders is a matter of considerable topical interest, and partly because evidence of an additional asthmagenic effect is now emerging. Exposure to welding fume consequently brings the discussion full circle.

Consistent with the investigation of numerous work forces exposed regularly to respirable irritant or noxious dusts, vapours or fumes, many investigations of welders have demonstrated a clear excess prevalence of chronic productive cough (industrial bronchitis). Until recently none have found convincing evidence of an excess of airway obstruction, implying, perhaps, that if there is a COPD effect it must be of relatively small degree.⁴⁷⁻⁴⁹

A small but significant COPD effect was the conclusion of a cross sectional study of 607 shipyard workers aged 17-69 years carried out by Cotes and colleagues.⁵⁰ After allowing for age and height, the trades associated with welding fume exposure showed a mean and significant loss in FEV₁ of 250 ml compared with the unexposed trades. This effect was noted only among the smokers. Of the original study population, 487 were re-examined seven years later.⁵¹ Multiple regression analyses suggested that FEV₁ was declining at an annual rate of 16.2 ml for a 50 year old non-smoking worker without occupational exposure to welding fume. The additional losses attributable to smoking and welding

fume exposure were 17.7 ml/year and 16.4 ml/year, respectively. Interactions were noted between welding fume and smoking, and between welding fume and atopy. There was no effect from welding fume on gas transfer. The longitudinal study consequently suggested that a mild COPD effect attributable to welding fume might also occur in non-smokers, but it confirmed that this effect was disproportionate in smokers. The further enhancement of the effect in atopic subjects provides a hint of an asthmatic component, and the lack of any effect on gas transfer suggests that COPD was not occurring as a consequence of emphysema.

A further hint that welding fume from mild steel might influence asthma (asthma is increasingly reported in stainless steel welders as a consequence of presumed chromium hypersensitivity) has emerged from work of my own colleagues in a further shipyard.⁵² We examined cross sectionally apprentices in various trades from the age of 15-17 years (when they left school) to 27 years (when they had completed nine years at work) and we focused the investigation on methacholine tests to provide objective measurements of airway responsiveness. These were carried out using a locally designed microprocessor-controlled dosimeter and a locally developed protocol.⁵³ The results were expressed conventionally as PD₂₀ (the cumulative dose of methacholine estimated to provoke a decrement in FEV₁ of 20%). Airway responsiveness improved steadily with age in apprentices without exposure to welding fume, it changed little in those with ambient exposure (shop floor trades not associated directly with fume generation), and it showed a small increase in the regular welders. The odds ratios for the risk of having a positive methacholine test after five years work compared with the risk at 0 years are illustrated in fig 2. In essence, the observations suggest that, after five years of occupational exposure during the 1980s when exposure levels were rigorously controlled, welding fume exposure led to a mean PD₂₀ which was 50% of expected. This implies that, of the regular welders with a PD₂₀ ≤ 1000 µg (the range within which subjects with active asthma are usually found⁵³), some 15-30%, depending on atopic status and smoking habits, represent an excess attributable to welding fume exposure.

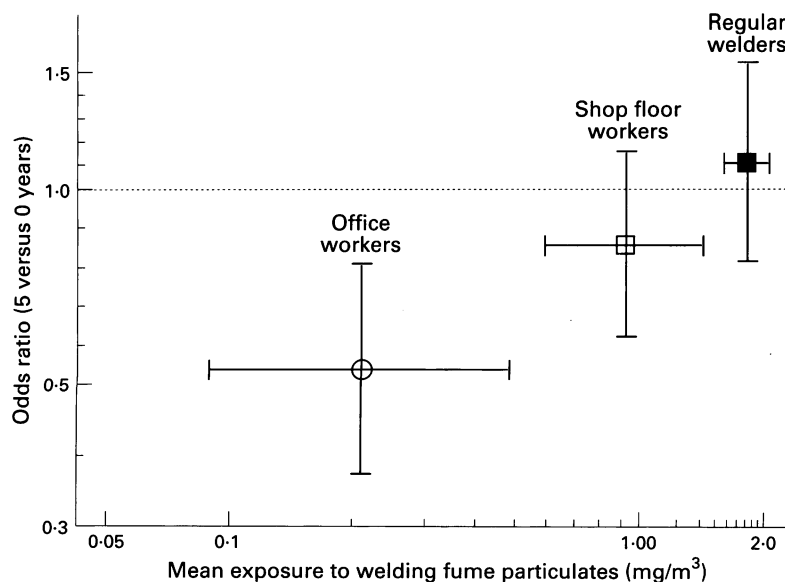


Figure 2 Odds ratios (with 95% confidence intervals) for a positive methacholine test after working for five years.⁵²

Perspective in the population at large

The relative risks posed to the general population by common allergens, outdoor air pollution, air pollution within the home, and respirable agents at work is a matter of increasing public concern, particularly with regard to the aetiology and progression of COPD and asthma. Both disorders are clearly dependent on changing patterns of life within developed countries, and so environmental factors must be of great relevance. It may be that many different respirable agents are capable of exerting an influence, and that in different individuals the measured COPD effects are due to different combinations of these agents (a

"multiple hit" hypothesis), together with some inherent susceptibility.

Recent investigations in the former East and West regions of Germany provide interesting comparisons within the developed world between an area of high smoking prevalence and relatively high outdoor air pollution from industrial emissions, and one of high domestic affluence.⁵⁴⁻⁵⁵ COPD appears to dominate in the former and asthma in the latter, though in the more affluent societies there is more rather than less outdoor pollution from vehicle exhausts. This is thought to be of relevance to asthma in Los Angeles where such pollution is persistently high and intermittently dramatically so, but a recent comparative study using measurements of airway responsiveness between an urban area with more modest exposure to vehicle exhaust (Newcastle upon Tyne) and a rural area with low exposure (Cumbria and the English lake district) showed no difference.⁵⁶

A further perspective regarding the possible role of occupational exposures in the aetiology of COPD in the population at large can be seen from the results of an epidemiological investigation of urban (Bergen) and rural (Hordaland) communities in western Norway.⁵⁷ A postal survey first sampled 5000 individuals from a total population of 250 000 and, from the respondents, an age stratified sample of 1512 was invited to undertake a more detailed investigation which included respiratory symptoms, smoking history, work history, and spirometric tests; 1275 individuals participated. When COPD was defined from strict spirometric parameters alone ($FEV_1/FVC < 70\%$, and $FEV_1 < 80\%$ of predicted), smoking proved to be the only explanatory variable of clear relevance from multiple regression analyses. When COPD was defined less stringently but more clinically from both objective spirometry ($FEV_1/FVC < 70\%$) and subjective symptoms (chronic productive cough together with undue breathlessness or wheeze), the odds ratios for participants reporting specific occupational exposure to aluminium, welding/metal fume, quartz, or asbestos all increased to significant levels, as did the odds ratio for heavy exposure to any source of occupational dust. An increased prevalence of COPD was also noted in the urban compared with the rural communities, but this was attributable to the greater number of elderly individuals living in Bergen, who were affected disproportionately. The study population was consequently sufficiently large for subjective evidence of occupational productive cough to be demonstrated, but the excess prevalences of airway obstruction which were noted among certain groups of workers did not reach conventional levels of statistical significance.

Conclusions

Evidence relating occupational environments to COPD is extensive but conflicting, and this inevitably stimulates controversy. Any summary is necessarily influenced by personal, biased, and possibly preconceived views, so it should be emphasised that the following

conclusions reflect a changing scene and a personal current interpretation of it. They also depend on additional, but often controversial, conclusions that COPD occurs with excessive prevalence in a number of other occupational settings, including paper pulping mills, printing, firefighting, and flour mills.⁵⁸⁻⁶⁰

1. Some occupational environments are likely to exert a COPD effect.
2. Its impact is likely to be less than that of smoking (perhaps much less), but will vary from industry to industry depending on potency and exposure level of the agent involved.
3. Complex adverse interactions probably exist with smoking, and (presumably) with other environmental agents.
4. Many environmental factors may be of relevance to its aetiology – the so called "multiple hit" hypothesis.
5. It is plausible that both asthmatic and non-asthmatic pathways could play a role.
6. It will be found rarely in the absence of both smoking and asthma.

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