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Lung Cancer in World War I Veterans: Possible Relation to Mustard-Gas Injury and 1918 Influenza Epidemic [1,2]

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SUMMARY

Army and Veterans Administration records were used to investigate the possible significance of influenza and mustard-gas poisoning in the etiology of lung cancer. Three groups of World War I Army veterans were traced for mortality from 1919 through 1955: 1,855 men who had pneumonia during the influenza pandemic, 2,718 men who were hospitalized for mustard-gas poisoning in 1918, and a control group of 2,578 soldiers who had wounds of the extremities. No relationship was seen between pneumonia in 1918 and subsequent cancer; there was, however, suggestive evidence that the incidence of lung cancer was slightly increased in men who had been subjected to mustard-gas poisoning in 1918.—J. Nat. Cancer Inst. 25: 1231–1252, 1960.

IN THE 1920 report (*1*) of their pathological studies of the influenza epidemic in the United States, Winternitz and coworkers commented on the striking similarity of the epithelial proliferation seen in some fatal cases of postinfluenzal pneumonia and in an invasive, malignant neoplasm. These findings were so dramatic the investigators were led to speculate that the influenza pandemic of 1918–19 might later lead to some increase in the incidence of respiratory cancer. Laboratory experiments with influenza virus in mice (*2–4*) have not produced support for this hypothesis. The current emphasis in cancer research is on specific carcinogens, an emphasis greatly strengthened by the results of epidemiological studies on the smoking of tobacco, but there is also historical evidence, recently reviewed by Finke (*5*), which suggests that virtually any chronic pulmonary lesion may enhance the risk of lung cancer. Chronic bronchitis has been shown in the 1951 Impairment Study of the Society of Actuaries (*6*) and in a report by Case and Lea (*7*) to imply

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[3] Grateful acknowledgment is made to Dr. Michael B. Shimkin, Dr. Gustave Freeman, and Mr. Seymour Jablon for suggestions as to the design of the survey, to Dr. Benno K. Milmore for advice on the classification of clinical material, to Dr. Harold F. Dorn for access to his questionnaires on smoking history, and to Mrs. Alice Dolman for advice in coding cause of death. Mr. A. Hiram Simon, Mrs. Dorothy J. Mahon, Miss Vivian Heidenblut, and Mrs. Lucille Pogue of the Follow-up Agency staff have supervised the records and statistical work entailed by the survey. Mr. Seymour Jablon edited the report for publication.

increased risk of lung cancer, and Papanicolaou (*8*) lent some support to the view that a protracted chronic inflammatory process may pave the way for the development of a malignant respiratory neoplasm.

A further stimulation for the present study derives in part from experimental work on the carcinogenic activity of both nitrogen and sulfur mustards (*9–12*) in mice of a strain known to be highly susceptible to the development of pulmonary tumors. In addition, occasional isolated cases of lung cancer in man have been reported after occupational exposure to mustard compounds (*13*). In contradistinction to the experimental work on the influenza virus as a carcinogen, that on the mustards is quite provocative, so that any really relevant human data would be of great interest.

After the present study had been planned, the report of Case and Lea (*7*) appeared and seemed to provide a partial answer to the question about mustard gas. In a sample of 1,267 British World War I veterans alive on January 1, 1930, and receiving pensions for the effects of mustard-gas poisoning in 1917–18, they found 29 deaths from cancer of the lung and pleura in contrast to 14 expected on the basis of mortality rates for the male population of England and Wales over the calendar period of observation; in addition, there were 217 deaths from bronchitis versus 21 expected. Since the pensions usually had been granted because of chronic bronchitis, Case and Lea added a parallel series of 1,421 men pensioned for bronchitis but who had not been exposed to mustard gas. In this series also 29 deaths were observed from cancer of the lung and pleura versus 14 expected. Since the the same discrepancy as to lung cancer was found in the two series, Case and Lea concluded that mustard gas had not acted as a direct carcinogen, but had increased the risk of lung cancer indirectly through the mechanism of bronchitis. In a control group of 1,114 amputees studied in the same way, they found 13 deaths from lung cancer in comparison with 15.5 expected.

MATERIALS AND METHODS

Epidemiologic and follow-up studies on the veteran population (*14–18*) have demonstrated that this large segment of the U.S. male population is readily sampled and highly accessible to follow-up study. Medical record systems of the Armed Forces and the Veterans Administration are standardized, usually include punch-card indexes, and provide for central filing and access to all individual records. It appeared, therefore, that both problems involving lung cancer could be efficiently investigated via U.S. Army World War I veterans chosen on the basis of history in 1918.

The nature of the original observations by Winternitz *et al.* (*1*) on fatal cases of pneumonia implied that the population of interest was not the 792,000 U.S. Army primary admissions for influenza in World War I but the estimated 100,000 secondary cases (*19*, *20*) of pneumonia plus 78,000 primary cases of pneumonia. The pandemic consisted of a number of

waves during the period 1917–20, but its peak was reached in October, 1918. Accordingly, admissions were sampled from daily reports prepared by the numbered base hospitals in the American Expeditionary Forces which showed name, serial number, unit, and diagnosis. The period used was September through November, 1918.

Sulfur mustard was a war gas in World War I and led to an estimated 28,000 casualties in the U.S. Army (*21*). Admissions for gas poisoning in the A.E.F. were first recorded in February, 1918. However, it was not until the summer of 1918 that the daily hospital "report of casualties and changes" routinely showed the probable nature of the gas, so that it was necessary to sample admissions from August through October, 1918, and to depend chiefly on the special gas hospitals (*21*).

The most important problem visualized in sampling the mustard-gas injuries was the validity of the diagnosis. It was felt necessary to minimize the two chief errors of diagnosis: (1) influenza or other respiratory disease wrongly diagnosed as mustard-gas injury, and (2) the man injured by another gas whose record alleges mustard gas to be the agent. Accordingly, any case was rejected unless either the skin or the eyes were affected. If the clinical records were equivocal in attributing the injury to mustard gas, it was required that there be evidence of burns of the skin. In addition, it was required for all mustard-gas cases that there be evidence of some injury to the respiratory tract.

Although a reasonable basis of expected mortality in the present study might be provided by appropriate general mortality rates, it was considered safer to include an explicit control group for which mortality information would be obtained and processed in the same way as for the pneumonia and mustard-gas groups. Men with wounds of the extremities were selected as the most nearly comparable diagnostic group.[4]

Men born in the years 1888 through 1893 were chosen. The sample was further restricted to white males alive on January 1, 1919.

To determine sample size, preliminary computations were made on the U.S. life table for white males in 1930 and on the data of Cutler and Loveland (*22*), which suggested that about 35 percent of the men on the proposed rosters would have died from all causes by the end of 1956, and approximately 1 percent from lung cancer. Calculation showed that 2 samples of 2,500 each, in tests based on the 0.01 criterion of significance, would have about 60 percent power (in the Neyman-Pearson sense) in detecting a differential lung-cancer mortality of 2 to 1, and 99 percent power against a differential of 3 to 1, if expectation were 1 percent in the controls. Accordingly, the desirable sample size was set at 2,500 for each of the 3 rosters. The various restrictions, however, led to a sample of 1,855 men in the pneumonia group, 2,718 men in the mustard-gas group, and 2,578 in the control group with wounds of extremities.

[4] Case and Lea (*7*) make a point of the saturation of areas of French soil with mustard gas and stress the desirability of selecting controls from among men who had never served in France after July 12, 1917, when mustard gas was first used. The necessity for this restriction had not been suggested by review of the U.S. Army historical sources (*21*), and it was deemed sufficient to examine in detail the medical history of each potential control to insure that he had never been gassed, regardless of type of gas.

NATURE OF OBSERVATIONS

Baseline Data From Military Records

In addition to such information as date and place of birth, date of enlistment, and military unit, clinical records were abstracted with respect to date of admission for reference illness, supporting evidence of gas injury (involvement of eyes), supporting evidence of mustard-gas injury (involvement of skin), evidence of injury to respiratory tract, and complicating history.

The 3 rosters proved to be quite homogeneous with respect to place and year of birth. However, while the mustard-gas and control rosters were drawn overwhelmingly from the infantry (79 and 88%), only 52 percent of the pneumonia cases were infantrymen.

Mortality Data

Records of substantially all deaths of World War I veterans are in VA central files. The latter were therefore used to determine the mortality experience of veterans selected for this study. Initial processing established the fact of death or survival on January 1, 1956, and for all 2,542 veterans known to have died the VA claims folders were reviewed. Deaths before January 1, 1956, numbered 2,441, and these are used in the subsequent analysis. Proof of death is contained in these folders, ordinarily as a photostatic copy of the death certificate. If cancer appeared on the death certificate, a copy of the autopsy protocol, if any, was requested. If cancer did not appear on the death certificate, the responsible medical authority was asked whether cancer was an autopsy finding. If cancer was so reported, then a copy of the protocol was obtained.

By these procedures comparable mortality information was obtained on the several rosters, both at the level of the death certificate and the postmortem examination. The 3 rosters compared very closely with respect to the relative frequency of autopsy, 18.6 percent in the pneumonia roster, 20.7 percent in the mustard-gas roster, and 19.3 percent in the controls. For about a third of the deaths in each roster it was clear that no autopsy had been done, and for nearly half it was unknown whether autopsy had been done.

Of all 76 deaths during 1919–55 with primary cause cancer of the trachea, bronchus, and lung, 33 are known to have been brought to autopsy, 20 were stated not to have been so studied, and in 23 it is uncertain whether autopsy was performed. The proportions do not vary appreciably by roster. Review of the 31 autopsy protocols which could be obtained showed that lung cancer was found as primary site in 27 and as secondary site in 3. In but a single case autopsy failed to confirm respiratory cancer, stated on the death certificate to be the primary cause. In this case the right lung had previously been removed for squamous-cell carcinoma. Histologic information was sought, but since only

27 protocols were obtained for primary lung cancer the results were unrewarding.

In addition, among the 354 autopsy protocols obtained for deaths in which the death certificate gave a primary cause other than lung cancer, 5 contained evidence of lung cancer: 2 in the mustard-gas roster, 1 in the pneumonia, and 2 in the controls. It was concluded that the death certificate diagnoses were unbiased with respect to the 3 rosters, and accurate enough to serve as the basis for the roster comparisons to which the study was directed.

For purposes of analysis each death was coded as to cause. The primary or underlying cause of death was determined on the basis of the death-certificate together with coding rules developed for use with the last two revisions of the *International Statistical Classification of Diseases, Injuries and Causes of Death*. The assistance of the National Office of Vital Statistics proved invaluable. The rubrics of the Sixth Revision were employed for coding purposes. In addition to the primary cause, other causes or related conditions stated on the death certificate were also coded and without further attempt to determine priorities among them.

Morbidity and Disability Data

The study was enlarged to include morbidity after Case and Lea had suggested that an excess of lung-cancer deaths among victims of mustard-gas injury in World War I might arise via the intermediation of chronic bronchitis. As a practical matter, only illnesses that led to hospitalization within the VA system could be systematically brought into the study. There is reason to expect VA hospital reporting to provide a biased roster comparison, since veterans with gas injury in World War I would be expected to apply for VA hospitalization more often than other veterans with bronchitis. However, interest in chronic bronchitis arose only out of the possibility that bronchitis might be a factor in any excess lung-cancer mortality that the mustard-gas or pneumonia rosters might show. This possibility can be examined by comparison, within a particular roster, of the probability of a history of bronchitis for veterans who died of lung cancer with that for men who did not. If the suggestion of Case and Lea held for the American veterans, this would be reflected by an excess of bronchitis among men who died of lung cancer. Information was therefore obtained for a 10 percent sample of all men alive on January 1, 1956, or who died prior to that date of causes other than lung cancer, and for all men who died of lung cancer before that date. Note was made of VA hospitalizations for diseases of lung, bronchi, and pleura and of diagnoses made on an outpatient status, as in connection with the adjudication of claims. Note also was made of all diagnoses acknowledged to exist at the last VA examination for rating purposes, regardless of service connection.

Smoking History

Through the generosity of Dr. Harold F. Dorn, of the National Institutes of Health, it became possible to inquire into the smoking history of a

small subsample of each roster to learn whether any of the roster conditions had affected the smoking history. Dr. Dorn made available his file of questionnaires about smoking that were returned by World War I veterans with VA insurance in force on December 31, 1953. Collation of the files on the 2 studies yielded 170 men covered by both, 66 from the mustard-gas roster, 36 from the pneumonia roster, and 68 from the control roster. For all 170 men, only 34, or exactly 20 percent, declared that they had never used tobacco in any form; 52, or 31 percent, claimed never to have used cigarettes. Among the 118 who were at one time cigarette smokers, 35, or 30 percent, declared they had stopped before returning Dr. Dorn's questionnaire.

The percentages of men claiming never to have smoked do not vary significantly, being 18 for the mustard-gas group, 31 for the pneumonia roster, and 16 for the control group. Similarly, those alleging never to have smoked cigarettes also vary insignificantly, being 27, 42, and 28 in the same sequence. The percentage who stopped smoking cigarettes varies somewhat more, but also insignificantly (P about 0.11), being 40, 33, and 20 in the same order. The percentage who stopped before age 40, however, does vary significantly (P about 0.01), being 25, 14, and 4 in the same order. That is, men who were gassed almost certainly cut down on their smoking. The change in smoking habits thus implied might well reduce the incidence of lung cancer among men who were gassed.

FINDINGS AS TO MORTALITY

Mortality From All Causes

Table 1 shows the comparison of observed and expected numbers of deaths for each of the 3 rosters in various time intervals from 1919 through 1955 as well as for the entire period. The expected numbers of deaths were calculated on the basis of death rates for the U.S. white male population over the calendar period of interest. For this purpose U.S. life tables for white males in 1919–21, 1929–31, 1939–41, 1949–51, and 1955 were drawn upon for age-specific mortality rates in decennial census years and 1955, the rates for intervening years being obtained by linear interpolation. This made possible the determination of net mortality and survival ratios for any particular year-of-birth cohort.

Comparison of 1919–55 total figures indicates that the 3 rosters differ among themselves, and that in all of them mortality was either somewhat under-reported or actually below that of U.S. white males. In table 1 the experience is divided into broad time intervals, from which it may be seen that the deficit in observed mortality is largely confined to the first decade of the study period, when the effect of military screening would have been most influential. This comparison suggests that the mortality experience of World War I veterans has been somewhat more favorable than that of U.S. white males generally.

TABLE 1.—Observed and expected deaths, by roster, in relation to calendar time

Calendar period	Number of deaths		Ratio
	Observed	Expected	Observed/Expected
Mustard-gas roster			
1919–29	116	163	0. 71
1930–39	248	190	1. 31
1940–49	312	323	0. 97
1950–55	276	298	0. 93
Total	952	974	0. 98
Pneumonia roster			
1919–29	94	112	0. 84
1930–39	121	130	0. 93
1940–49	222	221	1. 00
1950–55	206	203	1. 01
Total	643	666	0. 97
Control roster (wounded)			
1919–29	95	155	0. 61
1930–39	167	180	0. 93
1940–49	300	307	0. 98
1950–55	284	283	1. 00
Total	846	925	0. 91

Text-figure 1 presents observed death rates for each roster and for U.S. white males of comparable age, and reveals that:

1) In the first postwar decade mortality in all 3 rosters was well below that for U.S. white males of comparable age, but among men on the pneumonia roster the rate was rather higher than among men on the other two rosters.
2) In the second decade the death rate for men on the mustard-gas roster advanced rapidly to occupy a position well above that for the other two rosters and for U.S. white males; the latter three curves were very close.
3) In the third decade the several rosters were indistinguishable from one another and from U.S. white males.

Mortality by Cause

Primary interest here, of course, attaches to death from lung cancer and other conditions involved in the hypotheses underlying the investigation. The latter include, for mustard gas, neoplasms of lymphatic and hematopoietic tissues (especially leukemia), anemias, and respiratory diseases generally. For pneumonia the conditions of interest, in addition to lung cancer, are respiratory diseases generally. However, in addition, the whole spectrum of cause was reviewed.

Lung Cancer in Relation to Roster Conditions

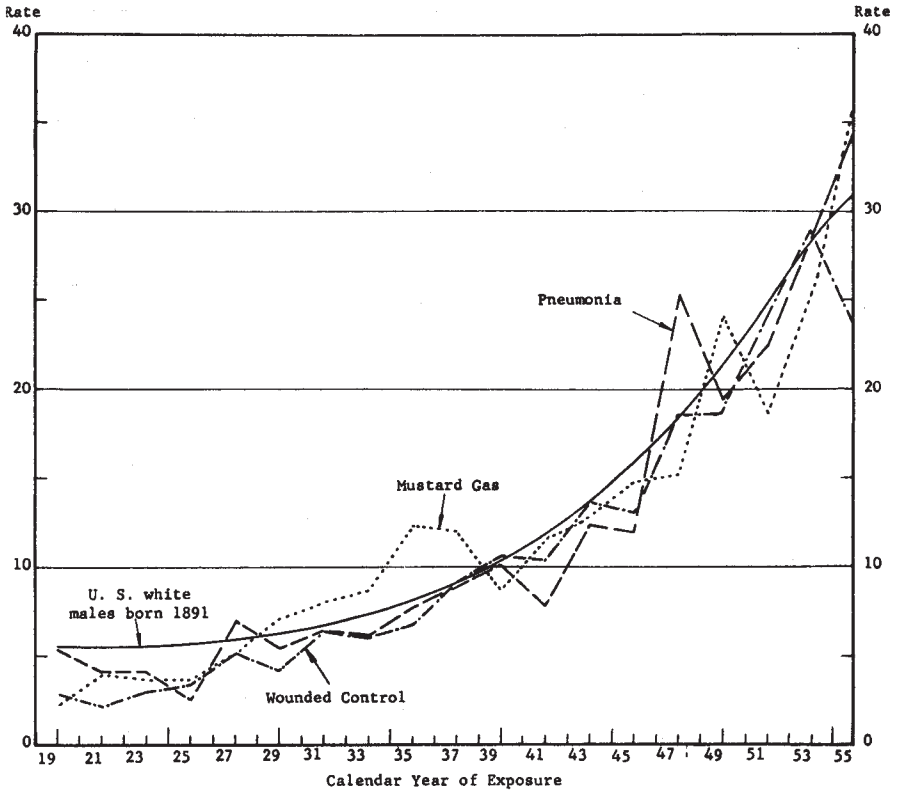
The precise rubrics of interest are the following in the Sixth Revision of the International Lists:

162 Malignant neoplasm of trachea, and of bronchus and lung, specified as primary.

163 Malignant neoplasm of lung and bronchus, unspecified as to whether primary or secondary.

For the period 1919–55, there were 76 deaths so classified as to primary cause; the number of deaths in which these diagnoses appear as associated conditions is negligibly small, 1 in the mustard-gas and 1 in the control roster. Moreover, such autopsy evidence as could be obtained failed to suggest that many deaths from lung cancer were actually attributed to other conditions. Lung cancer was found in 5 among 354 postmortem examinations on men whose deaths were ascribed to conditions other than lung cancer. These are distributed among the 3 rosters, and in only one was another pulmonary disease (bronchial pneumonia) given as primary cause of death. In one instance an early squamous-cell carcinoma of the bronchus was an incidental finding in a death attributed to portal cirrhosis, while in 3 cases the death certificate gave as primary cause a malignancy of another site shown on autopsy to be metastatic extension of bronchogenic carcinoma.

In the absence of competent autopsy of every death, one cannot have an entirely satisfactory count of deaths either from lung cancer or in which lung cancer is demonstrable. The available counts clearly include



TEXT-FIGURE 1.—Deaths per 1,000 men per year, by calendar period of exposure, and by roster, in comparison with U.S. white males of comparable age.

few deaths attributed to lung cancer in which this condition did not exist; among 31 autopsies none falls into this category, although in 3 the lung was found to be a secondary site. While errors of exclusion are undoubtedly present, there is no suggestion or reason to believe that the roster comparisons are in any way biased by such errors.

The design of the present study assumes a direct comparison of two independent samples, and when this method of comparing the rosters is used, the ratios of lung-cancer deaths to total sample size become:

For mustard-gas vs. wounded controls

36/2,718 vs. 26/2,578
or
1.3 percent vs. 1.0 percent
for which a one-tailed P is about 0.17.

For pneumonia vs. wounded controls

14/1,855 vs. 26/2,578
or
0.8 percent vs. 1.0 percent, which does not suggest a positive association of lung cancer with pneumonia.

These comparisons may be made directly and simply because the samples are homogeneous as to age. In both instances, therefore, the conclusion is clear that the observed discrepancies lie well within the usual range of sampling variation.

The sampling plan was devised so that the study would have a high chance (about 99%) of detecting a differential of 3 to 1, and a 60 percent chance of detecting a differential of 2 to 1, with 0.01 employed as the significance level. The evidence since published by Case and Lea suggests that a 2 : 1 ratio might be observed for the mustard-gas versus wounded comparison.

Although it was not planned that the analysis of the present study should rest on expected values calculated from the experience of the general population, in view of Case and Lea's results it seems essential to make such calculations for the 3 study rosters. For this purpose, rates for all cancer of the respiratory system have been used rather than for lung cancer. For U.S. white males the National Office of Vital Statistics provided annual age-specific rates for 5-year age groups, from which rates for each single year of age were obtained by interpolation. These were applied to the observed years of exposure at each age in the interval 1919–55 to obtain the expected number of deaths from cancer of the respiratory system. On this basis 71.4 deaths would have been expected in the entire sample in contrast to 84 observed, a statistically insignificant discrepancy. Table 2 presents these observed and expected deaths over the range of age at exposure, and by roster.

When the roster comparison is approached on the basis of expected values calculated from death rates for U.S. white males, rather than by a direct comparison of rosters processed in identical fashion, the results are

TABLE 2.—Observed and expected deaths attributed to malignant neoplasms of respiratory system, by age at death and by roster

Age at death	Mustard-gas		Pneumonia		Wounded controls		Total	
	Observed	Expected	Observed	Expected	Observed	Expected	Observed	Expected
26–29	0	0. 03	1	0. 02	0	0. 03	1	0. 08
30–34	0	0. 13	0	0. 09	0	0. 12	0	0. 34
35–39	0	0. 27	0	0. 19	0	0. 26	0	0. 72
40–44	1	0. 66	0	0. 45	0	0. 64	1	1. 75
45–49	5	1. 85	0	1. 28	2	1. 80	7	4. 93
50–54	3	3. 80	5	2. 66	1	3. 73	9	10. 19
55–59	13	7. 69	5	5. 36	12	7. 55	30	20. 60
60–64	13	10. 17	3	7. 09	12	10. 07	28	27. 33
65–67	4	2. 04	1	1. 42	3	2. 01	8	5. 47
Total	39	26. 64	15	18. 56	30	26. 21	84	71. 41

quite different. A summary for all cancer deaths of the respiratory system is as follows:

Roster	Observed deaths	Expected deaths	*P**
Mustard-gas	39	26. 6	<0.01
Pneumonia	15	18. 6	>0.05
Controls	30	26. 2	>0.05

*One-tailed for mustard-gas and pneumonia, two-tailed for controls.

Since a significant proportion of the men on the mustard-gas roster had given up cigarette smoking prior to age 40, it may be asked whether this might have served to reduce an otherwise greater excess of lung cancer in these men. The sample of men with smoking histories—only 170—is much too small to permit a direct correction for this possibility, but an upper bound can be set on the possible error. This can be done by making the extreme assumption that men who stopped smoking cigarettes before age 40 were subject to the same risk of lung cancer as were nonsmokers. It is estimated that 15 percent of the men on the mustard-gas roster were at one time regular cigarette smokers, but gave up smoking as a result of being gassed, while the corresponding percentage for the pneumonia roster is 6 percent. The percentage of regular cigarette smokers in each roster at the time of Dorn's survey was 44 for the former and 39 percent for the latter. On another extreme assumption, *viz.*, that *all* lung cancer occurred in regular cigarette smokers, then the addition of 15 to the 44 percent cigarette smokers in the lung-cancer roster might be expected to increase the number of deaths from lung cancer by about a third. For the pneumonia roster, the similarly derived upper limit would be an increase of about one sixth in the number of deaths from lung cancer.

Since the effect of increasing the 1.3 percent incidence of lung cancer in the mustard-gas roster by a third would be to achieve a level of about 1.7 percent, it appears that, even had there been no alterations of smoking patterns, the lung-cancer rate in the mustard-gas group would not achieve

twice control levels. With the pneumonia roster the effect would be smaller and the "adjusted" percentage with lung cancer only 0.9.

As the present study was originally designed it fails to prove, beyond reasonable doubt, that mustard-gas injury in World War I had a carcinogenic effect. However, the observations are not inconsistent with those of Case and Lea, who reported a 2:1 ratio of observed-to-expected deaths in British veterans drawing war pensions for chronic bronchitis after mustard-gas injury in World War I. Although the analysis of Case and Lea rests on the indirect comparison of rosters through the medium of death rates in the general population, the applicability of the latter to British veterans in 1930–52 seems well established by the agreement Case and Lea obtained between deaths expected and observed, among men in their control sample, not only for all causes and for lung cancer but also for cancer of other sites. In view of the close agreement in the present study between observed and expected respiratory-cancer deaths for the pneumonia and control rosters (45 vs. 44.8), parallel reasoning might be applied to the present study to favor the conclusion that the observed and expected values for the mustard-gas roster (39 vs. 26.6) constitute a valid comparison. It is concluded from the present study that it is extremely unlikely that the influenza epidemic of 1918 has contributed in any way to the increasing death rate from lung cancer in the United States.

Other Causes of Particular Interest

Since the mustard-gas sample was chosen for acute respiratory involvement, and since the mustards are regarded as radiomimetic, analysis was made of deaths attributed to leukemia and lymphoma, anemias, and diseases of the respiratory system. However, except for diseases of the respiratory system, none of these conditions was very often mentioned as either the principal or the associated cause of death, and there was no evidence of significant roster variations with respect to any of them. Thus, leukemia and aleukemia (code 204) was cited 14 times as cause of death, 5 in each of the mustard-gas and pneumonia rosters, and 4 in the control roster.

Diseases of the respiratory system, exclusive of tuberculosis and neoplasms, accounted for 96 deaths among men on the mustard-gas roster and 50 among men on each of the other 2 rosters. The difference between the mustard-gas and control rosters is well outside the expected range of chance, but that between the penumonia and control rosters is small and of borderline significance (P about 0.06) in a one-tailed test. The percentages dying of respiratory diseases over the interval 1919–55 are 3.5 for the mustard-gas roster, 2.7 for the pneumonia roster, and 1.9 for the control roster. Mortality trends over time are exhibited in table 3 to facilitate comparison of the 3 rosters. Except for the period 1954–55 the respiratory-death rate is highest for the mustard-gas roster, especially in the period 1934–38. From the particularly elevated rates for the mustard-gas roster in the period 1934–38, it would appear that the

TABLE 3.—Number of deaths and deaths per 1,000 men per year for respiratory disease,* by roster, and by period of exposure

Period of exposure	Mustard-gas		Pneumonia		Wounded controls	
	Deaths	Rate	Deaths	Rate	Deaths	Rate
1919–23	10	0. 74	6	0. 66	0	—
1924–28	9	0. 68	4	0. 45	5	0. 40
1929–33	15	1. 17	10	1. 15	10	0. 81
1934–38	24	1. 96	10	1. 18	10	0. 84
1939–43	11	0. 95	5	0. 62	6	0. 53
1944–48	12	1. 10	7	0. 92	9	0. 84
1949–53	11	1. 11	4	0. 58	5	0. 51
1954–55	4	1. 09	4	1. 60	5	1. 40
Total	96	1. 09	50	0. 83	50	0. 59

*Exclusive of tuberculosis and neoplasms.

respiratory diseases contribute heavily to the high general mortality of men on this roster during this period, as noted earlier.

In view of the large excess of deaths from respiratory diseases among men on the mustard-gas roster, the distribution within the individual diagnostic rubrics of this general category is of particular interest, and the significant detail is given in table 4. For no other respiratory diagnosis are deaths frequent enough to warrant analysis.

From the data of table 4 it is apparent that the mustard-gas roster had an excess of deaths from pneumonia but not from the other respiratory diseases. The 1918 pneumonia roster had a relative excess of later deaths from pneumonia of only borderline significance, and no excess from other respiratory diseases.

When the deaths from respiratory disease are distributed over time so as to permit comparisons of trends between pneumonia and other respiratory diseases, additional meaning is given to the temporal variation seen in table 3. As may be seen from table 5, the two respiratory components

TABLE 4.—Comparisons of rosters as to deaths from pneumonia and from other respiratory diseases, 1919–55

Cause of death		Mustard-gas		Pneumonia		Wounded controls	
Code	Title	Deaths	Percent of roster	Deaths	Percent of roster	Deaths	Percent of roster
480	Influenza with pneumonia	9	0. 3	7	0. 4	2	0. 1
490	Lobar pneumonia	37	1. 4	21	1. 1	19	0. 7
491	Bronchopneumonia	23	0. 8	7	0. 4	12	0. 5
493	Pneumonia, other and unqualified	9	0. 3	3	0. 2	3	0. 1
	Subtotal—Pneumonia	78	2. 9	38	2. 0	36	1. 4
480–527	Respiratory disease other than above	18	0. 7	12	0. 6	14	0. 5
	Total	96	3. 5	50	2. 7	50	1. 9
P in one-tailed tests against wounded controls:							
	Pneumonia	<0. 01		0. 06			
	Other diagnoses	>0. 05		>0. 05			

TABLE 5.—Deaths and annual death rates per thousand for pneumonia and for other respiratory diseases, by roster, over time, 1919–55

Period	Mustard-gas roster				Pneumonia roster				Control roster			
	Pneumonia deaths		Other deaths		Pneumonia deaths		Other deaths		Pneumonia deaths		Other deaths	
	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Number	Rate
1919–28	17	0. 64	2	0. 07	8	0. 44	2	0. 11	4	0. 16	1	0. 04
1929–38	37	1. 47	2	0. 08	18	1. 05	2	0. 12	18	0. 74	2	0. 08
1939–48	16	0. 71	7	0. 31	7	0. 45	5	0. 32	10	0. 45	5	0. 23
1949–55	8	0. 59	7	0. 52	5	0. 53	3	0. 32	4	0. 30	6	0. 45
Total	78	0. 89	18	0. 20	38	0. 63	12	0. 20	36	0. 42	14	0. 16

TABLE 6.—Comparison of study rosters as to mortality from broad groups of causes, 1919–55

Cause of death		Mustard-gas		Pneumonia		Wounded controls		P*
Code	Title	Number	Percent	Number	Percent	Number	Percent	
00	Tuberculosis, respiratory	99	3. 6	54	2. 9	54	2. 1	<0. 01
01	Tuberculosis, other	3	0. 1	4	0. 2	2	0. 1	>0. 05
02	Syphilis and sequelae	13	0. 5	8	0. 4	11	0. 4	>0. 05
04–13	Other infectious and parasitic diseases	8	0. 3	6	0. 3	8	0. 3	>0. 05
14	Cancer, mouth and pharynx	7	0. 3	2	0. 1	7	0. 3	>0. 05
15	Cancer, digestive system	57	2. 1	32	1. 7	51	2. 0	>0. 05
16	Cancer, respiratory system	39	1. 4	15	0. 8	30	1. 2	>0. 05
17–19	Cancer, other and unspecified sites	19	0. 7	12	0. 6	22	0. 9	>0. 05
20–23	Other neoplasms	16	0. 6	15	0. 8	18	0. 7	>0. 05
24–28	Allergic, endocrine, nutritional diseases	13	0. 5	12	0. 6	18	0. 7	>0. 05
29	Diseases of blood and blood-forming organs	3	0. 1	1	0. 1	4	0. 2	>0. 05
30–32	Mental, psychoneurotic, and personality disorders	11	0. 4	4	0. 2	11	0. 4	>0. 05
33–39	Diseases of nervous system and sense organs	44	1. 6	52	2. 8	57	2. 2	0. 03
40–41	Rheumatic fever and rheumatic heart disease	12	0. 4	9	0. 5	8	0. 3	>0. 05
42	Arteriosclerotic and degenerative heart disease	225	8. 3	173	9. 3	216	8. 4	>0. 05
43–46	Other diseases of circulatory system	73	2. 7	49	2. 6	59	2. 3	>0. 05
47–52	Diseases of respiratory system	96	3. 5	50	2. 7	50	1. 9	<0. 01
53–58	Diseases of digestive system	55	2. 0	36	1. 9	52	2. 0	>0. 05
59–61	Diseases of GU system	33	1. 2	13	0. 7	27	1. 0	>0. 05
69–79	All other diseases and conditions	15	0. 6	7	0. 4	16	0. 6	>0. 05
	Trauma	109	4. 0	87	4. 7	124	4. 8	>0. 05
	Unknown	2		2		1		
	Total	952	0. 1	643	0. 1	846	0. 0	
	Number of men	2, 718	35. 0	1, 855	34. 7	2, 578	32. 8	

*Comparison of all 3 rosters.

moved very differently over time. For all 3 rosters, deaths from pneumonia were at their peak in 1929–38 and fell off rapidly thereafter, while deaths from other respiratory diseases increased over this period. The high death rates for respiratory diseases in 1929–38 are thus entirely attributable to pneumonia.

General Review of Mortality

Other causes of death were reviewed by means of a two-digit classification of primary cause of death. Table 6 provides data which compare rosters for mortality from broad groups of causes. In addition to those groups of causes that have already been discussed, significant variation is noted for only two: tuberculosis of the respiratory system ($P<0.01$) and diseases of the nervous system or sense organs ($P = 0.03$).

Table 7 shows tuberculosis death rates for the 3 rosters as functions of calendar time and provides further information on the cause of the abnormal rise in the death rate of men on the mustard-gas roster during the decade 1929–38: Not only pneumonia but also tuberculosis contributed to that increase. The table also shows why the death rate for men on the pneumonia roster was abnormally high at the very outset of the follow-up period: In the decade 1919–28 the death rate for tuberculosis among men on this roster was 1.28 (23 deaths) and suggests that at least 10 of the 1,855 men on this roster actually had acute tuberculosis (of which disease they subsequently died) at the time they were thought to have had pneumonia. To compare tuberculosis mortality in these samples with that which would have been expected from rates for U.S. white males, suitable rates were developed from a summary (*23*) published by the National Office of Vital Statistics.

TABLE 7.—Number of deaths and deaths per 1,000 men per year for respiratory tuberculosis, by roster, and by period of exposure

Period of exposure	Mustard-gas		Pneumonia		Wounded controls	
	Number of deaths	Rate	Number of deaths	Rate	Number of deaths	Rate
1919–28	17	0. 64	23	1. 28	15	0. 59
1929–38	41	1. 63	12	0. 70	13	0. 54
1939–48	27	1. 20	15	0. 96	19	0. 86
1949–55	14	1. 03	4	0. 43	7	0. 53
Total	99	1. 13	54	0. 89	54	0. 63

Table 8 presents the resulting data by age. During the first decade, although the observed mortality was about half of expectation for the mustard-gas and control rosters, it was slightly above expectation for the pneumonia roster. One might conclude that military screening depressed the death rate from tuberculosis for this period, but that errors in diagnosis (tuberculosis mistaken for pneumonia) account for the deviant behavior of the pneumonia roster. The data suggest that, in the control roster, the effect of medical selection progressively diminished to zero during the second and third decades. For the pneumonia roster, on the

other hand, by the second decade after selection the tuberculosis death rate had returned to general population levels, there to remain. The suggestion is strong that the tendency occasionally to misdiagnose tuberculosis as pneumonia resulted in selection for this disease in men on the pneumonia roster. On this view, the agreement between observed and expected mortality is merely a coincidence: The influence of this error in selection offsets the effect of medical screening.

TABLE 8.—Observed deaths from tuberculosis, all forms, and expected deaths based on experience of U.S. white male population of comparable age at calendar time of exposure

Age	Mustard-gas		Pneumonia		Wounded controls	
	Observed	Expected	Observed	Expected	Observed	Expected
26–34	11	23. 7	19	16. 0	12	22. 5
35–44	39	23. 9	16	16. 2	15	22. 8
45–54	27	19. 6	13	13. 6	15	19. 2
55–	25	13. 1	10	9. 1	14	12. 9
Total	102	80. 3	58	54. 9	56	77. 4

The experience of men on the mustard-gas roster is most atypical, and one cannot escape the conclusion that some interaction occurred between the mustard-gas injury, or its residuals, and tuberculosis. Although the experience of the first decade seems normal enough, thereafter men on the mustard-gas roster consistently died from tuberculosis more often than would be expected in relation to the civilian population; the excess amounts to 34 deaths above the expected 57. The excess is even greater with respect to the control roster. It may be remarked incidentally that none of the 5 cases of lung cancer found at autopsy, but not so diagnosed on the death certificate, occurred in an individual whose death certificate stated tuberculosis as the cause.

The only other causes to show any evidence of heterogeneity in table 6 are diseases of the nervous system and sense organs. Primarily, this rubric represented cerebral vascular disease; just over half of all deaths were attributed to "cerebral hemorrhage." The variation among rosters is not remarkably large: the calculated probability of a sampling result as extreme as that observed is about 1 in 30, on the hypothesis of homogeneity. Inspection of data on individual causes revealed no marked discrepancy for any single one; it is only when all are added that the low count for the mustard-gas roster attracts attention. The variation is localized in time to the last decade; at a time when rates for men on the pneumonia and control rosters were doubling, the rate for men on the mustard-gas failed to rise sharply. Since, directly and by implication, hundreds of such comparisons have come under scrutiny here, it may well be that this particular discrepancy is merely a chance event.

In addition to the individual causes that have already been discussed because of either intrinsic interest or their dominance of a large class of deaths in which roster variation was observed, those individual causes were examined for roster variation which accounted for at least 16 ob-

served deaths in the 3 rosters combined. There were 15 such causes, but for only one—cancer of the pancreas—was there apparently significant roster variation. Of the 16 deaths observed, 12 were in the mustard-gas roster, and the remaining 4 in the controls. This distribution of the 16 deaths by roster is a most unlikely one (P about 0.005).

BRONCHITIS AND LUNG CANCER

Information on bronchitis has been sought in this study because Case and Lea indicated that any excess of lung cancer attributable to mustard gas in their British series probably stems from the fact that the men in their mustard-gas sample all drew pensions, chiefly for chronic bronchitis. Earlier studies (*24*) on U.S. veterans with mustard-gas injury in World War I have indicated that chronic bronchitis is a common sequel of such injury.

In the expectation that a relationship between bronchitis and lung cancer would be found in this series, and that its maximum strength would be exhibited in mortality ratios based on deaths forward of a given calendar date before which bronchitis had already manifested itself, tabulations were centered on various calendar dates. For each tabulation date, separately for men who subsequently died of lung cancer and for those who did not, these tables show which men already had bronchitis, which men first had bronchitis later, and which men never had bronchitis. Table 9 provides a summary of these data for the 1926, 1936, and 1946 tabulation points, and shows that evidence of a relationship between bronchitis and lung cancer is completely lacking. There are important roster differences in the reported prevalence of bronchitis, but they pertain equally to lung-cancer deaths and to others. For the mustard-gas and control rosters, with their more stable numbers of cases, the percentages involved in the horizontal comparisons are especially close.

Why the U.S. material should differ from the British has no answer in these data, but one would at first suspect that either chronic bronchitis has very different significance in Great Britain or, possibly, that sampling bias has crept into one or the other of the studies.

Bronchitis and Roster Conditions

As indicated, the rosters vary quite significantly as to reported prevalence of bronchitis. However, since each roster was chosen on the basis of a specific item of medical history during military service, and in this study the morbidity information was developed from VA claims folders, it is to be feared that the direct comparison of the rosters may be biased. The objectives of the study did not include comparison of men on the rosters as to morbidity, and, accordingly, the only measures of relative bias are quite indirect. With respect to bronchitis, it may be mentioned that morbidity, as measured by reported admissions to service or VA

TABLE 9.—Relation between lung cancer and bronchitis, by roster, for various calendar periods of observation

Calendar period			Deaths from lung cancer			Other deaths and survivors to 1956 in 10-percent sample			
				Bronchitis present			Bronchitis present		
For deaths	For first report of bronchitis	Roster	Total	Number	Percent	Total	Number	Percent	P
1926–55	1919–55	Mustard-gas	36	21	58.3	264	157	59.1	>0.05
		Pneumonia	13	6	46.2	174	58	33.9	>0.05
		Controls	26	5	19.2	247	48	19.4	>0.05
1926–55	1919–25	Mustard-gas	36	14	38.9	264	105	39.8	>0.05
		Pneumonia	13	3	23.1	174	27	15.5	>0.05
		Controls	26	2	7.7	247	21	8.5	>0.05
1936–55	1919–35	Mustard-gas	35	18	51.4	242	124	51.2	>0.05
		Pneumonia	13	5	38.5	163	38	23.3	>0.05
		Controls	26	3	11.5	235	37	15.7	>0.05
1946–55	1919–45	Mustard-gas	29	15	51.7	210	119	56.7	>0.05
		Pneumonia	9	5	55.6	146	38	26.0	>0.05
		Controls	26	5	19.2	208	35	16.8	>0.05

hospitals with this diagnosis, bore essentially the same ratio to mortality from this cause (primary or associated) in the 3 rosters. With this *caveat*, table 10 shows the continuing build-up of cases by roster, starting in 1919–20, when one fourth of all men on the mustard-gas roster registered evidence of bronchitis, through 1957.

TABLE 10.—Cumulative percentage distributions of men as to first diagnosis of bronchitis, 10-percent sample, by roster

Period of first diagnosis	Roster		
	Mustard-gas	Pneumonia	Controls
	(*Cumulative percentage*)		
1919–20	24. 5	8. 1	3. 0
1921–25	43. 1	16. 8	9. 4
1926–30	49. 4	18. 6	12. 4
1931–35	56. 5	24. 8	16. 7
1936–40	59. 7	28. 0	17. 6
1941–45	61. 7	28. 6	17. 6
1946–50	62. 8	31. 7	18. 9
1951–55	63. 2	34. 2	20. 6
1956–57	63. 6	36. 0	21. 0
Number of men (folders reviewed)	253	161	233

Men on the mustard-gas roster not only reported more bronchitis—their onset was much earlier.

CONCLUSIONS

Two problems in the epidemiology of lung cancer have been attacked on the basis of a mortality study of U.S. Army veterans of World War I: the 1918 influenza epidemic and war injuries attributed to mustard gas. The basic design is that of a prospective study initiated entirely on the basis of military records created in 1918, aimed at the detection of 3 : 1 differences between samples of approximately equal size compared as to mortality from lung cancer. Representative rosters of 2,718 white men with mustard-gas injury, 1,855 with pneumonia in 1918, and 2,578 with wounds of the extremities (controls), were created from retired Army records in the St. Louis record depot. Year of birth was confined to 1888–93, inclusive. The original Army clinical records of mustard-gas injury were reviewed according to criteria thought sufficient to insure the validity of the diagnosis and the determination of the responsible agent. The entire roster of 7,151 men was then traced forward through 1955 on the basis of records of insurance, hospitalization, and disability maintained by the Veterans Administration.

Soon after the study was begun, a report became available by Case and Lea on 1929 British Army pensioners with residuals of mustard-gas injuries received in World War I. Their report suggested that men with mustard-gas injury had about twice the expected incidence of lung cancer, but only because of an intervening residual in the form of chronic bron-

chitis. In view of this report the design of the present study was modified to obtain data on VA hospitalizations, outpatient visits, and disability ratings for 10 percent of the sample.

The total of 2,441 deaths reported through 1955 was 95 percent of expectation on the basis of age- and time-specific death rates for U.S. white males over this interval. While in the first decade only 71 percent of the expected deaths were found, in the period 1940–55 the proportion of expected deaths was 98 percent. It is believed that the early deficit represents the influence of screening for military service in World War I, and that VA reporting of deaths is substantially complete.

The 3 rosters differ significantly as to gross mortality only in the second decade of the follow-up period, when men on the mustard-gas roster suffered from considerably higher mortality rates. Examination of the deaths by cause revealed that this excess arose primarily from pneumonia and tuberculosis.

The data on mortality from lung cancer are equivocal with respect to the influence of mustard-gas injury, but contain no hint that postinfluenzal pneumonia in the 1918 fall epidemic increased the risk of lung cancer. Observed lung-cancer deaths are 36/2,718, or 1.32 percent, for the mustard-gas roster, and 26/2,578, or 1.01 percent, for the control roster. These percentages do not differ significantly and thus provide but weak support for the view that mustard-gas injury sets the stage for the later development of bronchogenic cancer. However, the study was planned to have good power against a 3 : 1 ratio but not against a 2 : 1 ratio, and since Case and Lea reported only a 2 : 1 ratio in their material, the present finding is not inconsistent with their conclusion. It seemed essential, therefore, to make a supplementary comparison of observed mortality in relation to expectation based on the general U.S. population experience for white males. This can be done for all respiratory cancer and provides a more powerful, if less direct, comparison. In these terms the ratios of observed to expected deaths are 39/26.6, or 1.47, for the mustard-gas roster, 15/18.6, or 0.81, for the pneumonia roster, and 30/26.2, or 1.15, for the control roster. Only the first differs significantly ($P < 0.05$) from unity. Although the study was not designed on the basis of this approach, because a direct comparison of two sociologically similar samples, followed up in the same way, seemed distinctly preferable, correspondence between veteran and civilian mortality seems sufficiently close to invest this indirect comparison with more merit than could be assumed for it in the planning stage. As originally planned, therefore, the study renders a verdict of "unproved," but the indirect comparison with population values is quite suggestive that an association exists. However, it is not consistent with the view that the increment of risk is large, relative to that existing in the entire control population, the 95 percent confidence interval on the observed ratio of 1.47 being 1.02 to 1.96. The Case and Lea result of 2.07 falls just outside this confidence interval. To the extent that cigarette smoking could be an important source of risk for the control population, for nonsmokers the relative increment of risk associated with a single mustard-gas exposure could, nevertheless, be large.

The relationship between bronchitis and lung cancer was studied directly by comparing the percentages exhibiting bronchitis at a fixed date, *e.g.*, January 1, 1926, in (*a*) men who later died of lung cancer, and (*b*) men who did not later die of cancer. This was done for each roster and for a quinquennial series of dates, but no evidence of association was found. Large roster differences were observed, however, in the reported incidence of bronchitis, in that about 65 percent of the VA records of men on the mustard-gas roster, 35 percent on the pneumonia roster, and 20 percent on the wounded roster, showed evidence of bronchitis. The failure of these data to confirm those of Case and Lea, therefore, suggests that bronchitis may not be a uniform clinical entity in Britain and the United States.

Deaths from neoplasms of the lymphatic and hematopoietic systems were few and did not vary among the several rosters. There were 14 deaths from leukemia and aleukemia, almost evenly divided among the 3 rosters. The experience with respect to other cancers was not remarkable, except for cancer of the pancreas: 12 of the recorded 16 deaths were among men on the mustard-gas roster and none on the pneumonia roster ($P<0.01$). Deaths from the anemias were also infrequent and did not vary by roster.

Deaths from diseases of the nervous system and sense organs also differ significantly ($P = 0.03$) among the 3 rosters, the discrepancy favoring the mustard-gas sample. In view of the large number of significance tests performed here, a discrepancy of this degree of improbability (1/30) may well be an accident of sampling.

Deaths from tuberculosis were much more frequent among men on the mustard-gas roster than among men on the wounded controls roster (3.8 vs. 2.2%), with the excess being experienced only after age 35. Before age 35 the tuberculosis mortality experience was about the same in both groups and about half that of U.S. white males generally.

Pneumonia, like tuberculosis, caused significantly greater mortality in the mustard-gas roster than in controls (2.9 vs. 1.4%). However, in this instance the difference varied little in time.

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