

MUSTARD GAS POISONING, CHRONIC BRONCHITIS, AND LUNG CANCER

AN INVESTIGATION INTO THE POSSIBILITY THAT POISONING BY MUSTARD GAS IN THE 1914-18 WAR MIGHT BE A FACTOR IN THE PRODUCTION OF NEOPLASIA

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INTRODUCTION

Mustard gas ($\beta\beta$ -dichlor-ethyl-sulphide) and its analogues, the nitrogen mustards, are known to be carcinogenic to experimental animals (Boyland and Horning, 1949, Heston, 1953a, b). It was first used on the Western Front in the 1914-18 war on the night of July 12-13, 1917, and after that date was used so extensively that areas of the country became saturated with it and had to be abandoned by both sides. Because of this persistence it is not possible to assume that any man serving in the front line after July 12, 1917, escaped some exposure to the gas.

Between this date and the end of the war the total number of British cases treated for war gas poisoning is recorded as 160,970, and 80 per cent. of these are estimated to be due to mustard gas (Medical Services Diseases of the War, 1923). 124,702 of these cases were admitted to hospitals, and 4,167 died before discharge. These figures must be an underestimate of the total British casualties, since they do not include the unknown number of men who were gassed and taken prisoner.

An experience of this sort, where a chemical stimulus of an easily identifiable type is applied to a human population for a short time, at a known date, resembles in some ways a carefully planned animal experiment, and the size of the operation should provide ample material for an investigation into any possible carcinogenic action of the gas.

METHODS AND MATERIALS

The ideal method of investigation would be to take all or a random sample of the men known to have been gassed and to follow up their histories until the present

date. This could not be done since the absence of extensive and reliable morbidity data for neoplastic diseases compels the use of mortality data, and the Registrar-General's records cannot answer the questions "Is this person dead or not, and if so when and why?". Before a particular death certificate can be traced, it is necessary to know firstly that death has taken place, and secondly the approximate date and the district where the death was registered.

Fortunately, in the present circumstances, an alternative method was available, to follow up the histories of those men who were pensioned for the effects of mustard gas poisoning, since if death had occurred sufficient data would be recorded to enable the death certificates to be traced.

The Ministry of Pensions and National Insurance has complete records of all men who were receiving a pension in 1930, but this was the earliest date at which the records were complete. The disability for which the pension was granted, and often the grant of the pension itself, were of course in existence for varying periods before this date. On January 1, 1930, 1,267 men in England and Wales were receiving a pension for the effects of mustard gas poisoning, resulting from the 1914-18 war. A small number of cases in Scotland and Ireland were excluded, since it would otherwise have been necessary to prepare extensive additional analytical tables for these countries. Apart from these cases, the whole of the available data is used, so that no question of further selection arises. The mortality experienced by these 1,267 men was examined from January 1, 1930, until December 31, 1952, this closing date being determined because it was the end of the last year for which the Registrar-General's Annual Reports had become available. This mortality experience (subsequently referred to as the experience "found") was compared with a standard ("expected") mortality experience based on the male population (including non-civilians) of England and Wales, calculated by a

method (see statistical appendix) that makes allowances for age-specific and secular changes of mortality rates.

Since data for environmental cancer studies on carefully and completely defined populations are scanty, arrangements are being made to ensure that adequate records of the men surviving after the end of 1952 are maintained. It will then be possible to make periodical surveys of the mortality experience, until eventually a complete mortality study from 1930 until the demise of all the men concerned can be made. Such a study might provide interesting information about any possible alteration in cancer mortality at more advanced ages, and help to elucidate whether the increase of lung cancer found in two of the series discussed below represents an absolute increase in the carcinogenic process or merely an earlier induction in susceptible subjects.

Discussions had indicated that there were two opinions about the type of possible carcinogenic effect of mustard gas. One suggested that the effect might be specifically confined to the respiratory tract, the other that the effect might be non-specific and affect the general process of neoplasia. Since the number of deaths from neoplastic disease in the series was too small to warrant a complete analysis by site, analytical tables were selected for the two disease classifications "all neoplasms" (including malignant tumours, non-malignant or undefined tumours, leukaemia and lymphadenoma) and "cancer of the lung and pleura". By subtraction, a third classification, "neoplasms other than cancer of the lung and pleura", is obtained.

The problem of the possible effect of mustard gas was studied by comparing the mortality expected and that found from "cancer of the lung and pleura" and from "neoplasms other than cancer of the lung and pleura". In addition to these, deaths from "all causes" were also studied.

As will be shown later, the men in the mustard gas series experienced an excessive mortality from bronchitis, and the case histories were examined to see why a pension was being issued in 1930. This investigation revealed that, although the *label* in each case was "mustard gas poisoning" or some similar phrase, the *reason* for granting the pension was not that the man had been gassed but that in 1930 there were sufficient clinical findings present to warrant the view that permanent damage had been sustained. In 81 per cent. of the cases the pension was given because of bronchitis, bronchiectasis, emphysema, or fibrosis of the lung, and in most of the remaining 19 per cent. there was clear evidence of bronchitis. Evidently we were studying not simply a population which had at some time been poisoned by mustard gas, but a population poisoned by mustard gas and extensively affected by chronic bronchitis, either as a result of gassing or for other reasons.

It was, therefore, decided to investigate the mortality of soldiers from the 1914-18 war who on January 1, 1930, were being pensioned, and who were recorded as having bronchitis, but who had never been exposed to mustard gas. Ample material was available, but a limitation was imposed so that only individuals who had not served as soldiers overseas after the date of the first

use of mustard gas were studied. This was necessary as there can be little doubt that many men exposed to small doses of the gas had no severe symptoms, and such cases would not be recorded in the Ministry's records as having been gassed.

Apart from this limitation, the choice from the available material relating to bronchitis cases without mustard gas exposure was made at random, and a series of 1,421 cases was studied.

It is of course possible that a man might be diagnosed as suffering from chronic bronchitis or a chest disability resulting from his war service when in fact he was suffering from an unrecognized lung cancer, which might later be correctly diagnosed. Thus a bias might exist because of the selective admission of lung cancer cases to the series, but this bias would be limited to cases dying in the first few years of the survey because of the limited survival time of sufferers from untreated cancer of the lung. Furthermore, it has already been stated that, although the survey starts in 1930 because this is the first year for which complete records are available, the men who were pensioned at that date had for the most part been pensioned or suffering from their disability for some time.

In order to gain some idea of how seriously a bias of this type might be affecting the findings discussed in this paper, the medical histories of those men in the mustard gas series or the bronchitis series who died of lung cancer within the arbitrary limit of 6 years from the starting date, January 1, 1930, were re-examined. Seven men in the mustard gas series and five in the bronchitis series fell into this category. This scrutiny revealed that in each of these cases the diagnosis of chronic bronchitis had been made as early as 1918. In fact, it appeared that all the cases of chronic bronchitis in these two series had been so diagnosed before the end of 1921. We therefore consider that the possibility of a bias due to the selective admission of lung cancer sufferers to the series under the mistaken diagnosis of chronic bronchitis can be ignored in assessing the results of these studies.

All the men in the two series so far considered were by definition serving soldiers in the 1914-18 war. This in itself might mean that the standards used, derived from the whole of the male population of England and Wales, might not be applicable to men selected in this way. From the time of their enlistment until they left active service, the men were presumably selected for physical fitness and the absence of any obvious sign of disease, and it might be thought that this would affect their subsequent mortality experience. There is also a widespread belief that members of the armed forces in the 1914-18 war smoked to excess (the colloquial term "gasper" originated at this time). Any analysis of the incidence of cancer of the lung and pleura might therefore be open to the objection that there would be a systematic bias in respect of smoking habits.

Whilst it is highly desirable that such a bias should if possible be excluded, or at least detected, the composition of the general population used for forming the standard of comparison must be considered. Of the cases studied, 70 per cent. were between the ages of 20 and 35 in 1917.

The Registrar-General's (1927) population estimates (Decennial Supplement, 1921) show that 58 per cent. of males in these age groups were in the armed forces in 1917, and the method used ensures that the mortality experience at any given date is the experience of these men as they pass through life. Thus the discrepancy between the armed forces and the general population is not so extreme as might be imagined.

Nevertheless, we thought it advisable to analyse a further sample of men drawn from the armed forces in 1914-18, who had not been exposed to mustard gas and who were not selected for bronchitis, although they might reasonably be assumed to develop it at a rate comparable with that in the general population. Ideally, such a series would consist of men who had served in the 1914-18 war, had not been exposed to mustard gas, and had been discharged from the forces without any obvious medical abnormality, but the Ministry of Pensions and National Insurance obviously do not keep such records.

A reasonable approximation to such a series, and one that was readily available, was found amongst men who had served in the 1914-18 war, had been wounded in a manner that necessitated a single leg amputation, and left France before July 12, 1917 (thus excluding unrecorded poisoning by mustard gas), and were receiving a pension for the disability of single-leggedness in 1930. A random selection of 1,114 such cases was made from the available data.

The method of statistical analysis adopted, the technical details of which are discussed in an appendix, allowed us to study both the number of deaths from each disease classification that were found (and that would be expected if the rates of death acting on the general population were also acting on each series of cases) and also the age at which these deaths took place. A study of age-incidence in human cancer is desirable, because few data exist to help elucidate how far the biological age of the host is important and how far the length and the subsequent period of exposure to outside influences is important. This form of analysis has therefore been applied to each disease classification and to each series.

RESULTS

The records of all the men in each series were examined, and the following information was extracted:

- (a) age;
- (b) whether alive or dead;
- (c) if dead, date of death;
- (d) if dead, cause of death.

In all cases where death had occurred, the death certificate was scrutinized, and the category to which the Registrar-General had assigned the death was determined. This was done since all the standard rates are based on deaths assigned to the disease classifications named; a death certificate might mention more than one disease, but be assigned to the category of only one of these.

Calculations were made from these data and from the analytical tables, and the expected numbers of deaths from all causes and in each of the disease classifications studied were determined. "Expected" in this context means the number that would have occurred had the mortality that affects the general population, defined as the male population of England and Wales, acted with the same severity in the series studied. These expected numbers and the mortality ratio (M.R.), which is defined as the number of "deaths found" expressed as a percentage of the number of "deaths expected", are shown in the Table. The mortality ratio for deaths from all causes is here calculated from Tables which allow the population to be depleted at the standard rates for England and Wales. Where the mortality ratio for "deaths from all causes" is markedly raised, the calculation of mortality ratios for individual diseases will be biased, since the actual number of years lived at each age period will become progressively less than the theoretical number as the population is

TABLE
MORTALITY FROM EACH CLASS OF DISEASE FOUND AND EXPECTED IN THREE SERIES STUDIED

Source of Data		Disease Class								
		All Causes		All Neoplasms		Cancer of Lung and Pleura		Neoplasms other than Cancer of Lung and Pleura		
		Deaths	Mortality Ratio	Deaths	Mortality Ratio	Deaths	Mortality Ratio	Deaths	Mortality Ratio	
Series	Mustard Gas	547		79		29		50		Found
		357.3	153* (VHS)	60.8	130 (S)	14.0	207 (HS)	46.8	107 (NS)	Expected
	Bronchitis	932		104		29		75		Found
		673.8	138* (VHS)	95.0	109 (NS)	14.4	201 (HS)	80.6	93 (NS)	Expected
	Amputation	383		72		13		59		Found
		365.7	105* (NS)	72.2	100 (NS)	15.5	84 (NS)	56.7	104 (NS)	Expected

VHS = very highly significant ($P < 0.0001$).

S = significant (P between 0.05 and 0.01).

HS = highly significant (P between 0.01 and 0.0001).

NS = not significant ($P > 0.05$).

*Mortality ratios based on theoretical number of years lived.

depleted by the excessive mortality. In the present study a complete statement of mortality has been made, and from this the actual number of years lived at each age period can be calculated. The mortality ratios for the classes of neoplastic disease have been calculated from this actual life experience.

In the Figure, where the age-distribution of deaths is shown, all the results have been calculated from the actual life experience, since the theoretical attenuation would tend to bias the results where the mortality ratios for "deaths from all causes" is high.

MUSTARD GAS SERIES.—In the mustard gas poisoning series, 1,267 men were alive on January 1, 1930, and between that date and December 31, 1952, 547 deaths had occurred, leaving 720 men still alive. The total number of deaths expected was 357, so that an excess of 190 deaths was found, the mortality ratio being 153. This difference is statistically very highly significant.*

*See Table for definition of significance levels, and for the rates from which the ratios are calculated, since these rates have been rounded off to whole numbers in the text.

Deaths from Neoplasm.—79 were found, and 61 expected, an excess of eighteen deaths, the mortality ratio being 130. This difference is statistically significant.

When these deaths are sub-divided into deaths from "cancer of the lung and pleura" and deaths from "neoplasms other than cancer of the lung and pleura", it is seen that the excess deaths from neoplasm can be attributed to a large excess of deaths from cancer of the lung and pleura. In this disease classification, 29 deaths were found and fourteen expected, giving an excess of fifteen and a mortality ratio of 207. This difference is statistically highly significant.

Fifty deaths from "neoplasms other than cancer of the lung and pleura" were found, and 47 expected. This is an excess of three deaths and a mortality ratio of 107. This difference is not statistically significant, in fact, the numbers expected and found are in very close agreement.

Finally, deaths from bronchitis were investigated, and it was found that 217 deaths classified as due to

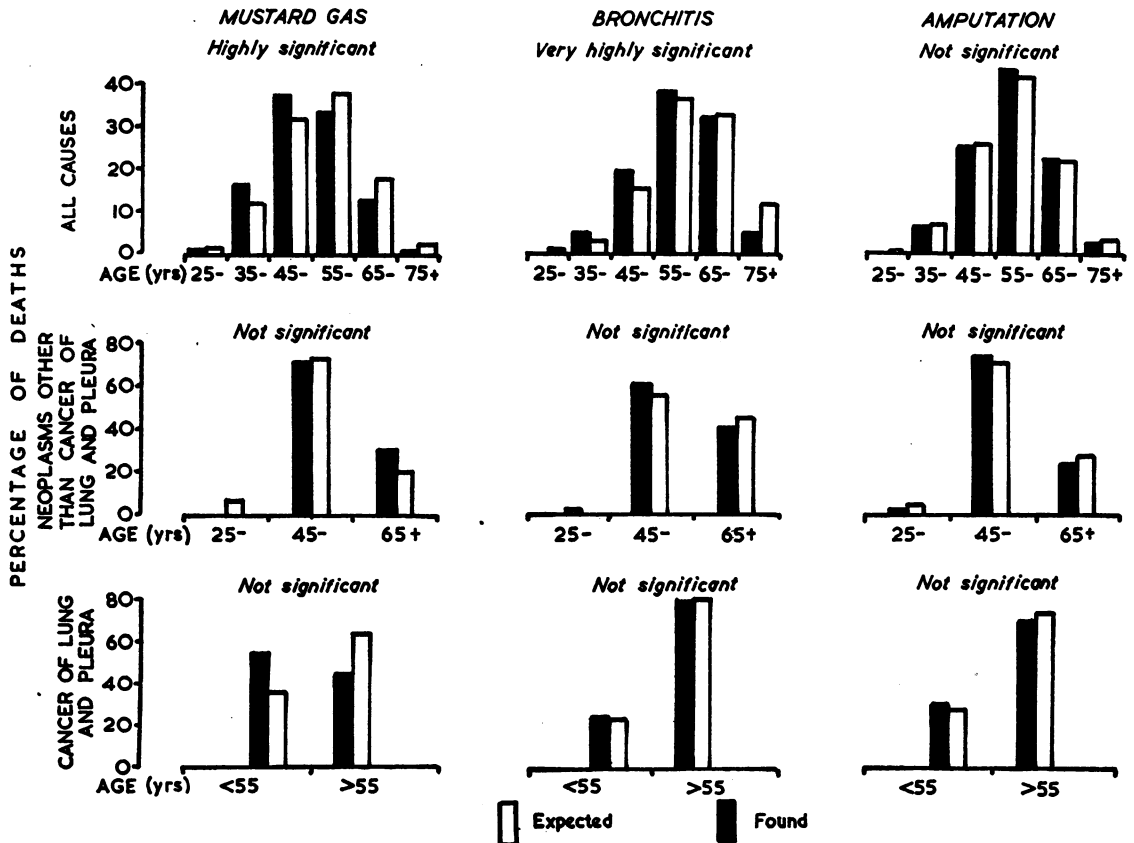


FIGURE.—Age distribution of deaths found and expected in each disease classification. Not significant, $P > 0.05$. Highly significant, $0.01 > P > 0.001$. Very highly significant, $P < 0.0001$.

bronchitis (all types) had occurred as against 21 expected. This is a statistically very highly significant excess of 196, the mortality ratio being 1,033. This excess of 196 deaths could wholly account for the excess of 172 deaths left after the excess of neoplasm deaths had been taken into account. There remain 251 deaths from causes other than bronchitis or neoplasm, the expected number being 276. This deficit of 25 deaths is not statistically significant ($P = 0.1$).

Considering the Figure showing the observed and expected frequency (as a percentage of the total deaths considered), the pattern of the age-specific mortality (*i.e.* percentage age distribution of deaths) from all causes is seen to have been altered, being relatively higher in younger age groups. This difference is statistically highly significant. Deaths from neoplasms other than cancer of the lung and pleura do not show this altered pattern, and although there is a suggestion that deaths from cancer of the lung and pleura do show such an effect, the difference is not statistically significant.

Bronchitis Series.—In this series 1,421 men were alive in 1930, and 932 deaths had occurred by December 31, 1952, leaving 489 survivors. The total number of deaths expected was 674, giving an excess of 256 deaths with a mortality ratio of 138. This difference is statistically very highly significant.

Deaths from Neoplasm.—104 were found, and 95 expected, an excess of nine and a mortality ratio of 109. This difference is not statistically significant.

Splitting these deaths into the two sub-divisions, 29 deaths from "cancer of the lung and pleura" were found and fourteen expected, an excess of fifteen deaths and a mortality ratio of 201. This difference is statistically highly significant.

Seventy-five deaths from "neoplasms other than cancer of the lung and pleura" were found, and 81 expected. This is a deficiency of six deaths and a mortality ratio of 93. This difference is not statistically significant.

Since the object of this work was to study the relationship between mustard gas poisoning and neoplasia, no detailed studies on causes of death other than from neoplasms were made on this series.

The Figure shows that, as in the previous series, there is a tendency for the age-specific mortality from all causes to be disproportionately increased in the younger age groups, this difference being statistically significant. Neither of the two classes of neoplasms show any significant effect of this sort.

AMPUTATION SERIES.—1,114 men were alive in 1930, and by December 31, 1952, 383 deaths had

occurred, leaving 731 survivors. 366 deaths were expected, and an excess of seventeen deaths were found, the mortality ratio being 105. This difference is not statistically significant.

Deaths from Neoplasm.—72 were found and 72 were expected. The mortality ratio is therefore 100.

Thirteen deaths from "cancer of the lung and pleura" were found and sixteen expected. This deficiency of three* (mortality ratio 84) is not statistically significant.

59 deaths from "neoplasms other than cancer of the lung and pleura" were found and 57 expected. This excess of two* (mortality ratio 104) is not statistically significant.

The Figure shows no statistically significant alteration of the age-specific mortality pattern in any of the disease classes.

DISCUSSION

The foregoing results show that both the men who had been poisoned with mustard gas (and who nearly all suffered from bronchitis) and the men who suffered from bronchitis but were not poisoned with mustard gas, showed a very high general mortality. In the mustard gas series the excessive mortality could be completely accounted for by an excessive number of deaths from bronchitis and, to a lesser extent, by an excessive number of deaths from cancer of the lung and pleura. The reason for the excessive general mortality was not sought for in the bronchitis series, but an excessive number of deaths from cancer of the lung and pleura was found.

In both cases the deaths from cancer of the lung and pleura occurred at twice the rate for the general population. Deaths from other forms of neoplasia occurred at the same rate as in the general population.

The amputation series showed no deviation from the rates for the general population in any of the criteria studied, and so confirm that the standards derived from the general population can be used on these series of men who were by definition serving soldiers in the 1914–18 war.

The finding of a high incidence of cancer of the lung and pleura in both the mustard gas series and the bronchitis series does not support the view that mustard gas has acted as a direct carcinogen, but it does provide evidence that chronic bronchitis can be associated with an increased number of deaths attributed to carcinoma of the lung and pleura. This view has been advanced in the past, and some evidence for it published, especially with reference to bronchitis and the squamous-celled type of carcinoma of the bronchus (Lea, 1952).

*These figures do not exactly balance owing to rounding-off to whole numbers (See Table).

Unfortunately the Ministry of Pensions records do not contain histological findings, but it is proposed to attempt to obtain the pathological material from the hospitals concerned and to review the histopathology of the series.

It is of course a matter of common knowledge that diagnostic errors affect mortality rates based on death certificates. This topic has been discussed extensively by Kennaway and Kennaway (1936) and by Willis (1953). In the present studies most of these errors will affect the general population, the control series, and the two bronchitis series equally, and will not affect the conclusions. It only remains to consider whether there is a common factor in the mustard gas series and the bronchitis series which might systematically bias the diagnosis of cancer of the lung and pleura, and which will not be operating in the amputation series. A history of chronic chest disease, present by definition in the mustard gas and bronchitis series, might well be such a factor, but it is not obvious which way any bias from this source would work.

It might be argued that the pre-existing chest disease would cause more careful and more frequent examination of the respiratory system, with a consequent picking out of cases of malignant disease which would otherwise be missed, or it might be argued that more frequent incorrect diagnoses of lung cancer might be made because of the misinterpretation of abnormal physical signs due to the underlying chronic condition. Both these sources of error would tend to give an increase of the number of cases found compared with the number expected, but, if they do operate to any extent, it is somewhat surprising that a connexion between chronic chest disease and lung cancer is not well recognized by diagnosticians, since both would presumably operate amongst the chronic bronchitics in the general population.

On the other hand, it might plausibly be argued that a chronic chest lesion would lead to a diminished tendency to diagnose malignant disease of the lung, since it is not commonly thought that lung cancer is associated with a long history or is compatible with a long survival time in an untreated state; since superimposed physical signs due to the development of carcinoma in a chronically diseased lung might easily be missed against the pre-existing background of abnormality; and since clinical teaching discourages the diagnosis of a double pathology.

These questions cannot be resolved by the present studies, but the different possibilities presented should be borne in mind. The authors' opinion inclines to the possibility of underdiagnosis of lung cancer rather than to its overdiagnosis in the two bronchitic series.

If we accept that the excess of cancer of the lung and pleura in the two bronchitic series is real and also has a common aetiological factor in the bronchitis, the cancer experience of both groups can be pooled and used to examine a hypothesis advanced by Cramer (1936):

There appears to be a general law that when in a given population the incidence of cancer in one particular organ is markedly increased as compared with another population, then there is a compensating decrease in the incidence of cancer in a number of the other organs. As a result, the incidence of cancer in different populations, whether of the same sex or not, may be composed of a very different distribution over the various organs or tissues, but the sum total, the total incidence of cancer, remains on an even level.

This hypothesis seems to have been made into the implicit basis of recent speculation in relation to the smoking and lung cancer problem (Blond, 1954; Price Thomas, 1955). Possibly by an extension of the original intended scope of Cramer's "law", they suggest that the excess of lung cancer in tobacco smokers reported by (amongst others) Doll and Bradford Hill (1952, 1954) does not mean that cancer is being induced, but that the site where it becomes manifest is determined by the effect of smoking.

In the two bronchitic series studied, 58 deaths from cancer of the lung were found and 28 expected. If the increase in this site is being compensated for by a decrease in cancer of other sites, as required by the hypothesis extended in the sense required by the speculations about smoking, then there should be a deficit of about thirty cases of death from neoplasm other than cancer of the lung and pleura. In fact 125 are found and 127 expected. This close agreement does not support the view that Cramer's "law" is valid in this case.

SUMMARY AND CONCLUSIONS

(1) We have made an examination of the mortality experience of 1,267 war pensioners who suffered from mustard gas poisoning in the 1914-18 war, and who were still alive on January 1, 1930. It was found that almost all (over 80 per cent.) had chronic bronchitis at that date. In subsequent years a statistically significant excess of deaths attributed to cancer of the lung and pleura has been observed amongst them (29 deaths found compared with fourteen expected).

(2) A similar and statistically significant excess of deaths attributed to cancer of the lung and pleura was found amongst a series of 1,421 war pensioners

who served in the 1914–18 war, and suffered from chronic bronchitis, but had never been exposed to mustard gas (29 deaths found compared with fourteen expected).

(3) No statistically significant difference between the number of deaths from cancer of the lung and pleura found and expected was detected in a series of pensioners from the 1914–18 war who were receiving a pension because of having had one leg amputated, who had never been exposed to mustard gas, and whose inclusion in the series was independent of any selection for chronic bronchitis (thirteen deaths found compared with sixteen expected).

(4) No statistically significant difference between the number of deaths from neoplasms other than cancer of the lung and pleura found and expected was detected in any of the three series.

(5) The possibility, that a systematic bias might arise from analytical tables based on a general population of all males in England and Wales being inapplicable to a series of men who were by definition serving soldiers in the 1914–18 war has been excluded, and the possibility of a diagnostic bias considered and discussed.

(6) The evidence presented does not support the view that mustard gas has acted as a direct carcinogen, either in relation to neoplasia in general or in relation to cancer of the lung and pleura.

(7) The evidence indicates that chronic bronchitis may be associated with the subsequent development of cancer of the lung and pleura, unless it is assumed that the excess of deaths attributed to this disease is entirely due to diagnostic bias.

(8) The increased incidence of cancer of the lung and pleura, whether real or apparent, in the pooled data derived from the cases of mustard gas poisoning, nearly all of whom were also suffering from chronic

bronchitis, and from the cases of chronic bronchitis who had not been exposed to mustard gas, was not compensated for by a diminution of mortality from neoplasms other than cancer of the lung and pleura.

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STATISTICAL APPENDIX

METHODS OF ANALYSIS AND DETAILED RESULTS

Comparative composite cohort analysis, the method that has been used in these studies, is a technique for comparing some or all of the morbidity or mortality experience of a "closed" and defined population with an expected experience calculated for that population at some standard rate. A "closed" population is one in which the whole of the life experience of each of its members, subsequent

to the entry of that member into the observational field, is of relevance to the analysis, regardless of whether or not the member has ceased to belong to the particular defined class (*e.g.* environmental, occupational, or industrial) which was used in circumscribing the observational field when designing the survey. This concept is in contrast to the "open" population, such as is necessarily used in the

Registrar-General's studies in occupational mortality (e.g. Registrar-General, 1938), where an estimate of the population in a stated environment in a given year or series of years is used, but where the member must be allocated to that environment on the death or sickness certificate for his experience to be used. This allows members who enter the observational field to leave it subsequently by changing their allocated environment, and only their life experience whilst still allocated to the environment which causes them to be classified in the observational field of the survey is relevant to the analysis.

The essential nature of the technique has been further discussed by Case and Hosker (1954), and a specific example of a method of deriving a standard rate for male mortality from bladder, tumour in England and Wales is given by Case (1953a, b).

From a practical viewpoint, the method requires a statement of the years of life experienced at different ages, since both morbidity and mortality are highly age-specific, and these experiences must be calculated so that allowance is made for the date to which the age experience refers, since contemporaneous conditions also affect morbidity and mortality. Once the statement of the life experience differentiated in this way is made, the morbidity or mortality to be expected under some defined standard conditions can be calculated by applying morbidity or mortality rates calculated for the age and date from data relating to the standard conditions. The sum of the expectation of experience over the whole array then gives the mortality or morbidity expected, and this can be compared with that observed.

In order to facilitate the study of environmental factors affecting neoplastic disease, Case and Pearson (work in progress) are preparing Tables for mortality experience in England and Wales from 1911 onwards. These will be calculated with respect to 5-year age grouping, e.g. 35- 40- 45- etc., and 5-year date grouping, e.g. 1911-, 1916-, 1921-. Thus the rate applicable to members of a cohort of men born in 1866-1869 will be found under 45- and 1911-, 50- and 1916-, and so on. These Tables, calculated for each sex separately, will cover the ${}_5q_x$ values of the Life Table, mortality rates from all causes, and mortality rates for neoplastic disease under 24 site-headings distinguishable since 1911.

In the present study, the mortality Tables for males in England and Wales for death from all causes, death from "all neoplasms" (as defined in the text), death from "cancer of the lung and pleura", ${}_5q_x$ Life Table values, and a specially computed Table for deaths from "bronchitis, all types" were used.

Since the data to be studied contain a complete statement of mortality, the actual life experience differentiated for age and date can be computed fairly accurately, and is therefore used where applicable.

The calculation is intricate but of general interest. We therefore give the details for the mustard gas series *in extenso* in Columns 1 to 9 of Appendix Table A (overleaf) as a "worked example". Columns 10 and 11 show the results of calculations made in the same way for the bronchitis series and the amputation series respectively.

The calculations may conveniently be arranged in a "staircase" array (see Table A), so that a diagonal line traced from Column 2 to Column 7 will follow a cohort of men born in the same quinquennium. This type of array has the advantage that a lateral summation of Columns 2 to 7 gives the expected age distribution of the deaths.

Two methods may be used to calculate the life experience in each cell. The first is the theoretical attenuation, but in this case this is only used when considering the expected mortality for all causes. The calculation is made by taking the figure in the *a* division of Column 2 and multiplying this by the appropriate ${}_5q_x$ value of the Life Table. Since Column 2 relates only to one year, 1930, the result is divided by 5, since the ${}_5q_x$ value refers to a 5-year period. This gives the number of deaths expected, and is entered in the *b* division. This number is subtracted from the figure in the *a* division, and the result transferred to the *a* division of Column 3, in the next highest age group. This process is repeated across the whole of Table A, except that in Columns 3 to 6 no division by 5 is required, and that in Column 7 the division is by 2.5. A cross summation gives the age distribution expected, and the sum of this column gives the number of deaths expected. The observed deaths are entered in the appropriate cells, and summated similarly for comparison.

The numbers of deaths from all causes, found and expected, for each series studied, are shown in the *b* divisions of Table A. The expected age distribution calculated on this basis is shown in Column 9, but the progressive departure of the theoretical attenuation from the factual attenuation render them unsuitable for use in the text Figure, although the final total is appropriate for consideration in respect of the mortality ratio.

If it were necessary to obtain the theoretical life experience in each cell, this could be done by dividing the expected number of deaths in each cell by the appropriate age-specific death rate from all causes. In the present studies the actual life experience can be determined fairly accurately by multiplying the

APPENDIX TABLE A

1,267 CASES OF MEN OF THE 1914-18 WAR WHO HAD BEEN POISONED BY
 COMPARATIVE COMPOSITE COHORT ANALYSIS ARRAY TO ANALYSE FOR DEATHS FROM ALL CAUSES, DEATHS FROM
 FROM NEOPLASMS OTHER THAN CANCER OF THE LUNG AND PLEURA, WITH AGE DISTRIBUTIONS

Column	1	2				3				4				5				6																			
Rank	Age	Date																																			
1		1930				1931-				1936-				1941-				1946-																			
2	25-	89	0	0	0																																
		0.31	0.01	0.00																																	
3	30-	388	1	0	0	89	4	0	0																												
		1.48	0.08	0.00	1.53	0.10	0.01																														
4	35-	331	4	0	0	387	22	0	0	85	7	0	0																								
		1.71	0.11	0.01	8.82	0.69	0.10	1.83	0.15	0.03																											
5	40-	259	1	0	1	327	24	0	0	365	22	0	0	78	9	0	0																				
		1.82	0.16	0.01	10.08	0.99	0.14	10.81	1.14	0.27	2.26	0.22	0.07																								
6	45-	150	1	0	0	258	25	1	1	303	19	3	2	343	29	2	2	69	5	0	2																
		1.44	0.17	0.01	11.64	1.44	0.23	13.46	1.58	0.40	13.71	1.66	0.63	2.74	0.36	0.19																					
7	50-	46	0	0	0	149	10	1	0	233	30	2	1	284	38	4	5	314	38	3	2																
		0.60	0.10	0.01	9.48	1.51	0.19	16.08	2.16	0.47	17.64	2.32	0.79	18.47	2.48	1.41																					
8	55-	4	2	0	0	46	6	0	0	139	22	2	0	203	32	1	3	246	31	2	0																
		0.08	0.01	0.00	4.19	0.77	0.07	13.35	2.14	0.37	21.25	2.81	0.83	24.11	3.34	1.57																					
9	60-					2	2	0	0	40	6	0	0	117	13	4	1	171	35	4	1																
						0.53	0.03	0.03	5.89	1.04	0.12	16.63	2.79	0.57	28.70	3.52	1.31																				
10	65-									0	0	0	0	34	6	0	0	104	29	6	1																
										0.70	0.00	0.00	6.86	1.26	0.15	20.72	3.12	0.77																			
11	70-													0	0	0	0	28	8	0	0																
														0.75	0.00	0.00	8.19	1.37	0.18																		
12	75-																	0	0	0	0																
																		0.79	0.00	0.00																	
13	80-																																				
14	85+																																				
15		a	b	c	d	a	b	c	d	a	b	c	d	a	b	c	d	a	b	c	d																
	Total	1,267																																			

a = men surviving to start of date period
 b = deaths from all causes
 c = deaths from neoplasms other than cancer of lung and pleura
 d = deaths from cancer of lung and pleura
 * = corrected for continuity
 Dotted lines indicate cells combined for χ^2 test

MUSTARD GAS
CANCER OF THE LUNG AND PLEURA, AND DEATHS
OF DEATH IN EACH CLASS

Results from Analysis of
1,421 Cases of Bronchitis in
Men not Exposed to
Mustard Gas

Results from Analysis of
1,114 Cases of Single Leg
Amputation in Men not
Exposed to Mustard Gas

7				8	9			10			11			12
1951 and 1952				Alive on January 1, 1953	Age Distribution of Deaths Σ Columns 2 to 7			Age Distribution of Deaths			Age Distribution of Deaths			
					0	0	0	0	0	0	—	—	—	Found
					0.31	0.01	0.00	0.02	0.00	0.00	—	—	—	Expected
					5	0	0	0	0	0	0	0	0	Found
					3.01	0.18	0.01	0.64	0.04	0.00	0.80	0.04	0.00	Expected
					33	0	0	9	0	2	7	0	0	Found
					12.36	0.95	0.14	4.52	0.34	0.05	6.69	0.50	0.07	Expected
					56	0	1	36	0	0	16	1	0	Found
					24.97	2.51	0.49	12.95	1.27	0.20	19.11	1.97	0.32	Expected
					79	6	7	66	2	3	36	8	0	Found
					42.99	5.21	1.46	29.44	3.47	0.77	36.26	4.62	1.12	Expected
64	3	1	0	61	119	11	8	119	7	1	62	7	4	Found
	1.69	0.21	0.15		63.96	8.78	3.02	56.46	7.92	1.90	58.09	8.81	2.63	Expected
276	16	2	3	260	109	7	6	161	21	5	86	14	4	Found
	11.52	1.49	1.00		74.50	10.56	3.84	93.32	13.96	3.26	77.10	12.73	4.30	Expected
215	15	3	4	200	71	11	6	191	15	5	81	15	2	Found
	14.35	1.83	0.94		66.10	9.21	2.94	123.46	17.98	3.55	75.57	12.73	3.93	Expected
136	14	6	0	122	49	12	1	184	16	9	62	11	2	Found
	15.60	1.74	0.66		43.88	6.12	1.58	167.10	17.42	2.75	53.30	8.97	2.19	Expected
75	15	2	0	60	23	2	0	113	11	3	24	2	1	Found
	10.56	1.36	0.30		19.50	2.73	0.48	103.16	11.09	1.24	28.69	4.65	0.75	Expected
20	3	1	0	17	3	1	0	40	3	1	8	1	0	Found
	3.51	0.55	0.67		4.30	0.55	0.07	57.45	5.21	0.46	9.18	1.52	0.16	Expected
0	0	0	0	0	0	0	0	11	0	0	1	0	0	Found
	0.27	0.00	0.00		1.42	0.00	0.00	21.31	1.68	0.18	0.94	0.15	0.01	Expected
					—	—	—	2	0	0	—	—	—	Found
					—	—	—	3.89	0.21	0.02	—	—	—	Expected
a	b	c	d		b	c	d	b	c	d	b	c	d	
				Total = 720										
Total found				..	547	50	29	932	75	29	383	59	13	
Total expected				..	357.30	46.81	14.03	673.82	80.59	14.38	365.73	56.69	15.48	
Difference				..	189.70	3.19	14.97	258.18	5.59	14.62	17.27	2.31	2.48	
P				..	<0.0001	0.6	0.005	<0.0001	0.5	0.008	0.4	0.8	0.5	
Difference of Distribution				χ^2 n P	42.15 8 <0.0001	5.77 4 0.2	3.60* 1 0.06	106.86 10 <0.0001	8.75 6 0.2	0.04* 1 0.85	3.54 8 0.9	3.09 5 0.7	0.31* 1 0.6	

APPENDIX TABLE B
 NUMBER AND AGE DISTRIBUTION OF DEATHS FROM ALL CAUSES CALCULATED FROM ACTUAL NUMBER OF YEARS
 LIVED AT EACH AGE PERIOD

Source of Data			Age Period										Mor- tality Ratio	Difference of Distribution	
			<35	35-	40-	45-	50-	55-	60-	65-	70-	75+			Total
Series	Mustard Gas	Found	5	33	56	79	119	109	71	49	23	3	547	173	$\chi^2 = 32.86$ $n = 9$ $P < 0.001$
		Expected	3.31	12.13	23.87	40.27	57.78	64.28	55.16	36.66	17.68	4.28	315.42		
	Bronchitis	Found	0	9	36	66	119	161	191	184	113	53	932	184	$\chi^2 = 53.13$ $n = 8$ $P < 0.0001$
		Expected	0.67	4.23	12.47	27.46	51.87	81.34	100.45	97.60	68.59	61.92	506.60		
	Amputation	Found	0	7	16	36	62	86	81	62	24	9	383	103	$\chi^2 = 5.24$ $n = 8$ $P = 0.7$
		Expected	0.80	6.68	19.27	36.38	58.29	76.88	75.86	53.29	29.63	13.16	370.26		

Dotted line indicates cells combined for χ^2 test.

number of survivors of each column by the number of years that the column refers to, and then adding the actual number of years lived in the period by those who have died on the assumption that each death took place in the middle of the year. Thus a person dying in 1943 would be regarded as having lived 2.5 years in the period 1941-44.

The number of deaths expected for each disease classification to be considered can then be determined by multiplying the years of life lived by the appropriate age specific death rate for that disease classification. The expectations for cancer of the lung and pleura and for neoplasms other than cancer of the lung and pleura with the figures actually found, are shown in the *d* and *c* divisions of Tables

A and B. The age distributions, being calculated from the factual attenuation, are suitable for use in the text Figure.

The expected age distribution for deaths from all causes, based on the factual attenuation, has been separately calculated for use in that Figure, and is shown in Appendix Table B.

The significance of differences of totals has been assessed by the approximation used by the Registrar-General (1949) of regarding the square root of the number of deaths found as the standard error. The *P* value is then determined from Tables of the normal curve from the observed difference between the expectation and the number found over the square root of the number found.