The Prescription of Disease

by

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Foreword

The Prescription of Disease is the third and final part of the short series of publications produced to mark the centenary of the Workmen's Compensation Act 1906 which introduced compensation for occupational diseases, and the 60th anniversary of the National Insurance (Industrial Diseases) Act 1946 under which the Industrial Injuries Advisory Council (IIAC) was founded. It sets out the history, development, and current science, of the attribution of disease to occupational causation.

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1: The Evolution of Prescription

The Industrial Injuries Disablement Benefit (IIDB) scheme and its predecessors have been providing compensation to workers who were sick or injured as a result of their work for over 100 years. The 1897 Workmen's Compensation Act gave a duty on employers to compensate their employees for loss of earnings due to accidents arising "out of and in the course of employment". This duty was without the need to show negligence. An accident was defined in 1903 by case law as an event "which is neither expected nor designed". In 1906 Workmen's Compensation was extended to cover both accidents and diseases caused by work. Initially, six diseases were included on the scheduled list of prescribed diseases – anthrax, ankylostomasis and poisoning by lead, mercury, phosphorus, arsenic or their sequelae. Beveridge described the Workmen's Compensation scheme as the "pioneer system of social security in Britain".

A list of prescribed diseases necessitated the means to update it. The Samuel Committee, set up in 1907 to address this issue, stated that for a disease to be prescribed it had to be:

a) outside the category of diseases already covered by the Workmen's Compensation Act
b) such as to incapacitate a worker for more than a week
c) so specific to the employment that causation could be assumed in the individual case.

The implication of this last point was that diseases associated with certain industries could not be scheduled if they were also common in the population, e.g. bronchitis in flax workers.

This scheme remained in operation until 1946. Why was there a need for change? In the foreword to the 'Social Insurance Part 2 Workmen's Compensation Proposals for an Industrial scheme' published in September 1944 it was noted that for "nearly half a century the compensation of workmen for industrial injury has been a liability, imposed by law, upon their employer. Under the existing scheme, it has been open to the employer, and in some cases obligatory on him, to insure himself against this liability; while it has been for the workman to make his claim and to take steps to enforce it, if challenged in the Courts of Law. Inevitably compensation has thus become a disputable issue between the two parties or their representatives." Beveridge noted in his report that there was a disproportionate cost of administering the scheme compared with the cost issued in benefits to sick and injured workers due to this 'disputable' system.

In 1946 the Industrial Injuries Act transferred the responsibility for payment and administration of benefits from employers and insurance companies to the Ministry of National Insurance. Under the Act workers were compensated not for loss of earnings but for "loss of faculty in proportion to loss of health, strength and the power to enjoy life attributable to industrial accident or prescribed disease". One additional benefit of the new scheme was an exception in providing earnings replacement, Special Hardship Allowance (SHA) (which later became Reduced Earnings Allowance [REA]), introduced by the Minister for National Insurance, Mr Jim Griffiths. This was a particularly enlightened part of the scheme enabling workers to relocate and remain in work without suffering financial hardship.

The Minister of National Insurance commended the Industrial Injuries Bill to the House of Commons in October 1945 “not only because of its cash benefits, but also because it provides the foundation upon which a great constructive human service can be built, to restore the injured workman to his old job, or if that is impossible, to care for him and his dependents”.

Since its inception in 1946 until today the Industrial Injuries scheme has developed and adapted to the challenge of a constantly changing world of work and associated diseases with benefits providing social value. I will use i) occupational exposure to coal resulting in pneumoconiosis and chronic bronchitis and emphysema and ii) occupational exposure to asbestos resulting in asbestosis, lung cancer and mesothelioma as relevant examples during the period.

Workmen’s Compensation and Coal

The Samuel committee in 1907 was unable to recommend prescription for silicosis, as silicosis, prior to the advent of the chest radiograph, was indistinguishable from other prevalent chest diseases, particularly tuberculosis. With the development of radiographs, silicosis could be distinguished on a chest X-ray, enabling silicosis in 1919 to become a prescribed disease. In 1928, prescription was extended to coal miners who could demonstrate silica rock dust exposure and were “totally disabled”. The scheme was further extended to include “partially disabled” workers three years later. In 1934, the scheme was extended to include any coal miner with silicotic nodules, whether or not they worked with hard rock. All coal miners with radiological evidence of pneumoconiosis from coal dust exposure were included in the scheme only in 1943.

Workers compensated under the Workmen’s Compensation Act for Coal Workers Pneumoconiosis (CWP) were “certified” and received weekly payments or a lump sum in benefits with compulsory suspension from mining to protect workers from further lung deterioration. Large numbers of workers were certified which resulted in unforeseen social problems. By the end of 1945, 12,000 men had been certified in South Wales and new cases were being certified at a rate of 100 men per week. Over two thirds of these men were under 50 years old and a quarter were under 40 years old. The majority of the men had been coal hewers and faced the prospect of being out of work with no training for alternative employment. Hugh Jones and Fletcher (1951) noted that “at present some 5,000 men with pneumoconiosis, three quarters of whom are probably capable of work under normal industrial conditions, are unemployed”.

Advance only became possible with understanding of the nature and determinants of progression of CWP. The lungs have several mechanisms to remove inhaled coal dust. However, if these are overwhelmed the dust accumulates in the lungs, appearing as nodules on chest radiographs. These nodules, which are retained coal dust, are not a cause of impairment or disability. This form of the disease was classified as simple pneumoconiosis. The severity of simple pneumoconiosis was graded according to the profusion of nodules seen on a chest radiograph, which is a reflection of the coal dust which has accumulated in the lungs. In some cases of simple pneumoconiosis large nodules of fibrosis develop resulting in Progressive Massive Fibrosis (PMF), resulting in significant disability and premature mortality. In the 1950s it was believed that PMF was a form of tuberculosis. However, Cochrane (1962) showed that the risk of PMF was related to the category of simple pneumoconiosis, i.e. due to the amount of coal dust in the lungs. He showed that if workers with category 2 pneumoconiosis were removed from further dust exposure the disease would not progress to PMF. Jacobsen and his colleagues at the Institute of Occupational Medicine in Edinburgh showed that category 2 pneumoconiosis occurred in 4% of those exposed to exposures of 4mg m^{-3} coal dust over a 35 year working lifetime. Therefore, procedures were put into place to reduce the risk of exposures linked to the onset of category 2 pneumoconiosis. Also, workers with category 2 pneumoconiosis were moved to less dusty working conditions. The Special Hardship Allowance part of the Industrial Injuries scheme enabled the redeployment of workers to less dusty conditions by providing earnings replacement for the move to less hazardous but less financially rewarded work.

Asbestos and asbestosis, lung cancer and mesothelioma

Asbestos was increasingly used from the late nineteenth century because of its thermal insulating properties. Inhaled asbestos fibres of greater than 5μ in length are too long to be cleared from the lungs. The fibres accumulate in the lungs and can cause fibrosis and cancer. The following timeline shows the evolution of knowledge about the adverse health effects associated with asbestos:

- 1899 Montague Murray reports a post-mortem case of pulmonary fibrosis in an asbestos worker.
- 1900 Cooke reports the case of 33 year old Nellie Kershaw who died of pulmonary asbestosis after working 20 years in an asbestos textile factory. First use of the term ‘asbestosis’.
- 1930 Merewether and Price report the increased prevalence of asbestosis in asbestos textile workers.
- 1947 Merewether reports excess lung cancer deaths in those with asbestosis compared to those with silicosis.
- 1955 Doll provides evidence of the association between lung cancer and asbestos.
- 1960 Wagner *et al.* provides evidence of the association between mesothelioma and asbestos.

Merewether and Price (1930) reported that there was an increased risk of fibrosis in asbestos textile workers, which increased with increased duration of employment.

Years employed	Number examined	Prevalent cases of fibrosis		
		Number	%	Average age
0-4	89	0	-	-
5-9	141	36	25.5	36
10-14	84	27	32.1	40.4
15-19	28	15	53.6	43.4
20+	21	17	80.9	52.7
Totals	363	95	26.2	41.4

After Merewether and Price, 1930

The numbers of prevalent cases of fibrosis was probably an underestimate as employees whose health was most affected by the asbestos would have left the workforce due to ill-health.

The contemporary Chief Medical Inspector of Factories' Annual Report showed the number of deaths from asbestosis was small compared to the number of those with CWP, primarily because of the considerably larger number of people working in the coal mining industry. The importance of asbestos was therefore underestimated as a risk to health. However, this changed with Doll's report of the association of lung cancer, and Wagner's report of the association of mesothelioma, with exposure to asbestos.

Mesothelioma is a rare respiratory cancer. In 1960, Wagner, Sleggs and Marchand reported the association between mesothelioma and exposure to asbestos in the North Western Cape Province of South Africa. They found that mesothelioma has a long latent interval between first exposure and the onset of the disease (usually > 20 years) and a short survival from diagnosis (< 1.5 years). At present in the UK the great majority of cases of mesothelioma are caused by exposure to asbestos.

Exposure (crocidolite)	Mesothelioma (number)	Latency in NW Cape Province, South Africa (years)
Mining or transport	10	21-43
Insulation work	4	18-29
Neighbourhood	18	35-44
Unknown	1	-
	Mean age = 49 years	
	Mean survival = 15 months	

After Wagner, Sleggs and Marchand, 1960

In the UK there has been a high incidence of cases of mesothelioma clustered in areas historically associated with asbestos work, where ship and railway manufacture and repair was undertaken. Before the 1960s the Royal Naval Devonport dockyards used considerable quantities of crocidolite and amosite asbestos. However, from the mid 1960s alternative insulation material was used and respiratory protection provided. Hilliard *et al.* (2003) have shown that these measures have resulted in a decrease in the number of cases of mesothelioma since the early 1990s. However, these preventative and protective measures were not implemented in the UK in the construction industry until the 1970s or

1980s with a consequent continuing increase in the incidence of mesothelioma. Peto *et al.* (1995) has estimated that the peak of the UK epidemic of mesothelioma caused by this continuing asbestos exposure will not be reached until 2011-2015, with two thirds of the cases yet to occur.

Mesothelioma is almost exclusively caused by asbestos and can be caused by relatively low levels of exposure to asbestos which was reflected in the IIDB prescription as "exposure to asbestos, asbestos dust or any admixture of asbestos at a level above that commonly found in the environment at large". Claims for mesothelioma are now 'fast-tracked' by the Department for Work and Pensions meaning there is no 90 day waiting period, claimants are automatically awarded 100% assessments and there is no absolute requirement for corroborative evidence of occupational exposure.

In contrast to mesothelioma, which other than in those exposed to asbestos is a rare tumour, lung cancer is common, primarily caused by cigarette smoking, making its relationship to asbestos exposure more difficult to discern. Montague Murray recognised in 1947 that cases of asbestosis were more likely than cases of silicosis to die of lung cancer.

Pneumoconiosis and lung cancer (at post-mortem)		
	Deaths (n)	**Lung cancer (%)**
Asbestosis	235	13.2
Silicosis	6884	1.2

After Merewether, HM Inspector of Factories, 1947

Subsequently Doll in 1955 provided unequivocal evidence of a greatly increased risk of lung cancer in those with asbestosis.

Causes of death in men employed in a Rochdale asbestos textile factory		
Cause of death	**Number of deaths**	
	Observed	**Expected**
Lung cancer		
With asbestos	11	-
Without asbestos	0	1
Other lung diseases		
Asbestos	14	-
Other	6	8
Other cancers	4	2
Other causes	4	5
All causes	39	16 (15.4)

After Doll, 1955

The case for prescription of lung cancer in asbestos workers without asbestosis was more complex due to the lack of specific clinical features to differentiate cases of lung cancer in the general population. Evidence suggested that in certain workers, such as asbestos textile workers, there was an excess of cases of lung cancer in those working with asbestos compared to the expected number.

The criteria for prescription of an occupational disease which, like lung cancer, also occurred in the absence of occupational causation was given by the Beney Committee (Minority Report) 1955:

> “Prescription should be regarded as satisfied in relation to a disease where it was probable that more cases than not were occupational in origin whether or not individual cases could be attributed to the nature of employment”.

In other words, a prescribed disease should be a) a recognised risk to workers in an occupation or exposed to a particular agent and b) that attribution of the disease to an occupation or agent should be based on the balance of probabilities, i.e. is more likely than not.

IIAC recently reviewed the evidence for asbestos-related diseases and recommended that lung cancer in the absence of asbestosis be prescribed for “exposure to asbestos for at least 5 years before 1975 and 10 years after 1975 in the following occupations i) workers in asbestos textile manufacture; ii) asbestos sprayers and iii) asbestos insulation work, including those applying and removing asbestos containing materials in shipbuilding.

Chronic bronchitis and emphysema (COPD) and coal dust

Cancer is an ‘all or nothing’ disease, i.e. you either have cancer or you do not. IIAC also has to consider prescription where the nature of the disease is ‘more or less’, i.e. there are degrees of disease, such as airway narrowing in chronic bronchitis and emphysema.

Lung function can be assessed by measuring the volume of air a person can exhale. The total volume of air that can be exhaled is called the forced vital capacity (FVC) and the volume of air that can be exhaled in one second is forced expiratory volume in 1 second (FEV_1). A person with airflow limitation will have a lower FEV_1 and FEV_1/FVC than a normal individual. Cochrane and Higgins (1961) showed that while miners and ex-miners had lower lung function than non-miners, miners and ex-miners with simple coal workers’ pneumoconiosis did not show increasing loss of FEV_1 with increasing category of simple pneumoconiosis, although lung function was decreased in miners and ex-miners with progressive massive fibrosis. He inferred that chronic bronchitis and emphysema was not a hazard of coal mining. However, Cockcroft *et al.* (1982) found that emphysema was more frequent in coal miners than non-miners, with an odds ratio of 10.35 after adjusting for age and smoking. Subsequently, Marine *et al.* (1988) showed that the proportion of coal miners with a $FEV_1 < 65\%$ was doubled in those with high, as compared to low, exposure to coal dust in both smokers and non-smokers. Taking this evidence together IIAC were able to recommend prescription for chronic bronchitis and emphysema in coal workers. In considering the terms of prescription for coal workers the Council asked the following questions:

What is a disabling loss of FEV_1? Studies had shown that a reduction in FEV_1 of 1L was association with shortness of breath when walking with others on level ground.

Is there evidence of at least a doubling of risk of this FEV_1 loss? Evidence suggested that a doubling of risk occurred at cumulative exposures to coal dust of 60-120mg m^{-3} yr^{-1}.

What is the nature of occupational exposure in which this occurs? Data from the Institute of Occupational Medicine in Edinburgh showed exposures to respirable coal dust for UK miners to be:

coal face workers	2.5-6.5 mg m^{-3}
development operations	1.5-5.5 mg m^{-3}
other underground workers	1.0-3.0 mg m^{-3}
surface workers	0.2-0.7 mg m^{-3}

Can this be translated into job titles and duration of employment for purposes of prescription? On average this translated into 20 years employment underground in a coal mine.

Conclusions

As can be seen from the examples given, since 1946 the Industrial Injuries Scheme has adapted to the changing nature of disease associated with work. The scheme has been broadened to allow inclusion of diseases of occupational cause, but which are also common in the general population e.g. lung cancer, hearing loss, osteoarthritis of the hip and chronic bronchitis and emphysema. There are mechanisms within the scheme to enable early recognition, investigation and, where sufficient evidence exists, to prescribe new conditions in a timely fashion, such as recently extrinsic allergic alveolitis due to metal working fluid.

An important loss to the IIDB scheme was the abolition of Reduced Earnings Allowance in 1990. This was arguably the most enlightened part of the scheme. It provided an earnings replacement benefit, to enable those with occupational disease, whose health would be adversely affected by remaining in their job, to move to other less well paid work, providing the means to prevent disease progression to a severe and irreversible level of disability.

Provision of a benefit with these aims and incentives would seem a worthwhile addition in a reformed scheme.

The IIDB scheme today faces several challenges. The nature of work continues to change in the UK with less heavy industry, more service workers and more self-employed. The nature of the associated ill-health is also changing. The scheme needs to align more closely with modern social security objectives, in particular, support to enable claimants to remain in, to change, or to return to work. Finally, the name of the scheme itself should be changed to reflect its modern purpose.

2: The Scientific Basis of Attribution

The Industrial Injuries Disablement Benefit scheme provides benefit, without the need to demonstrate negligence, to employed earners who have had an accident at work or developed disease as a consequence of their work.

In the case of an **accident** the scheme provides compensation for disablement from "an accident arising out of or in the course of employment". Each case is considered on its merit: for example, take an individual who is suffering long term brain damage following an accident at work, when a heavy block of concrete fell from a height onto his head, causing a depressed fracture of the skull. The injury to the skull is a wholly plausible consequence of a concrete block falling on his head from a height and brain damage a plausible consequence of injury to the skull. The brain damage followed within a short time of the accident and is a plausible consequence of it. Here, the probability is near certainty that the disablement arising from the brain damage is a direct consequence of the accident.

Determination of the cause of a **disease** in the individual case is often more difficult, and especially so where the exposure to a hazardous substance at work increases the frequency of a disease which is common in the population. For example, lung cancer is strongly associated with cigarette smoking and occurs several years after the onset of exposure. So, attributing lung cancer in an individual to an occupational hazard depends on demonstrating a) probable causation, b) a magnitude of risk sufficient to be confident that it is unlikely the disease would have occurred in the absence of the occupational exposure.

Causes: necessary, sufficient or neither

In a recent essay, David Coggon defined a cause as "something which at least in some circumstances makes a disease more likely if it is introduced or less likely if it is removed"[1]. Cigarette smoking is a cause of lung cancer and high blood pressure a cause of stroke; stopping smoking reduces the risk of lung cancer and reducing blood pressure the risk of stroke.

Aristotle distinguished "necessary" from "sufficient" causes and this distinction can be applied to disease causation. In the absence of a necessary cause a disease will not occur. Infection with Mycobacterium tuberculosis is a necessary cause of the disease tuberculosis, since cases of tuberculosis do not occur in its absence. Similarly, inhalation of respirable silica dust is a necessary cause of silicosis. But, infection with M. tuberculosis is not a sufficient cause of tuberculosis since only some 10% of those infected with the organism develop tuberculosis. Other factors, which include age, poverty, malnutrition, HIV infection and silicosis, increase the risk that those infected with M. tuberculosis will develop the disease.

Identification of the cause or a combination of causes "sufficient" to cause a disease is uncommon other than for single gene disorders and chromosomal abnormalities. The presence of 2 abnormal haemoglobin genes (HbS) is sufficient to cause sickle cell disease, and 3 copies of chromosome 21 are sufficient to cause Down's syndrome.

The majority of diseases are caused by a combination of factors (both genetic and environmental) which, when present, can be shown to increase the frequency of the disease (or when absent, reduce it) but which are neither necessary nor sufficient. Cigarette smoking is a potent cause of lung cancer, but not all cases of lung cancer have smoked cigarettes (not necessary) and not all smokers develop lung cancer (not sufficient).

Demonstration of disease causation is clearest, and attribution in the individual case most confidently made, for diseases where the cause is necessary or nearly so. We describe the cause in these conditions as being specific for the disease. Such diseases include the chemical poisonings e.g. lead and mercury, the pneumoconioses, caused by inhaled coal and silica, mesothelioma caused by inhaled asbestos and osteolysis of the terminal phalanges caused by inhaled vinyl chloride monomer (VCM). For these diseases the probability of causation, for those exposed at work to the particular agent, is similar to that of the accident example and can be, or approach, certainty. It is not surprising that many of these (the poisonings and silicosis) were the first occupational diseases to be recognised in this country, under the Workmen's Compensation Act 1906.

Other diseases, which form the majority, are the outcome of multiple causes, none of them necessary or sufficient, and evidence for attribution to an occupational cause depends on the results of epidemiological studies of workforces, which demonstrate consistently an increased incidence of the disease, not due to chance, bias or confounding. No studies are perfect and determination that an observed association is causal is a matter of judgement, based on the strength and consistency of the evidence and of its coherence: does it hang together?[2]

Evidence of causation

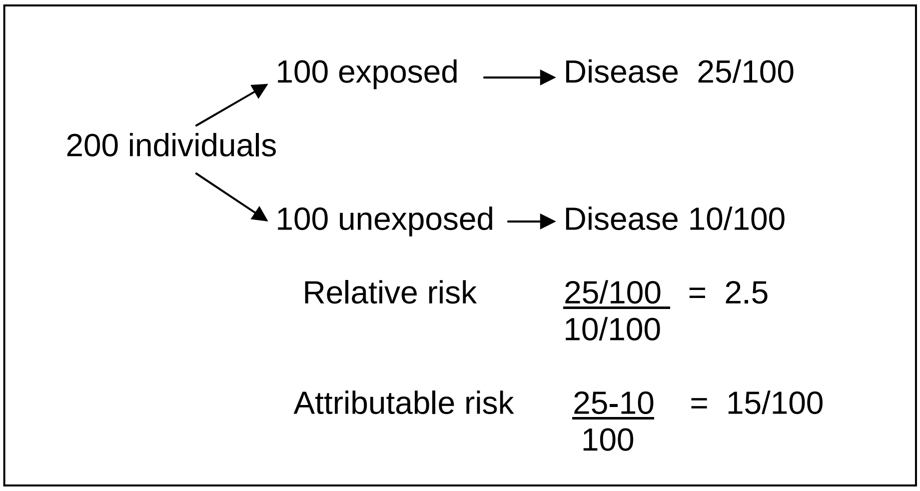
Two types of epidemiological ("observational") study are used to investigate causal associations: case-referent and cohort studies. In the case-referent study the question asked is: is the suspected exposure found more frequently in persons with the disease than in persons without, after consideration of other potential explanatory factors such as age, sex and means of ascertainment? In cohort studies: do exposed persons develop the disease more frequently than persons who have not been exposed? The outcome of those exposed to a particular agent, often stratified by level of exposure is compared to the experience of a similar group, not exposed to the agent of interest. In general, inferences from cohort studies are regarded as stronger than those from case-referent studies, where the risk of bias is greater.

Causal inferences from cohort and case-referent studies are stronger than from the third type of epidemiological study – the cross sectional study. A cross sectional study of a workforce, for instance, would survey all of those currently employed and might relate any variation in disease frequency within the workforce to current levels of exposure. A cross sectional study therefore estimates disease prevalence in a survivor population, from which a disproportionate number of those with ill-health may well have left. Furthermore, current levels of exposure may be different from those in the past which were associated with the development of disease.

The strength, or potency, of an agent as a cause of disease may be expressed as a relative risk (or odds ratio): the ratio of risks of disease in the presence and in the absence of the cause; or alternatively as an attributable risk: the additional risk associated with the cause.

For example:

Cohort Study



Doll and Bradford Hill demonstrated that cigarette smoking was more frequent in cases of lung cancer than in hospitalised cases with other types of cancer (case-referent study). They subsequently showed that male doctors who smoked were considerably more likely to die of lung cancer than non-smokers and the more cigarettes they smoked, the greater their incidence of lung cancer (cohort study). Finally, they demonstrated a progressive reduction over 20 years in the incidence of lung cancer in those who gave up smoking as compared to those who continued to smoke.

The essence of such studies is the comparison of "like with like" to ensure, as far as possible, that any observed differences in the frequency of disease (cohort studies) or exposure (case-referent studies) are attributable to the factor of interest. Comparison of the experience of workforces can pose particular problems in this regard. In general, those who enter work are likely to be healthier than those not in work (healthy worker effect); and those who remain in work healthier than those who leave work (survivor effect). In a study of workers engaged in the manufacture of polyvinyl chloride (PVC), Fox and Collier[3] quantified the magnitude of these contributions to a lower than expected mortality in the workforce:

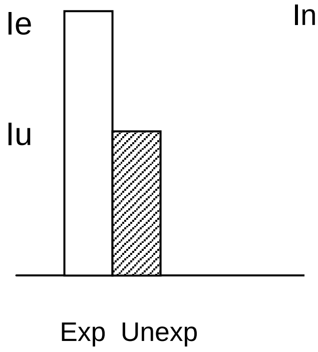
- <u>Selection</u> of a healthy population for employment: the mortality experience within 5 years of entering the industry was 37% of that expected for circulatory and 21% expected for respiratory disease. The standardised mortality ratio (SMR) for these conditions progressively increased during the period of employment, so that it had become similar to the general population after 15 years.

- Survival in the industry of healthier men. Those who had left the industry during the first 15 years of employment experienced an SMR 50% higher than those who remained in the industry.

Valid comparisons of the mortality experience, particularly for respiratory and cardiovascular disease, of a workforce with the general population probably require at least 15 and probably 20 years of follow up.

Attribution or probability of causation

The conclusion that a disease in an individual case is, on the balance of probabilities, due to a hazardous exposure in the workplace, requires evidence of a probability of causation of 50% or more. This is equivalent to more than 50% of the cases in the exposed population being attributable to the particular exposure: i.e. an attributable fraction >50%, and a relative risk of >2



Incidence in exposed (Ie) $= 100/10^5$/yr

Incidence in unexposed (Iu) $= 50/10^5$/yr

$$\text{Relative risk} \quad \frac{Ie}{Iu} = \frac{100}{50} = 2$$

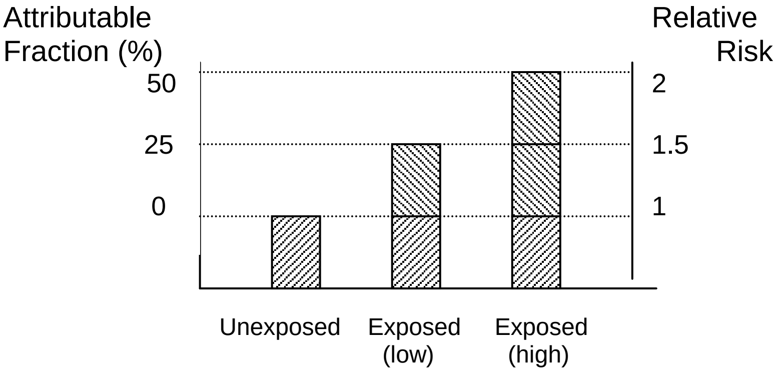
$$\text{Attributable fraction} = \frac{Ie - Iu}{Ie} = \frac{100 - 50}{100} = 50\%$$

The relationship of relative risk and attributable fraction in the exposed population is :

$$\underset{\text{(in exposed)}}{\text{Attributable fraction (AF)e}} = \frac{\text{Relative Risk (RR)} - 1}{\text{Relative Risk}} = \frac{2-1}{2} = 50\%$$

In the absence of any specific identifying characteristics to distinguish a case of lung cancer caused by asbestos from one which would have occurred in the absence of asbestos exposure, attribution to asbestos can only be based on the attributable fraction in the exposed workforce and therefore the relative risk in comparison to those not exposed. The relative risk of lung cancer for an asbestos textile worker is doubled or more in those employed for 10 or more years, implying, that in those employed for this long, more than 50% of cases would not otherwise have been expected to occur. The probability of causation for an asbestos textile worker employed for more than 10 years is 50% or more.

The attributable fraction (and therefore relative risk and probability of causation) can vary in relation to the level of exposure, usually increasing with increasing cumulative (intensity x duration) exposure.



<u>The problem of small numbers</u>

Epidemiological studies aim to provide an estimate of the true frequency of disease in a defined population (say asbestos workers), by studying a sample of the population (say all employees in an asbestos factory). Clearly the results obtained in different samples (say different asbestos factories) will vary between each other and from the true value in the underlying population (all asbestos workers). The larger the sample, the more likely are findings from it to represent the values in the underlying population, and therefore the more confidence we can have in the sample estimate, e.g. disease frequency or relative risk. Conversely, the smaller the sample the less confidence can be placed on the sample estimate as a precise measure of the true value in the population.

The confidence in a sample estimate is often expressed as the 95% confidence interval, which includes the true population value 19 times out of 20. A narrow confidence interval, which reflects a large sample size, provides more confidence in the validity of the result than a wide confidence interval from a small sample.
For instance :

	Sample size	RR	95% CI
Lung cancer (asbestos workforce v gen population)	10,000	3	2 – 4
	100	3	0.5 – 5.5

Confounding and modifying factors

Confounders are extraneous factors which are associated with both the exposure and the outcome of interest, and which may provide an alternative explanation of the findings.

Modifiers (or effect modifiers) are factors which interact with the exposure of interest to increase the risk of the outcome in certain groups.

Cigarette smoking is a potential confounder for asbestos as a cause of lung cancer: smoking increases the risk of lung cancer and those most heavily exposed to asbestos are, on average, more likely than those less heavily exposed to smoke more cigarettes. Unless cigarette smoking is adjusted for, an exposure response relationship between asbestos and lung cancer may simply be a reflection of increasing cigarette consumption with increasing asbestos exposure.

In fact the risk of lung cancer increases with both increasing cigarette consumption and increasing cumulative asbestos exposure (i.e. they are independent risk factors)

In addition, cigarette smoking modifies the carcinogenic effect of asbestos, increasing the risk of developing lung cancer, at any level of consumption, by up to 5 fold at the highest levels of asbestos exposure.

Relative risk of lung cancer (in US asbestos insulation workers)				
		Asbestos exposure		
		No	Yes (high)	RR
Cigarette smoking	No	1	5	5
	Yes **(high)**	10	50	5

Because the effect of cigarette smoking is to multiply the risk of lung cancer caused by asbestos, it does not have to be taken into account in considering the probability of causation (which in this example is $\frac{5-1}{5}$ $\left(\frac{RR-1}{RR}\right)$ 80% for both smokers and non-smokers).

Problems would arise if the risk of disease (say lung cancer) in relation to an occupational exposure (say asbestos) varied in relation to the level of exposure to the disease modifier (say cigarette smoking). It was originally reported that the increase in lung cancer in asbestos workers was confined to cigarette smokers. Logically in these circumstances compensation based on the principle of probability of causation of more than 50% (RR > 2) would only apply to cigarette smokers.

While this example is only theoretical, future knowledge from molecular genetics may bring this problem more directly to the Council's attention. A recent study has found that the risk of developing lung cancer in asbestos workers, exposed to similar levels of asbestos, varied in relation to different variants (polymorphisms) of the myeloperoxidase gene. The risk for lung cancer was nearly twice as great in those of G/G genotype as compared to those of G/A or A/A genotype[4]. Should the levels of exposure sufficient to qualify for benefit differ between individuals with different genetic polymorphisms?

"All or none" and "more or less"

Lung cancer is an "all or none" disease. One cannot have a little bit of lung cancer. The same is not true of diseases such as hypertension (high blood pressure) or chronic obstructive pulmonary disease (COPD). While diseases such as lung cancer are probably the outcome of amplifications of molecular events, blood pressure and forced expiratory volume in one second or FEV_1 (a measure of airways obstruction) are unimodally distributed in the population and disease represents the extreme of the distribution curve. As Geoffrey Rose put it, for these conditions the appropriate question is not "does he have it?" but "how much does he have?" COPD can be defined in relation to the lower extreme of the distribution curve of FEV_1.

In its prescription of chronic bronchitis and emphysema in coal miners, IIAC defined COPD for the purposes of prescription as an FEV_1 of 1L or more below the mean (average) value for a man of the same age and height. This equated to a value of 2 standard deviations or more below the mean value, which had been found to be associated with a significant level of disability (difficulty in keeping up with others when walking on the level).

Studies in the UK have shown that the proportion of underground coal miners with this level of lung function increased with increasing cumulative exposure to coal dust. Taking the average level of respirable coal dust underground, the level of cumulative exposure associated with an attributable fraction of more than 50% (and therefore a Relative Risk of more than 2) occurred in coal miners who had worked underground for 20 years or more. 20 years mining coal underground was required for the probability of causation to exceed 50% and therefore allow attribution in the individual case.

Excess risk as a measure of attribution

An alternative method of determining attribution in the individual case is by identification of the attributable risk, i.e. the number of additional cases of a disease in a workforce, and award compensation to this number of cases who have experienced the highest cumulative exposure, independent of attributable fraction or probability of causation. This was the basis for compensation for gold miners in Ontario, which compensated the number of cases of lung cancer due to silica exposure in excess of the number of cases among those not exposed, selecting for compensation those who had experienced the highest cumulative exposure. This equated to a relative risk of 1.4 and a probability of causation of 0.4/1.4 = 29%.

This approach to attribution is only possible in limited circumstances: for well defined workforces, with complete follow up for a sufficient length of time and sufficient information to allow estimation of cumulative exposure to the relevant agent.

Disease aggravation

Aggravation of disease does not indicate an increase in disease incidence, but rather a worsening of the disease, which may be reversible, in those in whom it has developed. Asthma, for instance, can be:

a) caused by a number of different specific agents inhaled at work (e.g. enzymes, isocyanates) which increase disease incidence and
b) aggravated in those who already have asthma by a number of non-specific agents encountered at work (e.g. respiratory irritants SO_2, Cl_2 + cold air) which provoke acute airway narrowing.

While the distinction is clear for a disease characterised by reversible airway narrowing, it is less clear in cases of chronic disease characterised by a progressive loss of function; such as deafness and COPD, where the effect of the occupational exposure is to increase the rate of loss of function associated with ageing or cigarette smoking. Unlike the aggravation of asthma, the occupational exposure (noise, inhaled coal dust) causes a progressive and irreversible loss of function which occurs in addition to that caused by ageing or cigarette smoking. In these circumstances the incidence of the disease, defined by a particular level of functional loss, is increased and in some well defined circumstances can be doubled.

Attribution and disease registers

The strength of good epidemiological studies is their investigation of the population at risk (or a representative population sample), which allows valid estimation of relative (and attributable) risk. Disease registers depend on the reporting by physicians of cases which they have seen and which they consider attributable to work. Clearly only cases seen by physicians and those considered as being caused by work will be reported. This leads to two serious potential sources of bias whose magnitude can be difficult to estimate: ascertainment bias and attribution bias. Reports to the Surveillance of Work and Occupational Respiratory Disease (SWORD) voluntary reporting scheme, by chest and occupational physicians, identify many cases of occupational asbestos-related pleural disease (diffuse pleural thickening and malignant mesothelioma), but few cases of lung cancer. This is probably because diffuse pleural thickening and mesothelioma are uncommon among those not exposed to asbestos (nearly a necessary cause), and are therefore readily recognised as attributable to asbestos exposure, whereas lung cancer is common in the general population and predominantly attributable to another cause (cigarette smoking). Lung cancer, particularly in cigarette smokers, is less likely to be recognised or reported as caused by asbestos.

Conclusion

We can consider the attribution of disease to occupation as a hierarchy of probability of causation and difficulty of attribution:

The Hierarchy of Attribution

Causation		Example
• Accident	→	Acute inhalation accident
• Disease with specific clinical features	→	Occupational asthma
• Epidemiological evidence: By inference from population studies to individual case ("more likely than not")		
Easy	→	Mesothelioma
Difficult	→	Asbestos and lung cancer Coal and COPD

The recommendations of IIAC to the Secretary of State in relation to diseases which are not specific to occupation are based on robust epidemiological evidence. This has enabled the Council to recommend prescription in which it was previously thought not possible to prescribe.

From time to time occupational association with disease comes to the Council's attention in which inadequate evidence is found, despite thorough investigation, of a probability of causation greater than 50%, sufficient to meet the requirements of properly applied epidemiological science. It is sometimes tempting to make allowances in these circumstances and to accept a lower standard of probability, but to do so would undermine the principles that enable Ministers to rely on the robustness of the recommendations that the Council makes to them. For this reason the Council does not recommend that such diseases are added to the list of prescribed diseases. However, from the human aspect this can mean that certain workers may develop a disease which had they not been employed in a particular occupation or exposed to a particular agent might not otherwise have occurred. The Council is aware of this and keeps such conditions under review in order that they may consider recommendations of prescription if robust evidence of a greater than doubling of risk is reported.

Selected References

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The publications to mark the 100th anniversary of the Workmen's Compensation Act 1906, and the 60th anniversary of the National Insurance (Industrial Injuries) Act 1946 and the foundation of IIAC are available on the IIAC website (www.iiac.org.uk), or, in hard copy, from the IIAC secretariat (iiac@dwp.gsi.gov.uk).

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The Changing Nature of Occupation and Occupational Disease
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