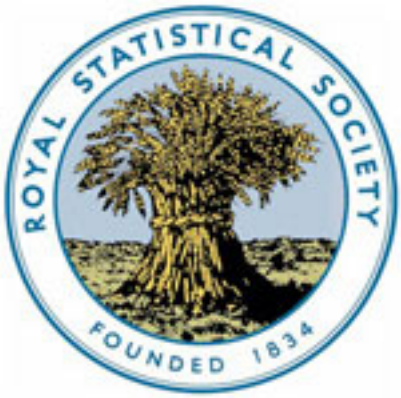

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Methods of Cohort Analysis: Appraisal by Application to Asbestos Mining

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SUMMARY

Longitudinal studies of occupational mortality have usually been analysed *a priori*: the cohort is subdivided in terms of potential stimuli and comparisons made between sub-cohorts in their patterns of mortality. The alternative *a posteriori* argument compares the dead with the living, searching for differences in the potential stimuli. We selected the following methods for appraisal: (a) comparative composite cohort analysis (Case and Lea, 1955), against external and internal standards; (b) the use of a fixed number of controls for each death (following Miettinen, 1969); and (c) that of Cox (1972) based on regression models. Method (a) argues *a priori*, the others *a posteriori*. These three methods have been applied to a large cohort study of mortality in the Quebec chrysotile asbestos-producing industry, focusing on lung cancer. The methods agreed in demonstrating a clear direct relationship, which may well be linear, between excess lung cancer mortality and total dust exposure. Method (a), with an external standard, is useful for placing the cohort in demographic context. In method (b), only three or four controls should suffice for each case, leading to possibilities of improved quality of data. Similar advantages might be achieved for method (c) through some sampling of the living, but it would remain more complex; while it facilitates the study of interactions and, without sampling, can provide absolute risks, it was very expensive.

Keywords: ASBESTOS MINING; CASE-CONTROL STUDIES; CHRYSOTILE EXPOSURE; COHORTS; DISCRIMINATION; EXPOSURE-RESPONSE RELATIONSHIPS; LUNG CANCER; MAN-YEARS; METHODS OF REASONING; MODELLING; OBSERVATIONAL STUDIES; OCCUPATIONAL MORTALITY; PARTITIONING OF CHI-SQUARED; PNEUMOCONIOSIS; STANDARDIZATION; SURVIVAL

1. INTRODUCTION

1.1 *Background*

IN a review of methods of epidemiological investigations, Doll (1964) concluded that the "prospective" approach had two main advantages over the "retrospective". "Firstly, there are less opportunities for the introduction of bias into the results: in particular, the data relating to the cause cannot be biased by knowledge of the effect since they are recorded before the effect is known to have occurred. Secondly, the results can be expressed simply and naturally in the form of incidence rates and the extent of the risk attributable to the factor under study can be measured quantitatively." For the definition of exposure–response relationships, so important in occupational and environmental health, the *a priori* logic employed in longitudinal or cohort studies has appeared to approximate to that in the experimental trial design, but in our investigations into the health effects of chrysotile asbestos in the mines and mills of Quebec we have come to appreciate how difficult it is in practice to express results "simply and naturally" as incidence rates. This is because we wish to compare the effects of exposure in terms of both dose (i.e. intensity or concentration) and time, and must deal correctly with subjects who have died or dropped out as a result of competing risks. Moreover, our research is prospective more in appearance than in fact, and, as in all such studies, it is

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only possible, in practice, to classify the subject's exposure in terms of length and intensity after it has ended. Further, termination of exposure may well be related to, or even caused by, the diseases under study. This is a common problem increasingly faced by occupational epidemiologists required to describe dose–response as a basis for environmental safety standards.

1.2. *Aim of Study*

The aim of the present paper is to review methods for the analysis of epidemiological cohort studies. We deal first with the conventional and subsequently with newer methods.

At first sight, application to data sets simulated with known hazards would have led to an objective evaluation of how well the various methods estimated the pre-set parameters. However, this would have required a large range of models, each with many data sets, and the costs would have been astronomic. Further, the results could not have been very definite, for if a data set included a hazard with a large effect, any analytical method would suffice, whereas, if the effect were subtle, the relation of model and techniques would be important. It therefore seemed reasonable to base evaluation on real data and, indeed, to use those of the Quebec asbestos study, outlined in Section 2. To exploit the methods to best advantage, the applications were carried out independently, including the selection of the exact forms of the stimulus variables.

1.3. *Definitions*

Methods for analysing cohort mortality fall into two broad classes, reasoning either *a priori* or *a posteriori*; these terms, from Latin, are used in the strict (*O.E.D.*) sense of characterizing argument from cause to effect, and from effect to cause, respectively.

As non-standard terminology can be misleading we have adopted the working definitions below:

Cohort: a population of subjects defined (usually by date of birth) for the purpose of follow-up.

Sub-cohort: a division of a cohort, according to some factor(s) such as quinquennium of birth, smoking habit, years of exposure.

Study interval: the interval over which each subject is studied in a particular facet of the study; this is not necessarily the same as the period over which the subject has been in view.

Because of ambiguity, the term "at risk" has been replaced by "in view", and "prospective" and "retrospective" have been avoided.

2. THE QUEBEC ASBESTOS MORTALITY STUDY

A cohort of all 10,951 men (and 440 women not considered here) born between 1891 and 1920, who had worked for at least one month in the chrysotile mining and milling industry in Quebec, was selected for study (McDonald *et al.*, 1971, 1973, 1974). For the purpose of this paper, the end of follow-up was December 31st, 1973. *For each man* the following information had been collected:

1. *Either* For the 4,037 known to have died before the end of 1973 (i.e. 37 per cent of the cohort) date of *death*, and cause for 97 per cent.
   or The fact of *survival* into 1974 (5,797 men, or 53 per cent of the cohort).
   or The last date, before the end of follow-up, when a subject "lost to view" was known to be alive; 1,117 men (10 per cent of the cohort) were lost to view, mainly after very short employment many years ago; only 176 men (less than 2 per cent of the cohort) were lost to view after 1935.

2. *History of employment*, up to November 1966, i.e. the dates of start and of termination of each job the man had had in the industry (averaging 5 per man). From estimates (provided by Dr G. W. Gibbs) of the concentration of airborne respirable dust, year by year, for each job identified, we calculated, for every calendar year from 1904 (the first recorded date of employment) to 1966, the proportion of the year for which the man was employed and his dust exposure (concentration × period, summed over jobs within the year). We also defined, for each man, his:
   Gross service: the period from start of first job to termination of last job (or to November 1966, if earlier).
   Net service: the total of periods of actual employment.
   Service gap: (gross service − net service)/(gross service).
   Total dust exposure: the total of annual dust exposures, summed over the period of gross service; the units are (million particles per cubic foot) × (years) or $10^6 pf^{-3} y$.
3. *Smoking habit*, assessed by questionnaire administered to 99·6 per cent of the living and to relatives of 93 per cent of those deceased after 1950; no attempt was made to determine smoking histories for about 900 men who died before 1950. Each man has been classified according to his reported smoking habit at the time of report as: non-smoker, ex-smoker, light smoker, medium smoker, heavy smoker, or not known.

The cohort was drawn from the two main chrysotile mining communities of Quebec, i.e. Asbestos (5,301 men) and Thetford Mines (5,650 men); the proportions of deaths, survivals and lost to view were closely similar. By the end of follow-up, the oldest men alive in the cohort were 82 years old, the youngest 53. Most of the deaths (2,791 or 69 per cent) occurred after 1955, a substantial proportion at ages greater than 65. Deaths in the years up to 1955 numbered 1,246 (31 per cent), most being at ages less than 45.

The primary aim of the epidemiological survey was "to define as accurately as possible the quantitative relationship between exposure to chrysotile asbestos and the incidence of lung cancer" (McDonald *et al.*, 1971). Mortality from lung cancer is, of course, known to be associated with smoking, and the concern must be to attempt to separate the hazards. It is also important to consider total mortality, if only to confirm that an excess of deaths from lung cancer does not blind us to a greater shortfall from other causes, as has sometimes happened. We selected pneumoconiosis (asbestosis) for special study, because of its assumed relation to dust exposure; it therefore allowed a test of the quality of our information relating to dust exposure, as well as of method.

A few of the possible hypotheses that can be advanced about the form of relationship between exposure to airborne particulate matter and mortality are: hazard increases in monotonic fashion with total exposure; a disease process is initiated when total retention reaches some threshold value; each quantum of retained dust has an equal, infinitesimal, chance of damaging cells and causing a disease process; once dust is retained in the lung it is not eliminated and each quantum of retained dust causes progressive disease.

3. METHODS BASED ON *A PRIORI* REASONING

3.1. *Bases*

The foundation of methods which argue from cause to effect is that the cohort is subdivided in terms of stimulus (and disturbing) variables, and, for each sub-cohort, measures of mortality are obtained in relation to some standard. This approach is traditional, simple in concept and provides the possibility of assessment of absolute risks.

3.2. *Standard of Comparison*

The usual external standard of national mortality is not necessarily relevant to a specific occupational cohort, because of geographic, socio-economic and selection factors. More localized rates (e.g. for provinces in Canada) may not overcome even the geographic objection:

for example, rates for the Province of Quebec are for a population roughly half of which lives in Greater Montreal and which differs in many ways from the inhabitants of the predominantly rural mining areas. Nevertheless, one object of any study of occupational mortality must be to compare the cohort in broad terms with the general population. However, more specific aims will usually require the comparison of sub-cohorts, and for this the internal standard will often be appropriate.

3.3. *Study Intervals*

Selection of an appropriate study interval has been discussed by, among others, Enterline and Henderson (1973) and Fox (1976), who point out that long exposure appears to improve life expectancy. To compare like with like, the study interval must start for all men at the same point relative to entry to employment; for example, the sub-cohort with at least 20 years of service must be contrasted with men who had also survived at least 20 years since their service began. In the Quebec cohort this would permit study of 3,168 deaths (78 per cent of all deaths); earlier deaths can be examined provided the study interval terminates 20 years after start of service.

It follows that, to investigate the effects of length of service or of any other stimuli which vary with time, it is essential to base the classification of sub-cohorts on the values of the stimulus variables at the start of the study interval. Otherwise, a man's classification will change from time to time during his service. Although Mantel and Byar (1974) suggested the reclassification of each subject at the instant he crossed a boundary between levels of classification, they noted that this procedure involves an implicit assumption that cannot always be justified.

3.4. *Man-years in View*

The measures of mortality considered most acceptable are obtained by what Case and Lea (1955) called "comparative composite cohort analysis", which compares experience in a "closed" population (i.e. a sub-cohort of unchanging definition) with an expected experience calculated for that population at some standard rate. The expected experience is found by applying age-, year-, cause-specific death rates from a standard population to "man-years in view" for the sub-cohort. Man-years are found by summing (over all men in the sub-cohort) the years between the start of the study interval and the earliest date of: death, end of follow-up (for survivors), last trace, or end of the study interval. Those lost to view are, thus, dealt with appropriately in the calculation of expectations, and, in theory, observed and expected deaths, by cause, become available for each one-year square (or triangle) in the relevant diagonal band of the Lexis (1875) age/time diagram. In practice, five-year squares have been used for calculation.

3.5. *Summarization and Analysis*

Once observed deaths and expected deaths have been obtained, it has been common to sum them over all eras and ages at death, and to form a ratio, which can be seen to be the Standardized Mortality Ratio (SMR), with all the disadvantages of standardization, and particularly those associated with the "indirect" method (Liddell, 1960). On theoretical grounds, there is some justification for standardizing by the "inverse" method (Kerridge, 1958), but the SMR is the more easily manipulated. However, it remains important to consider whether or not the ratios for different ages and eras of death are consistent within a sub-cohort. An indication of the *P*-value of any unusual SMR can be obtained from the "critical ratio", i.e.

$$(\text{observed} - \text{expected})/(\text{expected})^{\frac{1}{2}},$$

which has zero mean and variance close to unity when the number of expected deaths is large.

The observed deaths (O) and expected deaths (E) for desired combinations of age and era of death for each sub-cohort can also be subjected to some form of analysis or modelling.

They can be expressed in derived form, for example as the SMR or its critical ratio, or can be treated as covariates. GLIM (Nelder, 1975) appears the most suitable of extant programs for this purpose, if only because of its flexibility. Dr I. D. Hill has kindly agreed to explore the application of GLIM to the Quebec cohort; meanwhile, the analyses described in Section 4 below have relied on the partitioning of χ^2.

3.6. *Definition of Sub-cohorts*

There are several aims, mainly conflicting, in the definition of sub-cohorts; they should be mutually exclusive and comprehensive, fairly equal in size and large enough to provide reliable measures of mortality, yet small enough to be homogeneous, preferably with at least three classes of each factor of interest in the dose–response relationships. However, there are usually several such factors and their interactions may be important, so that there have to be many sub-cohorts. The compromise adopted for the Quebec cohort is illustrated in Table 1.

TABLE 1

Size of sub-cohorts taking account of gross service, age at start, dust exposure and service gaps

		Total dust exposure			
Gross service	*Age at start*	*Low*	*Medium*	*High*	*Very high*
Less than 1 *year*		<1†	1, <3	3, <10	$\geqslant 10$
	Less than 25	519	410	331	403
	25 or more	505	429	241	175
1 *yr, less than* 5		<6	6, <30	30, <100	$\geqslant 100$
	Less than 25	268	426	307	302
	25 or more	327	443	177	78
5 *yrs, less than* 20		<30	30, <100	100, <300	$\geqslant 300$
Gap less than 20%	Less than 25	103	160	211	269
	25 or more	325	393	205	131
Gap at least 20%	Less than 25	342		175	
	25 or more	150		41	
20 *yrs or more*		<100‡	100, <300	300, <600	$\geqslant 600$
Gap less than 20%	Less than 25	316	393	289	430
	25 or more	347	294	175	152
Gap at least 20%	Less than 25	432		143	
	25 or more	101		33	

† Total dust exposure in units of $10^6 pf^{-3}\,y$.
‡ Total dust exposure over 20 years from start of service.

Further sub-division by mining area (Asbestos or Thetford Mines) yielded 80 mutually exclusive sub-cohorts. Comparison between them had to be in terms of deaths after 20 years from the start of service; on average, each sub-cohort included 40 deaths from all causes, but only three from lung cancer and one from pneumoconiosis.

Attention must be drawn to the large number of simultaneous inferences that are implied in a study of interactions. If *P*-values are required, some adjustment, perhaps by appeal to the Bonferroni inequality, will be necessary.

4. APPLICATIONS TO THE QUEBEC COHORT: *A PRIORI* REASONING (COMPARATIVE COMPOSITE COHORT ANALYSIS)

As already stated, the first concern in any mortality study must be to place it in context; this can only be done through an external standard, chosen to be as relevant as possible. For the Quebec cohort, we assembled annual mortality rates for males in the Province of Quebec, based on deaths and on estimates of mid-year populations, in five-year age groups, 15 years and upwards, for the years 1936 to 1973. Where causes of death had been coded into earlier editions of the International Classification of Diseases, translation was made into the seventh edition with the advice of Statistics Canada, which kindly made available the raw material. The Quebec material related to all causes of death and to cancers of the lung and trachea and of certain other sites.

Table 2 shows deaths, 1936–73, from all causes observed in the cohort against expectations based on the Province's rates, by era and age of death blocks, of men who worked at Asbestos

TABLE 2

Deaths, all causes, in the Quebec cohort, observed 1936–73 and expected on the basis of the Province's rates

Block		*Asbestos*			*Thetford Mines*			*Quebec Cohort*		
Era of death	*Age at death*	*Observed (O)*	*Expected (E)*	*Ratio (O/E)*	*Observed (O)*	*Expected (E)*	*Ratio (O/E)*	*Observed (O)*	*Expected (E)*	*Ratio (O/E)*
1936–55	15–44	193	182·04	1·06	224	198·48	1·13	417	380·88	1·09
1936–55	45–64	250	281·30	0·89	291	269·27	1·08	541	550·54	0·98
1956–73	35–44	35	27·46	1·27	25	31·58	0·79	60	59·03	1·02
1956–73	45–64	699	663·92	1·05	755	688·66	1·10	1,454	1,352·47	1·08
1956–73	65–82	626	602·78	1·04	651	544·93	1·19	1,277	1,147·70	1·11
	Total	1,803	1,757·90	1·03	1,946	1,732·92	1·12	3,749	3,490·63	1·07

N.B. Expected deaths do not always "add up" because the programs were written in single precision.

and Thetford Mines. The excess at Asbestos (2·57 per cent) was small, but consistent over most blocks, but that at Thetford Mines (12·30 per cent), also consistent over most blocks, was significant in more than the statistical sense. Table 3 breaks down the observed deaths by cause, with expectations where available.

TABLE 3

Deaths in the Quebec cohort, by cause, 1936–73

Cause	*Observed (O)*	*Expected (E)*	*Ratio (O/E)*	*Excess (O–E)*
Cancer of lung and trachea	214	171·65	1·25	42·35
Cancer of abdomen	292	290·82	1·00	1·18
Pneumoconiosis	40	—	—	40
Cause unknown	93	—	—	93
Sub-total	639	462·47	—	176·53
All other causes	3,110	3,028·16	1·03	81·84
All causes	3,749	3,490·63	1·07	258·37

SMRs based on the complete cohort as standard revealed considerable differences between the two regions. In particular, an excess at Thetford Mines for abdominal cancer was brought to light, despite the evidence in Table 3, because of a shortfall at Asbestos when compared with the Province. Excesses due to respiratory tuberculosis and "other" respiratory disease could not be elucidated because Provincial rates were not available.

Mortality in the 80 sub-cohorts defined in Section 3.6 was investigated using an internal standard. Study of main effects and first-order interactions was not revealing. Therefore, for lung cancer, we found the χ^2 statistic with 78 degrees of freedom (one sub-cohort was void) as 123·43, and partitioned it into 78 orthogonal components, summarized in Table 4. The 55 sub-cohorts where total exposure was less than 300 $10^6 pf^{-3} y$ were homogeneous in the risk

TABLE 4

Lung cancer mortality in the Quebec cohort in relation to total dust exposure, relative risks and χ^2 statistics

Total dust exposure in units of $10^6 pf^{-3} y$ *over 20 years since start of service*	*Observed* (*O*)	*Expected* (*E*)	*Ratio* (*O*/*E*)	*Relative risk*	χ^2 *statistics* (*a*)	(*b*)
Less than 3	28	31·93	0·88	1	—	3·49 (7)
Less than 10 (c)	11	19·09	0·58	0·66	1·08	4·48 (7)
Less than 30 (c)	17	18·76	0·91	1·03	0·28	3·65 (7)
Less than 100 (c)	37	40·08	0·92	1·05	0·37	19·20 (14)
Less than 300 (c)	34	45·02	0·76	0·86	0·27	14·37 (15)
Sub-total	127	154·88	0·82	—	1·99	45·19 (50)
300 or greater (d)	43	31·04	1·39	1·58	8·26	36·00 (19)
600 or greater	28	12·13	2·31	2·63	22·13	9·85 (3)
Total	198	198	1	—	32·38	91·04 (72)

All men, followed from 20 years after start of service to 1973. Expected deaths are based on the cohort as standard.

(a) Each with one degree of freedom comparing each dust class with all above it in the table, except that the sub-total and total have four and six degrees of freedom, respectively.

(b) Comparing sub-cohorts within the dust class; figures in brackets are degrees of freedom.

(c) Excluding those sub-cohorts in class above this in the table.

(d) Excluding those sub-cohorts in class below this in the table.

of lung cancer (with the possible exception of three sub-cohorts at Thetford Mines involving gaps of at least 20 per cent in recorded service), the SMR being 0·82. As the external SMR for the complete cohort, 1936–73, was 1·25, and internal SMRs for the complete cohort were almost identical for 1911–73 and 1936–73, the external SMR for these 55 sub-cohorts would be around 1·03, undoubtedly close to unity. The 24 sub-cohorts where total exposure was 300 $10^6 pf^{-3} y$ or greater were much more heterogeneous, including several without apparent enhanced lung cancer risk, but also several with much higher risks. However, we were unable to determine any pattern in the heterogeneity. Of the 36 deaths from pneumoconiosis, five were in the 39 sub-cohorts with exposure less than 100 $10^6 pf^{-3} y$; these five may reflect exposure to dust hazards outside recorded experience in the Quebec asbestos mines and mills, but even so the (internal) SMR was 0·25. In the four sub-cohorts exposed to more than 600 $10^6 pf^{-3} y$, there were 15 pneumoconiosis deaths, yielding SMR = 6·88 and so the risk, relative to the 39 low exposure sub-cohorts, was 27·77. The 36 intermediate sub-cohorts accounted for 16 deaths, with SMR = 1·17 and relative risk 4·73.

Mortality from all causes, 1936–73, in the complete cohort classified by smoking habit is summarized in Part (1) of Table 5. The enormous SMR among those whose habit was "unknown" is an artefact because questionnaires were not administered to the relatives of those who had died before 1951. That the "ex-smokers" had a very low SMR may also be a reporting artefact; there is some support in Part (2) of Table 5, which relates to deaths since 1971 because (a) most of those alive in that year supplied information themselves and (b) there was only a short period for a change of habits.

TABLE 5

Mortality in the Quebec cohort according to reported smoking habit

	Part (1): 1936–73			*Part* (2): 1972–73		
	Observed (*O*)	*Expected* (*E*)	*Ratio* (*O*/*E*)	*Observed* (*O*)	*Expected* (*E*)	*Ratio* (*O*/*E*)
Non-smokers	301	387·69	0·78	30	45·89	0·65
Ex-smokers	204	444·39	0·46	44	61·08	0·72
Light smokers	854	1,117·98	0·76	128	128·15	1·00
Medium smokers	1,327	1,179·16	1·13	154	132·86	1·16
Heavy smokers	284	243·14	1·17	30	26·74	1·12
Sub-total	2,970	3,372·36	0·88	386	394·72	0·98
Unknown	779	118·48	6·57	5	1·70	2·94
Total	3,749	3,490·84	1·07	391	396·42	0·99

Expected deaths based on Province as standard.

It would not have been possible to investigate interactions between smoking habit and dust exposure by further subdivision of the 80 sub-cohorts of Section 3·6, and so the longest service group (at least 20 years) was reclassified by five smoking habits (excluding the "unknown") and the same six exposure/gap combinations (but ignoring differences between age at start and mining area) to produce 30 sub-cohorts, comprising 3,020 men (97 per cent of the 3,105 in the complete group). The lung cancer SMRs were 0·48 and 0·46 for non-smokers and ex-smokers, thereafter increasing steadily to 2·06 for heavy smokers; these last had a relative risk of 4·30, compared with non-smokers, rather smaller than in other studies. For pneumoconiosis, the small numbers required grouping, leading to SMRs as follows: non- and ex-smokers: 1·11; light smokers: 1·11; medium and heavy smokers: 0·85. We could find little evidence of interaction between dust exposure and smoking habit, probably because there were so few deaths (87 from lung cancer, 31 from pneumoconiosis) and because of the artefacts of reporting smoking habits already discussed.

5. METHODS BASED ON *A POSTERIORI* REASONING

The foundation of methods which argue from effect to cause is some form of discrimination, in terms of exposure factors, between those dead and those living (controls); as always, the criteria of what constitutes an appropriate control are vital.

The simplest method is to obtain a single control for each case and use established techniques to calculate relative risks and assess statistical significance. An extension, proposed by Miettinen (1969), is to choose a fixed but greater number of controls for each case. Ury (1975) has shown that, on reasonable assumptions and with a single stimulus variable, the relative efficiency obtained with r controls is $2r/(r+1)$, i.e. from 1 with a single control to a maximum of 2.

As there is no fundamental reason why subsequent death should disqualify a control, the approach could be extended further to use all living as controls for each man dying, or more realistically for each age at death. One possibility is to proceed as follows: define a "section" of the sub-cohort born in a particular year as all those in view at a certain age who either died or remained in view throughout a defined number of further years, and discriminate between those dead and survivors, in terms of exposure factors; the process of definition and discriminant analysis can be repeated for as many sections as required. The discriminant analyses are orthogonal to each other, and further discrimination can be carried out, on those who have died in each section, according to cause of death. This procedure appears preferable to the use by Oldham and Rossiter (1965) of a $(K+1)$-group discriminant analysis where only one of the K degrees of freedom is used for comparing quick and dead.

In a more sophisticated approach proposed by Cox (1972) each death is compared to all those surviving to the same time, leading to maximum likelihood estimates of the parameters of a model of an individual's instantaneous risk of dying (force of mortality). This model makes no assumptions about the form of the relationship between the force of mortality and time, but assumes that it depends exponentially on a linear combination of the case's stimulus variables. In long-term observational studies, where it is not natural to measure time from the start of observation, the extensions of Cox's method discussed by Thomas (1976) are required. In the present paper, we treat age as the time dimension and date of birth as a disturbing variable, forced into the analysis in the first step. Cox (1972) has also shown how risks, both absolute and relative, can be obtained. However, methods using *a posteriori* reasoning do not provide a comparison with an external standard.

When there is only one dichotomous stimulus variable, Cox's method is the same as the "log rank" test (Mantel, 1966; Mantel and Byar, 1974), which compares survival curves for two groups defined by a stimulus variable, and so argues *a priori.*

In all the above methods, each comparison of dead with living allows the stimulus variables for the living to be determined in relation to the time of death of the case. Further, the number of variables that can be investigated is limited conceptually only by the number of deaths in the section; practicality imposes more serious restrictions. It is tempting to enter a variable such as place of work as a dummy; however, this forces certain further assumptions on the models (*cf.* Chang and Afifi, 1974) and it would seem desirable to carry out a separate analysis for each place of work.

6. APPLICATIONS OF *A POSTERIORI* REASONING TO LUNG CANCER MORTALITY IN THE QUEBEC COHORT

6.1. *Case and Fixed Multiple Controls*

The Miettinen approach was evaluated by considering five controls for each of the 215 lung cancer deaths. The selection of controls was strictly at random from among men born in the same year as the case and known to have survived at least into the year following that in which the case died. That there were only 1,290 men in this study made it possible to re-examine all smoking history questionnaires which failed validity checks or otherwise aroused doubts. As a result, codes were changed for 122 men (nearly 10 per cent of 1,290), although altering the classification for only 39 men (3 per cent). However, the opportunity was taken to reclassify those who had given up smoking, according to the report, into those who had been *ex-smokers* for at least seven years when the case died, and *recent smokers.*

Table 6 gives the distributions of smoking habits of the 215 cases and of each batch of 215 controls, according as they were first, second, etc. to be selected. A comparison of the distributions in these five batches of controls yielded $\chi^2 = 16{\cdot}79$, with 24 degrees of freedom, which provides a satisfying check on the selection procedures. This table also provides relative risks based on r controls for each case, with $r = 1, 2, 3, 4, 5$. Accepting that $r = 5$ gives risks closest to the truth, it would appear that approximations were adequate for $r = 4$ and, perhaps,

TABLE 6

Effects of numbers of controls on assessment of smoking habits and on relative risks of lung cancer

	Distributions										
		Control batch No.					*Relative risk based on*				
	Case	1	2	3	4	5	$r = 1$	$r = 2$	$r = 3$	$r = 4$	$r = 5$
Non-smokers	11	20	24	21	26	26	1	1	1	1	1
Ex-smokers	9	18	25	21	10	17	0·91	0·84	0·83	1·01	1·05
Recent smokers	8	15	15	17	14	13	0·97	1·07	1·01	1·08	1·15
Light smokers	37	74	68	67	62	65	0·91	1·04	1·05	1·13	1·17
Medium smokers	100	64	65	73	82	75	2·84	3·10	2·93	2·91	2·96
Heavy smokers	25	19	14	10	14	14	2·39	3·03	3·44	3·63	3·75
Sub-total	190	210	211	209	208	210					
Unknown	25	5	4	6	7	5	(9·09)	(11·11)	(9·85)	(9·40)	(9·85)
Total	215†	215	215	215	215	215					

† Including one death before 1936; *cf.* Table 3.

3. Significance tests were also carried out for each value of r. There was no suggestion that differences between the four groups who smoked least (non-smokers, ex-smokers, recent and light smokers) would have been revealed however many controls might have been selected, despite relative risks with five controls which, taken at face value, might seem to indicate a monotonic trend. The contrast between these four groups and medium smokers yielded a χ^2 statistic of 26·09 even with a single control; more controls did lead to higher statistics, with a maximum of 35·38 for $r = 3$. The contrast between heavy smokers and the rest led to χ^2 statistics which increased as the number of controls was increased, from 1·72 quickly at first but slowly thereafter to 9·16.

Three exposure variables were examined: (i) total dust exposure up to seven years before the death of the case; (ii) net service during the same period; and (iii) age at start of service. The null hypotheses that these factors have the same central tendencies in cases and controls were tested by the Friedman (1937) ANOVA of ranks, partitioned to contrast case against all controls, and so the test statistic was always χ^2 with one degree of freedom. The values of χ^2 with one control per case were: (i) 7·82; (ii) 4·76; (iii) 0·17; and with five controls for each case were substantially higher: (i) 16·27; (ii) 12·21; (iii) 4·40. The greatest discrimination between cases and controls was with (i), the only stimulus variable examined in the rest of Section 6.1.

Table 7 gives the distributions of the cases and controls by this variable, together with relative risks, and χ^2 statistics. There was no trace of significant differences between the five lowest exposure groups, despite a fairly consistent trend in relative risks. However, for exposure above 300 $10^6 pf^{-3} y$ there was an important increase in relative risk with each of the four increases of exposure: *cf.* Table 4. As to the effects of the numbers of controls, the various χ^2 statistics increased with r up to $r = 4$, but were probably by then close to the maximum possible.

It is a disadvantage of this approach that several stimulus variables can be considered simultaneously only if controls have been chosen matched for all but one of the variables. For example, we were able to choose (from among the original selections) one control for each case who came from the same mining area. We found that relative risks of exposure amounting to 300 but less than 1,000 $10^6 pf^{-3} y$ were similar in the two areas, but for the more heavily

TABLE 7

Dust exposure in lung cancer cases and controls (5 per case), relative risks and χ^2 statistics

Total dust exposure in units of 10^6 pf^{-3} y up to 7 years before death of the case	*Cases*	*Controls*	*Relative risk*	*χ^2 statistic, each with 1 d.f., comparing each dust class with all above it in the table*
Less than 6	43	285	1	—
6, less than 10	10	62	1·07	0·03
10 less than 30	24	166	0·96	0·04
30, less than 100	37	211	1·16	0·44
100, less than 300	31	168	1·22	0·45
Sub-total	145	892	—	0·95 (4 d.f.)
300, less than 600	27	95	1·88	5·22
600, less than 1,000	18	50	2·39	6·26
1,000, less than 1,500	10	19	3·49	7·36
1,500, less than 2,000	6	8	4·97	7·23
2,000 or greater	9	11	5·42	11·74
Total	215	1,075	—	38·76 (9 d.f.)

exposed the risk appeared higher at Thetford Mines than at Asbestos, although small numbers rendered this comparison rather unreliable. To examine the interaction of smoking habit and dust exposure, we would have had to select controls matched for the smoking habit of the case. This re-emphasizes the importance of the criteria for choosing controls: had the original selection of five controls for each case incorporated both the additional criteria just discussed, more precise statements could have been made about the effect of dust exposure and how they varied with smoking habit and mining area.

6.2. *Regression Methods*

For this approach, fully described by Thomas (1977), the 2,194 men without smoking questionnaires were excluded and the 1,472 questionnaires which failed certain feasibility tests were "edited" into conformity by replacing missing and unacceptable values by cohort averages. These data and those on dust concentration and length of service were used to obtain: a "crude" smoking index (based on the number of cigarettes smoked); a "crude" dust index (total exposure to the point of comparison); and "refined" smoking and dust indices (to allow tests of specific hypothesis about the form of relationships with lung cancer).

In a first stage, stimulus variables associated with mortality were selected by a "stepwise" version of Cox's method, using a test suggested by Cox (1972), based on the score function and locally equivalent to the Likelihood Ratio (LR) test, but not requiring iteration. After this selection of variables, the LRs were calculated: on the null hypothesis, they are distributed as χ^2 with one degree of freedom. Date of birth was entered first, followed by the "crude" indices of smoking and dust; thereafter the "refined" indices were selected by strict "build-up" selection until a stopping criterion had been met, i.e. the LRs for all remaining variables were below an arbitrary limit.

Because of the well-known secular trend in lung cancer mortality, date of birth led to a large LR (20·78), risk being higher for those born later. High LRs were also associated with the "crude" indices of (cigarette) smoking (29·09) and dust exposure (52·52). Only two more variables were selected before the stopping rule came into operation, but as in many multiple regression analogues, we have found interpretation impossible.

In the second stage, absolute risks were estimated after several more steps of the first stage had been carried out (with a lower LR in the stopping rule) to provide a better means of classifying each subject, at each observed death at which he was in view. That classification (above or below the mean of the selected index) varies over time because of change in the subject's index or in the mean. Observed and expected deaths computed by the method of Mantel and Byar are shown in Part (1) of Table 8, for which $\chi^2 = 58{\cdot}53$ (three degrees of freedom), compared with $\chi^2 = (29{\cdot}09 + 52{\cdot}52 =) 81{\cdot}62$ (two degrees of freedom) from Cox's method.

TABLE 8

Estimates of attributable risk of lung cancer

Classification		*Part* (1)			*Part* (2)	*Part* (3)
		Deaths			*Net probability of dying of lung cancer by age* 80	
Smoking	*Dust*	*Observed*	*Expected*	*Ratio*	*Cox estimate for "mean individuals"*	*Mantel–Byar estimate for groups*
Low	Low	31	71·46	0·43	0·0209	0·0405
Low	High	35	30·38	1·15	0·0497	0·0581
High	Low	67	61·85	1·08	0·0448	0·0841
High	High	58	27·31	2·12	0·1099	0·1451
		191	191	1	0·0387	0·0722

Groups classified in terms of mean values of derived smoking and dust exposure risk functions over each risk set.

We have also estimated the survivorship functions and, for comparative purposes, have used their values at age 80, i.e. the "net probabilities of dying, by 80, of lung cancer in the absence of competing risks" (Chiang, 1961). Parts (2) and (3) of Table 8 give the net probabilities obtained by two methods. As before, the Cox estimates were more sharply differentiated and indicated that the dust effect was the larger.

More practical probabilities were obtained by corresponding calculations for subjects allocated to various more plausible exposure patterns, and suggested that a non-smoker would have required the equivalent of 50 years exposure to a dust concentration around 15 $10^6 pf^{-3}$ for his net probability of dying of lung cancer by 80 to have been the same as that of a 40-cigarette a day man never exposed to dust.

7. DISCUSSION

As Cox has said, "formulating the precise question is often the most critical part of the statistical analysis". In most studies, at least one scientific hypothesis can be stated in general terms, but there may be several specific alternatives. For each alternative, at least one stimulus variable can be defined, and a selection has to be made of the most appropriate. Only then is it possible to define sub-cohorts which will allow quantification of the selected hypotheses, by obtaining measures of mortality for each sub-cohort, which then have to be summarized, with some estimate of error.

We remain of the view (Liddell, 1975) that the evaluation of hypotheses can best be carried out by *a posteriori* methods. The two such methods we have examined produced closely similar results and both can be used for hypothesis evaluation. Although there is, as yet,

little formal theory to back the Miettinen approach, it has the advantage of simplicity. In practice, it permitted the choice of one measure of exposure, among three, in terms of discriminating power. Further, because the data could be contained on one small index card per case, the work required to make that choice also provided insight into how the hypothesis based on that measure could be tested (Table 7). Multivariate generalization has not been explored, but several factors can be examined simultaneously by choosing controls matched for all but one factor. A "stepwise" procedure is possible within the regression method, but has been found expensive, and suffers from the inevitable and well-recognized problems of simultaneous inference, "intolerance" and interpretation, particularly in the assessment of synergisms.

Miettinen (1969) appears to have been first to propose more than one control for each case, and in his example selected four. The same selection was made, on intuitive grounds, by Eyssen and Liddell (1974) and has recently been shown (Ury, 1975) to provide about 80 per cent of the information possible. We have found that, with 215 lung cancer cases, three or four controls per case sufficed; thus the lung cancer questions could be answered satisfactorily on information relating to about one-tenth of the Quebec cohort. Although the complete cohort had to be defined and followed for the purpose of case-finding, work histories and smoking questionnaires would have been needed for only about a thousand men, and so effort could have been concentrated to improve quality. We consider this a powerful argument in favour of the fixed control method until the regression method has been modified to accept sampling of the living; there are, however, indications (Thomas, 1977) that such sampling is feasible.

Once the "best" hypotheses have been selected, risks have to be assessed. Cox (1972) has provided a means of calculating risks based on prediction from his model of relative hazards. Some evaluation of how well these predictions fit the data is necessary, particularly with extreme values of the stimulus variables. One means of testing fit is described by Mantel and Byar (1974). The regression method also permits the calculation of risks to the hypothetical individual.

Absolute risks can still be assessed *a priori* without sampling of the living. The process is relatively straightforward after hypotheses have been decided upon, when the problem of continuing variable exposure can be largely overcome. Analysis based on man-years in view would then seem to be best. An alternative might be to use the log rank method (Mantel and Byar, 1974), but we have not determined where its advantages lie.

Whether the standard of comparison is internal or external is unlikely to affect relativities, but only the use of an external standard would have revealed the considerable shortfall of deaths from abdominal cancer at Asbestos. Minor deviations may arise when the external standard is not strictly comparable with the cohort, but such a standard may yet be useful for setting the mortality of the entire cohort in context, and for demonstrating whether or not the sub-cohorts exposed to the smallest hazards have mortality close to that of the standard. Caution is still required: for example, non-smokers in the cohort should have better than standard lung cancer mortality where the standard contains the usual proportion of smokers.

Measures of mortality must, of course, be examined for variation by era and age of death, or other disturbing factors. Should variation be pronounced, no single statistic can describe a sub-cohort's mortality experience; otherwise, any of several statistics (SMR, survival to a pre-determined age, etc.) should reveal the pattern of differences between sub-cohorts. The SMR has the advantage that a standard error can be obtained easily, by the well-known method when the standard is external and by a slight adaptation otherwise, always bearing in mind that it may be desirable to determine the standard error for various eras and ages of death.

We agree with Bradford Hill (1961) that "if a collection of figures is worth a statistical analysis at all, it is, obviously, worth the best form of statistical analysis, i.e. the form which allows the maximum amount of information to be derived from the data". The first reported analysis (McDonald *et al.*, 1971) of the Quebec cohort was not the best possible. It relied on cumulative mortality (ignoring era and age of death), allowed imperfectly for losses to view,

and used a rather inflexible method of calculating expectations from an external standard, while the selection of sub-cohorts rendered particularly difficult the investigation of interactions. Nevertheless, its findings have been closely confirmed by our present studies. It is not surprising that various methods of analysis lead to essentially the same conclusion. However, the validity of the conclusion depends on the quality of the data—for Hill's dictum has the equally important converse, that no method can achieve good results with poor data. This perhaps is where an *a posteriori* approach combined with sampling of the living has the edge, for it allows effort to be concentrated on improving the accuracy of the basic information for analysis.

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ADDENDUM

By D. C. THOMAS

As most of the computing cost for the Cox method was in the calculations for the living, doing them on only a sample of each risk set can yield considerable savings. In the study of Section 6.1, the five controls are a random sample of the risk set for their case. The obvious way to reconstruct Cox's likelihood is to divide the contributions of the controls by their sampling fractions. However, an alternative generalization results from ignoring the sampling fraction, to obtain:

$$L^* = \prod_{i=1}^{n} [\exp(\beta z_{i0}) / \sum_{k=0}^{K_i} \exp(\beta z_{ik})],$$

where subscript i indexes the case/control sets and 0 and k represent cases and controls respectively. This is the conditional likelihood that the particular subjects $i0$ are the cases, given that one of each set of K_i+1 subjects is a case.

Repeating the analyses of Section 6.2 using L^* led to similar results, neither method producing systematically larger χ^2 statistics. The cost was about one twentieth that of the full cohort analyses.

When the number of controls is fixed (but not necessarily otherwise), the score function test based on likelihood L^* is identical to Pillai's (1960) trace criterion in multivariate analysis of variance, with the advantage for small samples of an approximate F-test, which takes sample size into account and appears to be slightly more powerful.

Table 9 compares the two tests for the continuous variables: 'crude' smoking and dust indexes and their product; the differences between the tests resulted from unequal numbers of controls because some smoking habits were unknown. (The denominator degrees of freedom of F are so large that critical values are nearly equal to those of χ^2.) Thus it appears that tests

TABLE 9

Differences between significance tests on continuous variables in lung cancer cases each with r_i controls ($0 \leqslant r_i \leqslant 5$)

Additional variable	*Degrees of freedom*	*Significance test*	
		Score function (Cox, 1972: χ^2)	*Trace criterion* (Pillai, 1960: F)
"Crude" smoking index	1	40·75	42·57
"Crude" dust index	1	57·74	66·00
Product of above indexes	1	0·01	0·49

of significance can be accomplished by any of the widely available MANOVA programs, but there is no obvious way to estimate relative risks from MANOVA.

For continuous variables, Cox's model provides an estimate of relative risk per unit change of each stimulus variable, holding the others constant. However, for descriptive purposes, it is often desirable to discretize the stimulus variables and find relative risks for each level.

Part (2) of Table 8 used the cross-product estimator for $2 \times L$ tables, because there was then no matched method for multiple controls *and* multiple levels of the stimulus variables. Miettinen (1970) had discussed the use of multiple controls but restricted to all-or-none stimuli, and Pike *et al.* (1975) had discussed multi-level discrete stimuli, but restricted to one control.

Now if the stimulus variable is all or none, $\exp(\beta z)$ can be replaced by 1 or r and, if the number of controls is fixed, **L*** reduces to Miettinen's (4.1). Similarly for an **L** level discrete stimulus, we need only set up **L–1** indicator variables z_l with $\exp(\beta_l z_l) = r_l$ and in the single control situation, L^* becomes Pike *et al.*'s (1). Thus, likelihood L^* represents a general solution incorporating the capabilities of both methods. Additionally, it allows a multivariate analysis of continuous or discrete stimuli and does not require the number of controls to be fixed.

TABLE 10

Significance tests and relative risks on discretized variables in lung cancer cases each with r_i controls ($0 \leqslant r_i \leqslant 5$)

SIGNIFICANCE TESTS

Additional variable	*Degrees of freedom*	*Likelihood ratio ($L^* = \chi^2$)*
"Crude" smoking index (a)	2	47·47
"Crude" dust index (b)	3	48·31
Product of above indexes	6	5·16

ESTIMATES OF RELATIVE RISKS

	"Crude" dust index (b)			
"Crude" smoking index (a)	*Less than* 10	10, *less than* 100	100, *less than* 600	600 *or greater*
0	0·20	0·09	0·28	0·85
	(0·14)	(0·17)	(0·31)	(0·82)
1, less than 23	0·37	0·51	1	2·75
	(0·46)	(0·54)	(1)	(2·63)
23 or greater	0·55	0·84	1·12	2·51
	(0·61)	(0·71)	(1·32)	(3·48)

Risk is expressed relative to that in the most populous group.
Risks in brackets were obtained by postulating a multiplicative model.

(a) Average number of cigarettes smoked a day.
(b) Total dust exposure to year of death of the case, in units of $10^6\ pf^{-3}\ y$.

Table 10 illustrates its application, after discretizing the smoking index into three levels and the dust index into four. The non-significance of the dust-smoking product suggests that, in these data, the estimates constrained to a multiplicative model are probably to be preferred.

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Discussion of the Paper by Professors Liddell and McDonald and Dr Thomas

Mr G. BERRY (Medical Research Council): It is indeed a pleasure to congratulate Professors Liddell and McDonald and Dr Thomas on their interesting and relevant paper; I am glad to see that Dr Thomas was able to come over from Montreal to be here tonight. The analysis of mortality in an occupational or environmental setting has been responsible for confirming many important results; e.g. the association between lung cancer and asbestos, and the need for this type of study is likely to continue. Therefore a comparison of methods on a real set of data is valuable at this time. I think the main value of such a comparison is not that it shows a definite superiority of any particular method but that each method has its place and the most informative analysis might be a combination of several methods.

The subject-years analysis has been frequently used since the method was elegantly set out by Case and Lea (1955) and, although most such studies are now analysed with the help of a computer, the details they give of the way to set out the calculations make worth-while reading. It would be no help to Professor Liddell and his colleagues in Canada but research workers in England and Wales are also greatly indebted to Professor Case and his colleagues for organizing the publication of death rates in 5-year groupings of age and period from 1911 to 1965 (General Register Office, 1957; Case and Harley, 1958; Case *et al.*, 1968a, b), a task now being continued under Professor Alderson (Institute of Cancer Research, 1976). The method has generally been applied after dividing the subjects available for study into a few relatively homogeneous sub-groups and as we have seen this is not always easy to do. However, it is not necessary to form sub-groups in order to take advantage of the main feature of the method, i.e. to make due allowance for expected mortality. It is possible to work with individual data and analyse the quantal variate of death due to a particular cause as follows. Suppose that the actual death rates of the particular cause are λ times the standard rates and that λ varies from individual to individual but may be expressed in terms of a number of individual characteristics, $\mathbf{x}$, and a number of parameters, $\boldsymbol{\theta}$; i.e. $\lambda = \lambda(\boldsymbol{\theta}, \mathbf{x})$. Let $m(t)$ be the subject-years expectation of death from the cause by time t. Then it can be shown that the probability density of death at time t is $\lambda \exp\{-\lambda m(t)\}\, dm$, which we may regard as a function of m. Hence if M is the value of $m(t)$ for the period in view the contribution to the likelihood is $\lambda e^{-\lambda M}$ for a subject dying of the cause under study and $e^{-\lambda M}$ otherwise. $\boldsymbol{\theta}$ may be estimated by maximum likelihood, giving a regression type analysis of the individual's excess risk of dying from the cause.

The authors have analysed the data they present in Table 7 ignoring that the controls were matched with the cases which is clearly not optimum. Where the factor under study has only two levels then the analysis with multiple matched controls has been known for sometime. More recently, the situation where the factor has more than two levels but where there is only a single matched control per case has been considered (Pike *et al.*, 1975). The data given in Table 7 represent multiplicity of both the number of factor levels and the number of controls and as far as I know the solution has not yet been given.

The relationship between excess lung cancer mortality and dust exposure is of great importance and I am sorry that this was not considered in more detail. The way the χ^2 statistics are presented in Table 7 suggests that the authors were considering a threshold model, i.e. that there was no excess below some non-zero exposure. Certainly there was no detectable excess for an exposure less than 300 $10^6\, pf^{-3}\, y$ but they obviously do not attach too much weight to this since they remark in the summary that the relationship may well be linear. It is difficult to quarrel with this in view of the fact that the χ^2 of 38·76 with 9 degrees of freedom (Table 7) may be subdivided into 38·00 with one degree of freedom representing a linear trend and 0·76 with eight degrees of freedom for deviations about the trend; this is almost too good to be true!

An important advantage that the authors put forward for the case control approach is the possibility of improving the quality of the data. This advantage was brought home to me only a week

ago when I was faced with the problem of setting up a mortality study working from personnel records occupying 55 filing cabinet drawers. To extract full details of the occupational history of each subject, with adequate controls on accuracy, may not be possible with the resources available. A possibility is to extract only the basic identification data for everyone and to extract fuller details later for a sample only. Because of the reduction in the amount of information being extracted the queries which inevitably arise in this type of exercise could be considered with greater care. For providing me with this extra option I am very grateful to this evening's speakers and it is a great pleasure to propose a vote of thanks.

Dr M. JACOBSEN (Institute of Occupational Medicine, Edinburgh): Long-term epidemiological research is time consuming and expensive. Anything which may help to expedite the production of valid inferences is to be welcomed; and this is the spirit of tonight's paper.

The brief review of summary mortality statistics, in Section 3.5, makes no mention of Dr Ogle's Comparative Mortality Figure (CMF). The CMF has been a Cinderella among mortality indices for too long. It is particularly suited for internal analyses of prospective data, such as that considered in Table 4. The ratio of CMF's from any two sub-cohorts is simply the ratio of the corresponding weighted average death rates, and the statistic is independent of death rates in other sub-cohorts. Moreover, the covariance between numerator and denominator of such a ratio is likely to be small compared with the sum of their variances, leading to fairly reliable tests of significance based on approximate standard errors which ignore the covariance. These desirable properties hold for the ratio of any two directly standardized summary statistics using the same standard. They do not apply to internal-analysis analogues of the SMR, such as that used in Table 4; to the alternative index suggested by Liddell (1960); or to the 'inverse SMR' discussed by Kerridge. (Kerridge did not recommend the method when the age distribution of the risk set is known, as of course would be the case in any prospective study.) The nomenclature for the ratio used in Table 4, "relative risk", is a possible source of confusion. As noted by Wong (1977), neither the SMR itself, nor the ratio of two such statistics, is equivalent to any of the estimates of approximate relative risk discussed by Mantel and Haenszel (1959).

In his 1969 paper, Miettinen dealt with the matched multiple control problem when there is a binary response variate. A possible extension of the analysis summarized in Table 7 might be to exploit the fact that in this case the response variate, conditional on year of birth, is continuous. We might consider differences in exposures between cases and single matched controls or between cases and mean exposures from corresponding matched multiple controls. What is the distribution of these differences for cases with exposures less than 300 units? Might this approach reveal a trend more clearly than the grouped data in the upper part of Table 7?

Mantel and Haenszel defined a retrospective study of disease as one which seeks to determine the degree of association between the disease and some factor, by comparing the frequencies of occurrence of the factor among those with and without the disease. In contrast, the prospective study was described as one in which the disease frequencies are compared in groups with and without the factor. There is a clear analogy with the O.E.D. definitions of *a posteriori* and *a priori* as adopted in Section 1.3. Mantel and Haenszel commented that were it not for the danger of biases inherent in the retrospective study setting, then this approach to the problem of hypothesized associations between disease and defined factors would be the method of choice—because of the reduced sample sizes necessary compared with the demands of prospective studies. The essence of tonight's paper is to suggest that by sampling from a population defined *a priori* as part of a cohort study, we may enjoy the advantages of the lower numbers required for the retrospective approach without incurring the hazards arising from selecting controls who may be unrepresentative of the population of interest. This is surely a good idea when there is a demand for speedy tests of hypotheses concerning possible associations. But, as noted by Mantel and Haenszel, and re-iterated in the paper, the short-cut will not provide estimates of parameters in models purporting to describe the form of the association. It seems that only *a priori* arguments can satisfy the primary aim of the study as described in Section 2: "to define as accurately as possible the *quantitative relationship* between exposure to chrysotile asbestos and the incidence of lung cancer" (my emphasis).

This raises the question of the authors' characterization of Cox's regression approach as falling into their *a posteriori* category. The analysis considers the probability of response conditional on realized values of explanatory variables in the risk-set at a particular point in time. This is an *a priori* argument in general, not only in the particular case of a single dichotomous explanatory variable.

The proof of the regression pudding is in the estimation. Cox's regression analysis provides estimates of parameters associated with variables which by hypothesis affect the probability of response.

Note that the model proposed by Cox does not require that the exponential term in the hazard function is to be a *linear* combination of explanatory variables. The exponent is a quite general function of the explanatory variables and the corresponding parameters. In principle, appropriate specification of the functional form of the exponent, and application to the data used for the *a priori* analyses, resolves many of the problems discussed in the paper. These include the concomitant effects of disturbing variables (such as smoking habits); possible interactions between such concomitant variables and the main explanatory variable of interest (dust exposure); and the major difficulty in prospective studies involving time-dependent exposure estimates, described in Section 3.3 as the problem of comparing like with like.

The results in Table 8 indicate that application of Cox's regression model provides a more sensitive measure of differences associated with variation of explanatory variables than the related procedure described by Mantel and Byar (1974). Perhaps this is because the Mantel–Byar estimates were based on grouped data, while the corresponding regression results are averages of estimates related to individuals. An analysis by Crowley and Hu (1974) of the Stanford heart transplant data considered by Mantel and Byar suggests a similar advantage for the regression approach. Crowley and Hu also describe how to test the adequacy of the chosen regression model by analysis of residuals.

I was taught that statistics is the application of probability theory to real data. In practice, real data are often "dirty data". Professor Liddell and his colleagues have suggested an approach to arranging priorities in epidemiological work which makes it easier to cleanse some of the data and thus to provide early answers to at least some of the research questions. We owe them a hearty vote of thanks.

The vote of thanks was passed by acclamation.

Professor D. R. Cox (Imperial College): We should be grateful to the authors for their very interesting account of a challenging investigation. Like Dr Jacobsen, I was a bit puzzled by some of the remarks about methods. The distinction between a "simple"comparison of groups and the fitting of regression models seems quite separate from that between forward and backward studies. I expect that we would all agree that in principle the simplest and most direct reasonable method should be used. With large amounts of data and simple contrasts involving explanatory variables one at a time, direct comparison of summary statistics or curves is likely to be preferable. With smaller amounts of data and if there is a clear need to examine several explanatory variables simultaneously, some kind of regression approach seems unavoidable. The relative importance of careful tests of significance also comes into the choice.

There are a lot of interesting technical statistical points outstanding connected with the analysis of this general kind of data.

Dr A. J. Fox (O.P.C.S.): The arguments against using simulation methods in this review have been strongly expressed without similar emphasis on the limitations of the approach used. Simulation leads to an understanding of the general conditions under which each method would be appropriate. The approach used here, taking a single example in order to derive a "definite" indication as to which method is the most appropriate, oversimplifies a complex problem.

Section 2 indicates that in only 93 per cent of deaths was the cause of death determined; a low proportion for this type of study. Were those men for whom the cause of death was not given older or did their exposure characteristics differ from those for whom the cause of death was available? The limited explanation of how this group have been treated in the analysis does not permit their effect on the conclusions to be assessed.

My third point concerns the inclusion in the analysis of the effects of exposure men who were still employed in the industry and were consequently subject to exposure during the study interval. Early in the paper the authors recognize the difficulties this creates but they nevertheless include this group in the various analyses. In an evaluation of the effect these may have had on the relationships found the authors may wish to consider how the alternative *a posteriori* methods would be used to measure the effects of selection into an occupation and survival in, or selective withdrawal from, that occupation.

Because it is simple in concept the traditional cohort approach can be readily explained to the wider audience of non-statisticians/non-epidemiologists who will be interested in the main findings of a particular study. It is with sadness, therefore, that one must endorse the authors' comments about non-standard terminology. Nevertheless, the definitions they have used appear as likely to add to the general confusion as to clear the way for standard definitions.

Despite these comments many of the conclusions the authors have drawn would be endorsed by others with experience in this field. The authors should therefore be complimented on their attempt to bring these together in a more formal assessment of current methodology.

Professor P. ARMITAGE (University of Oxford): Most aetiological surveys in epidemiology are either cohort or case-control studies, and their merits and demerits are well known. The case-control study, for example, has advantages of economy in time and number of subjects, but the retrospective recording of aetiological factors may be unreliable and there may be problems in the choice of controls. The authors of the present paper are dealing with a type of survey characteristic of the study of occupational risks, which is sometimes called a retrospective cohort study: the data are obtained retrospectively but refer to the longitudinal experience of workers over long time periods. I appreciate the authors' desire to avoid the common labels in distinguishing between alternative methods of analysis, although the terms they use clash regrettably with Bayesian terminology.

In a retrospective cohort study the same data about aetiological factors will be used for both the *a priori* and *a posteriori* analyses, so the drawback of unreliability cannot be used as an argument against the *a posteriori* approach. I wonder whether the authors would agree that an *a priori* approach will be reasonable if a high proportion of the subjects are eventually affected by the illness in question, but that where the proportions affected are low an *a posteriori* approach, with sampling of unaffected subjects, seems to be needed.

This paper is welcome not only for its substantive epidemiological results but also for raising some interesting points of methodology. There have been recently a number of papers dealing with regression analyses from case-control surveys, e.g. Anderson (1972), Breslow (1976), Prentice (1976) and a paper by Prentice and Breslow to appear in *Biometrika* deals with failure-time models. Other work, as yet unpublished, by G. J. Draper and V. T. Farewell is relevant, as is the paper dealing with analogous genetic problems by Smith (1972).

The authors replied later, in writing, as follows.

We thank all concerned for their comments, but point out that some of the criticisms would have been met by what was excised at the request of the referees, to the strict limit that was set. The main cut was in epidemiological results which will be published fully elsewhere. Thus, while we are pleased that Professor Armitage welcomes the substantive results, we do not apologize for giving less than Mr Berry and Dr Fox would have liked. On the latter's point about the use of *a posteriori* methods to elucidate the effects of selection as it applies to entering, continuing in and withdrawing from an occupation, there has never been any doubt in our minds that many hypotheses can be added to the short list in Section 2. Provided that explanatory variables can be devised to test any particular hypothesis(es), including those suggested by Dr Fox, all *a posteriori* methods discussed can be applied; this is a strength of the regression methods.

As to which data sets to use for appraising methods, we do not consider application to real data is in any sense oversimplification. It is true that simulation *if feasible* might lead to better understanding, but we are not aware of any institution with the resources for a convincing simulation study.

The term "prospective" has long been used in epidemiology (see, for example, Taylor and Knowelden, 1957) to describe a study which starts with a population of known characteristics and works *forwards* to the sick persons in that population, and the term "retrospective" for studies which work *back* from the sick persons to the factors which may have led to their illness. McMahon *et al.* (1960)—in an excellent summary of merits and demerits—point out that the terms prospective and retrospective define also the form of sampling: of exposed and not exposed, in prospective studies; of affected and not affected, in retrospective studies. Used in these special senses, the terms make no attempt to place an enquiry in time, and inevitably this has caused misunderstanding among those who expect them to have their everyday meanings (White and Bailar, 1956). Thus,

the expressions "cohort" and "case-control" are being used increasingly to describe these two types of study, although these also have their peculiar drawbacks.

However, quite apart from study design, there remains a need for separate description of the thought processes in the analysis of data bearing on questions of cause and effect, whatever the source of the data, whatever the type of study. It was for this purpose that we used the phrases *a priori* and *a posteriori*, both dating from 1710. Some analytical methods exploit both directions of thought at different stages, but regression methods are undoubtedly using *a posteriori* reasoning when they compare a death with its risk set.

The logical conclusion of one of Dr Fox's statements is that men who are still employed in an industry cannot be included in any analysis of the effects of exposure. When we included such men in our analyses, their classification always took account of the basic difficulty discussed in Section 3.3. Thus, our sub-cohorts were defined in terms of exposure up to the *start* of the study interval; see footnote ‡ to Table 1 and the heading of the first column of Table 4. Here, the hypothesis, although restricted to exposure in the first 20 years of employment, was well worth examining and the differences in mortality between the four levels of exposure up to 20 years of those exposed for at least this length of time are important. Corresponding problems arise also in *a posteriori* methods; if we had to exclude from the risk set those who were still employed, we would be introducing a serious and quite unnecessary bias. Extension of the hypothesis in a man-years analysis, although straightforward, would require a further definition of sub-sub-cohorts, which is one of the drawbacks of this approach.

A brief word of warning to those comparing the subject-years analysis of Case and Lea (1955) with one performed by a computer program such as MYCL (Hill, 1972): the original authors used probabilities of dying, while most programs use death rates.

Cause of death was available for 97 per cent of deaths in the Quebec cohort, and we apologise for the error in Section 2; Table 3 is correct. However, even had 7 per cent of the deaths been of unknown cause, this would hardly have been surprising in view of the fact that death registration was not universal in Canada until 1926, was introduced at different times in various Provinces and States, that some deaths took place outside North America, and that some States will not provide a copy of the death certificate. There are several ways of dealing with deaths of unknown cause in *a priori* analyses, some of which were discussed in the earlier version of the paper, but none are entirely satisfactory. However, they have a minimal effect in *a posteriori* analyses: there may be a slight shortfall of cases, but the risk set from which the controls are selected in relation to the enumerated cases is unaffected.

We do not share Dr Jacobsen's enthusiasm for the Comparative Mortality Figure. Although a ratio of CMFs is indeed a ratio of weighted averages of deaths rates, the coefficient of variation of the CMF cannot be less than that of the corresponding SMR (Liddell, 1960), and we are not aware of any evidence that the covariance between numerator and denominator of a ratio of CMFs is less or greater than that for a ratio of SMRs. In much of our experience, SMR and CMF have been sufficiently close to make them interchangeable in practice. In addition to having the lowest coefficient of variation of the various possible ratios, the SMR allows partitioning of χ^2, as well as having the greatest ease of summarization.

All four indexes mentioned by Dr Jacobsen are weighted averages of the age- and era-specific ratios of the mortality rate in the sub-cohort to that in the reference population. SMR and CMF are weighted by deaths, expected in the sub-cohort and observed in the reference population, respectively. Those of Kerridge and Liddell are weighted by man-years, which can be an advantage in certain circumstances, so that the former should not be restricted to use when the age distribution of the sub-cohort's man-years is unknown. Because some blocks may be void in a particular sub-cohort, Liddell's index does not compare like with like, and Kerridge's might well become the index of choice.

We certainly did not wish to suggest that there is a threshold in the relationship between lung cancer mortality and dust exposure. We were concerned to show one simple form of analysis, with orthogonal partitioning, which seems to be less well known than it should be; Professor Armitage provides an account of its use in his *Statistical Methods in Medical Research*. There is still a need, however, for a simple reliable method of fitting curves to data such as in Table 7, which would also permit the comparison of models within one body of data and the comparison of parameters of models between sets of data. We hope Mr Berry will soon publish his method of fitting a linear relationship for we would like to apply it to the fuller material of deaths up to end 1975, now available.

We would also welcome publication of the methods of curve fitting due to Dr G. J. Draper (personal communication) referred to by Professor Armitage, and of those developed by Dr P. G. Smith (personal communication) and his colleagues. The problems are comparatively minor in the case of a single explanatory variable, whether in *a priori* studies or where there is a fixed number of controls per case. With the proviso that the distribution of the explanatory variable may necessitate a transformation before means are obtained, Dr Jacobsen's proposal is accomplished by the MANOVA described in Dr Thomas's addendum. The test of significance so obtained will usually be more powerful than one based on grouped data, but this is not to say a trend will be more clearly revealed; there is a clear analogy in regression analysis. Relative risks are best obtained for grouped data, although as noted by Dr Jacobsen they may be inadequate for subjects near the extremes of the groups. In any case, some check on the validity of any regression model is required before its predictions can be accepted, particularly for individuals.

We look forward to seeing details of Mr Berry's proposed form of analysis published soon. It appears similar to other parametric methods of response-time analysis, but with two considerable advantages: age and year are accounted for simultaneously; and only one nuisance parameter specifies a realistic dependence of the hazard function on time. However, as with its competitors, the validity of the assumed model has to be tested. Cox's method is free of such assumptions and the loss of power which results may be slight (Kalbfleisch, 1974; Lee *et al.*, 1975).

Cox (1972, equation (9)) did propose a linear combination of explanatory variables, but this was a choice largely of convenience, and as Dr Jacobsen points out more general functions are acceptable. Most alternative models can be approximated by appropriate transformations of explanatory variables, and an extension described by Thomas (1977) allows the examination of any alternative. Dr Jacobsen and Professor Armitage provide further helpful comments and additional references of great value.

All should be grateful to Professor Cox for his dictum that the simplest and most direct reasonable method should be used. However, it is seldom possible to involve explanatory variables only one at a time in simple contrasts, and some kind of regression approach seems unavoidable. This might appear in conflict with Professor Armitage's suggestion that the choice between *a priori* and *a posteriori* approaches be governed by the proportion of subjects affected by the illness in question, but any such illness by itself will usually account for only a fairly small proportion of deaths, and so a "low" proportion of subjects. Thus, we would again be led to an *a posteriori* analysis in most cases.

Our recommendation that there should be some sampling of the unaffected subjects has been endorsed, given adequate safeguards against bias in data collection. Fortunately, as Professor Armitage emphasizes, bias is not a drawback of the *a posteriori* approach where the same data about aetiological factors will be used for both methods of reasoning, as in the Quebec study.

Finally, we have always accepted that findings from the traditional (man-years) method of analysis are more readily comprehended, and may be of particular value in determining relationships between absolute risks and explanatory variables. Nevertheless, more information about specific hypotheses and their interactions may be obtained by the more flexible *a posteriori* methods.

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The undermentioned were recommended by Council for election as Honorary Fellows, under Bye-laws 9 and 10:

Mr JEROME CORNFIELD. Chief of Biometrics Research Branch, National Heart Institute, New York.

Dr E. LUNENBERG. Director, Permanent Office, International Statistical Institute, The Hague.

Monsieur EDMOND MALINVAUD. Administrator, National Institute for Statistics and Economic Studies, Paris.

CHARLES FREDERICK MOSTELLER. Professor of Mathematical Statistics, Harvard University.

As a result of the ballot held during the meeting, the followihg were elected Fellows of the Society:

ABODUNDE, Tunji T.
ADAMS, Robert M.
ANDERSEN, Erling B.
BAXTER, Michael A.
BONDI, Andre B.
BURIK, Paul P.
CANDLISH, Raymond H.
DOBSON, Clifford B.
EDWARDES, Warren H. W.
HARRIS, Peter
HOWEL, Denise M.
JARRETT, Malcom L.
JORDAN, Andrew
JURITZ, June M.
LAMB, David R.
MCCABE, Brendan P. M.
MACDERMOTT, Susan T.
MEDHURST, John D.
PAPAGEORGIOU, Haralambos
SALES, David I.
SARHAN, Sarhan H.
SCHAGEN, Ian P.
SHAHLAEE, Abdol-Rahim
SHANMUGALINGHAM, Sithamparapillai
SILVERMAN, Bernard W.
SMITH, Alan M. R.
SORSKY, Mark
STRAF, Miron L.
TAYYEBI JAZAYERI, Seyed M. R.