Exhibit D
to Kalasinsky Declaration

Lung Cancer Mortality in World War I Veterans With Mustard-Gas Injury: 1919–1965 [1,2]

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SUMMARY—A study of the mortality experience of three samples of World War I veterans totaling 7,151 U.S. white males was extended from 1956 through 1965 to learn whether a single exposure to mustard gas with respiratory injury was associated with increased risk of lung cancer in later life. Rosters of men born between 1889 and 1893 [2,718 exposed to mustard gas, 1,855 hospitalized with pneumonia in 1918, and 2,578 with wounds of the extremities (controls)] were traced via the Veterans Administration's death records. The 4,136 deaths reported were 95% of that expected. The conclusions of the original study were not altered by the additional 10 years of follow-up. Observed deaths from lung cancer numbered 69, or 2.5%, for the mustard-gas group as compared to 33, or 1.8%, for the pneumonia group and 50, or 1.9%, for the controls. The risk of death from lung cancer among men gassed relative to that for the controls was estimated as 1.3, with 95% confidence limits of 0.9–1.9. These figures failed to make a strong case for a carcinogenic effect, apparently because a sufficent dose of mustard gas was not received.—J Natl Cancer Inst 54: 311–317, 1975.

LUNG CANCER DEATHS among World War I U.S. Army veterans who had been hospitalized in the fall of 1918 for mustard-gas injury, severe influenza with pneumonia, or extremity wounds were investigated by Beebe in a retrospective cohort study (*1*). No association of lung cancer with influenza was seen, but suggestive evidence (a relative risk of 1.3 with a one-tailed *P* of 0.17) was found for mustard-gas injury. Collation of these records with the roster used by Dorn in his investigation (*2*) of smoking and lung cancer in World War I veterans showed that significantly more men injured by mustard gas had given up smoking before age 40 than had those in the other two groups. Thus a real carcinogenic effect of mustard gas may have been obscured by the greater effect of cigarette smoking, more common among men not exposed to the gas. It seemed necessary, therefore, to estimate the independent and combined effects of the two agents.

Earlier, Case and Lea had reported (*3*) that the incidence rate of lung cancer in men pensioned for the late effects of mustard-gas poisoning (mostly chronic bronchitis) was twice expectation, but that this was also true of men pensioned for bronchitis who had not been exposed to mustard gas. They suggested that mustard gas had not acted as a direct carcinogen but led to respiratory-tract cancer by way of bronchitis. In a study of Japanese factory workers who manufactured mustard gas between 1929 and 1945, Wada et al. (*4, 5*) followed 495 men for 16 years and reported 33 deaths from cancer of the respiratory tract, compared with 0.9 expected.

In the present report, the mortality for 1956–65 is reviewed for the three World War I Army rosters studied by Beebe, in an effort to evaluate the carcinogenic effect of mustard gas. Also, the latest 10 years of experience is screened for other effects, since an elevated mortality from tuberculosis and pneumonia among men gassed was observed in the earlier study.

MATERIALS AND METHODS

From among an estimated 28,000 World War I Army casualties from sulfur mustard gas, a sample of 2,718 men admitted in August and October 1918 to special gas hospitals with unequivocal evidence of mustard-gas exposure and injury to the respiratory tract was selected for study. The postinfluenzal pneumonia population was sampled by random choice of admissions for primary or secondary pneumonia at base hospitals of the American Expeditionary Forces during September and November 1918, when the influenza pandemic reached its peak. After a number of restrictions were established, this sample totaled 1,855 men. Controls were 2,578 men with wounds of the extremities. Restrictions on the men in all three samples were that they be white, born in 1888 through 1893, and alive on January 1, 1919.

The fact of death or survival was ascertained from the Veterans Administration (VA) Master Index file, maintained for the processing of claims filed by U.S. servicemen or their relatives. Deaths among all cohort members before January 1, 1956, numbered 2,441 and the claims folders for all these men were examined to determine the cause of death, usually from a copy of the death certificate. Cancer, whether it appeared on the certificate or not, was carefully sought as a possible autopsy finding. There was no significant variation among the three rosters in accuracy of diagnosis shown on the death certificates.

In early 1966, the three rosters were updated for mortality through December 31, 1965. The date and cause of death were then obtained from claims folders maintained by the VA benefits section. This procedure

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[2] This study is part of a program of epidemiologic and medical follow-up studies organized by the National Academy of Sciences–National Research Council at the request of the Veterans Administration, the Department of Defense, and the Public Health Service. This project of the NRC Medical Follow-up Agency was supported by contract PH43-64-44, Task Order No. 54.

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has been shown (6) to yield accounts of 92% of all deaths among veterans of World War I. By the end of 1965, 4,136 (58%) of the original 7,151 men were listed as dead by the VA. This includes 1,662 deaths occurring since 1955: 655 in the mustard-gas group, 407 in the pneumonia group, and 600 among the controls. The slight discrepancies between these figures and the number of deaths through 1955 reported by Beebe are due to the fact that, among the three rosters, 33 deaths before 1956 were not known to the VA at the time of the original study.

Since the work of Case and Lea suggested that chronic bronchitis would be a factor in any excess lung cancer that might be found in the mustard-gas and pneumonia groups, details of VA hospitalizations and out-patient diagnoses were obtained for a 10% sample of all men alive on January 1, 1956 or who died before that date of causes other than lung cancer, and for all men who died of lung cancer before then.

Additional information on the smoking habits of the men under investigation has been collected to examine the possible interaction of effects of cigarette smoking and mustard-gas exposure on respiratory cancer. When the second follow-up was planned, arrangements were made to collect information from VA hospital records for admissions before onset of respiratory cancer on the smoking habits of all men dying of this disease before 1967, and for admissions between 1944 and 1955 for a random sample of all others. Information was obtained for 69 men dead of lung cancer by 1966 and for 167 other men in the study. The data, however, were incomplete; the amount smoked and number of years of smoking were often not available, but only the fact that cigarettes were among the man's personal effects.

Dr. Dorn's files had been augmented by the responses from a second questionnaire mailing in 1957 to all individuals who had not replied to the 1954 survey. When the tape files were again collated, 64 men were identified, in addition to 170 identified earlier, to provide a total of 234 individuals with detailed smoking information. Because of the way in which they were drawn, the two samples could only be analyzed separately: the former for possible roster differences with respect to lung cancer mortality among both nonsmokers and smokers, and the latter for any differences between rosters with respect to lifetime smoking histories.

RESULTS

All Causes of Death

A comparison of observed and expected numbers of deaths by decade from 1919 through 1965 for each of the three rosters is shown in table 1. The expected numbers were calculated on the basis of age-specific death rates for the U.S. white male population over the calendar period of interest applied to the 6 year-of-birth cohorts within each roster. However, these men clearly were not samples representative of the U.S. population of white males born in the years 1888 to 1893. The screening effect of the preinduction physical examination, as well as

TABLE 1.—*Observed and expected deaths, by roster and time*

Roster and calendar period	Number of deaths		Ratio
	Observed	Expected [a]	Observed/expected
Mustard gas			
1919–29	122	163	0.75
1930–39	248	190	1.31
1940–49	314	323	0.97
1950–59	519	534	.97
1960–65	413	426	.97
Total	1,616	1,636	.99
Pneumonia			
1919–29	97	112	.87
1930–39	121	130	.93
1940–49	224	221	1.01
1950–59	346	372	0.93
1960–65	269	300	.90
Total	1,057	1,135	.93
Control (Wounded)			
1919–29	99	155	.64
1930–39	169	180	.94
1940–49	305	307	.99
1950–59	507	527	.96
1960–65	383	421	.91
Total	1,463	1,590	.92

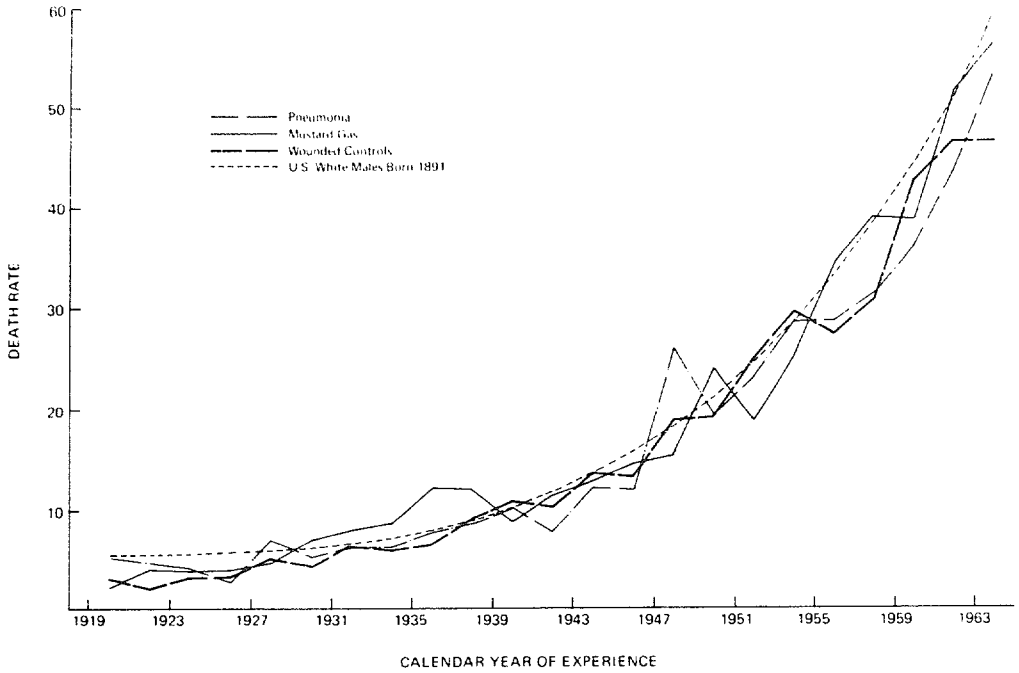
[a] Based on U.S. white male mortality data for 1919–65.

the subsequent military experience, has worked in various unknown ways to produce the mortality patterns depicted in the table and also in text figure 1. The substantially higher observed/expected death ratios found on the mustard-gas roster, 0.99 as compared to 0.93 and 0.92 for the pneumonia and control groups, reflected the correspondingly higher roster mortality percentages of 59.3 (mustard gas), 56.9 (pneumonia), and 56.7 (controls). The greater overall mortality among men exposed to mustard gas was due almost entirely to diseases of the respiratory system. In comparison to the controls, an estimated 122 excess deaths due to such diseases occurred among men on the mustard-gas roster, and the persistence of this excess through the last 16 years of follow-up accounted for most of the differences in the ratio column for the last two periods in table 1.

Text-figure 1 portrays the death rates in 2-year intervals for each roster over the 47-year period of follow-up from 1919 through 1965 in comparison with the death rate for U.S. white males born in 1891. Except for 1956–58, mortality during the last 10 years of follow-up for all three groups fell below the standard U.S. white male rate. The most pronounced characteristic during 1956–65 was that mortality among men on the mustard-gas roster was generally greater than that among the other two groups, except for 1959–60, when the death rate in the control group was slightly higher.

Deaths From Broad Groups of Causes

The 4,136 deaths among the 7,151 men during 1919–65 were classified into broad groups of causes



TEXT-FIGURE 1.—Deaths/1,000 men/year by calendar year of exposure and by roster.

based on the Seventh Revision of the International Statistical Classification of Diseases, Injuries, and Causes of Death (ICD). Only respiratory tuberculosis and other diseases of the respiratory system produced significant variations in roster percentages. Tuberculosis was a significantly greater hazard for men in the mustard-gas and pneumonia rosters than for controls, whereas for other respiratory diseases, only the men in the mustard-gas roster were at a significantly greater risk.

Lung Cancer

Respiratory cancer, coded 160–165 as a broad classification, was listed as the principal cause of death for 152 men. This is shown by specific site and by roster in table 2. All but one of these deaths were assigned to causes 160–164. The single exception was a death in the mustard-gas group attributed to a metastatic malignancy of some thoracic organ from a primary neoplasm of an unspecified site.

Neither individually nor as a group did the various sites of respiratory cancer reveal significant variation in roster percentages. The death rate from this condition was greater among the men exposed to mustard gas than for those in the other groups, even though the difference was not statistically significant. The excess was largely due to primary and secondary malignancies of the trachea, bronchus, and lung, ICD #162–163. Direct comparison of the mustard-gas and control roster percentages for deaths due to #162–163 yielded a one-tailed P value of 0.09; the same comparison for #160–164 produced a P value of 0.08.

As noted above, more men exposed to mustard gas died than did men from the other groups, so they had fewer person-years of exposure to the risk of lung cancer. Consequently, two other tests were made to compare mortality from this disease among the men gassed and the controls. Text-figure 2 depicts the survival curves of all three rosters for 1935–65. For these curves, individuals dying of causes other than lung cancer were treated as withdrawals from observation in the year of their death. The chi-square significance test developed by Mantel (7) for comparing survival curves resulted in a P value of 0.12 when the mustard-gas and control groups were compared.

A more sensitive test used the figures for lung cancer deaths per person-years of exposure to the disease. The 69 deaths among those men gassed amounted to 60.4 deaths/100,000 men/year, whereas the 50 deaths among controls were equivalent to 45.6 deaths/100,000 men/year. The one-tailed P value for this comparison was 0.05.

That lung cancer might characteristically emerge at a certain age among persons exposed to the gas was explored in table 3. The observed number of deaths was contrasted by age at death, for each roster, with the corresponding expected value calculated according to the standard age and calendar year-specific U.S. death rates for respiratory cancer. The only notable deviation for the mustard-gas group was for deaths at ages 55–59, but here it was matched by a similar though slightly smaller discrepancy among the controls.

The present data suggested that gassed men had about a 40% excess of lung cancer mortality. Taken in the context of earlier data, it appears that these men were at greater risk for the disease: Their risk relative to the controls was 1.3 with 95% confidence limits of 0.9–1.9. These considerations were based on tables 2 and 3 and ignored the possible interaction of cigarette smoking and mustard-gas exposure as they pertained to the risk of lung cancer.

Cigarette Smoking in Relation to Lung Cancer and Roster Status

Table 4 presents the information gathered on the 236 men from VA hospital records by roster, mortality status through 1965, and smoking classification.

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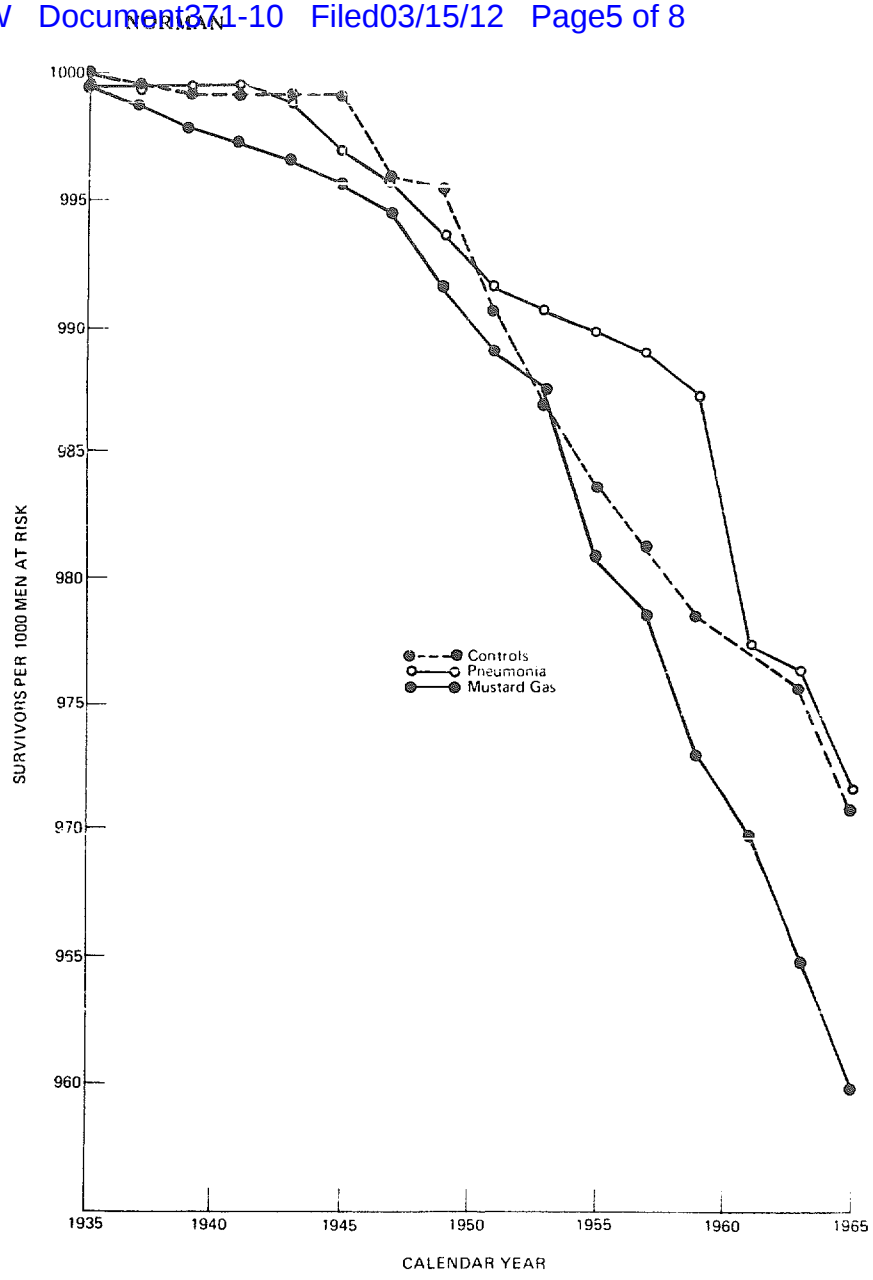

TEXT-FIGURE 2.—Lung cancer survival curves for mustard gas, pneumonia, and control rosters.

TABLE 2.— *Comparison of rosters of deaths from respiratory cancer, 1919–65*

Code	Title	Mustard gas		Pneumonia		Controls	
		Deaths	Percent of roster	Deaths	Percent of roster	Deaths	Percent of roster
160	Malignant neoplasm of nasal cavities, nose, middle ear, and sinuses.	1	<0.1	1	0.05	0	0.00
161	Malignant neoplasm of the larynx.	4	.15	4	.22	5	.19
162	Malignant neoplasm of trachea and of bronchus and lung specified as primary.	30	1.10	14	.75	25	.97
163	Malignant neoplasm of lung not specified as primary or secondary.	30	1.10	14	.75	19	.74
164	Malignant neoplasm of mediastinum.	3	0.11	0	.00	1	.04
	Subtotal 160–164	68	2.50	33	1.78	50	1.94
	Total 160–165	69	2.54	33	1.78	50	1.94

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TABLE 3. *Observed and expected deaths due to respiratory cancer (#160-164) by age at death and by roster, 1919-65*

Age at death	Mustard gas		Pneumonia		Wounded		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	. 13	0	. 09	0	. 12	0	. 34
35-39	0	. 27	0	. 19	0	. 26	0	. 72
40-44	1	. 66	0	. 45	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	15	12. 46	3	8. 51	14	12. 07	32	33. 04
65-69	14	16. 47	10	11. 44	13	16. 11	37	44. 02
70-74	14	13. 71	8	9. 92	5	13. 86	27	37. 49
Total	65	57. 07	32	39. 92	47	56. 17	144	153. 16

TABLE 4.—*Mortality status and smoking classification by roster based on VA hospital records*

Roster	Smoking classification	Alive	Deaths not from lung cancer	Deaths from lung cancer	Total
Mustard gas	I	3	2	0	5
	II	8	7	2	17
	III	11	34	28	73
	Total	22	43	30	95
Pneumonia	I	4	4	1	9
	II	3	1	2	6
	III	9	19	14	42
	Total	16	24	17	57
Controls	I	5	8	1	14
	II	4	5	0	9
	III	10	30	21	61
	Total	19	43	22	84
Total		57	110	69	236

The three categories of tobacco use are: class I: nonsmokers; class II: ex-cigarette smokers, pipe smokers, cigar smokers; class III: regular cigarette smokers. This classification was chosen in light of the risk of dying from lung cancer in Dorn's series as reported by Kahn (*8*) and because of the limited amount of detail on smoking available. A risk of 1 was chosen for nonusers of tobacco, so that the relative risk of lung cancer for class II smokers ranged roughly from 1 to 4, and for class III smokers from 4 to 10. Because of the small numbers in the first two classes, these were pooled and treated as a single group, designated "noncigarette smokers."

To estimate the independent and combined effects of mustard-gas exposure and cigarette smoking, the data of table 4 were rearranged as shown in table 5. The relative risks computed were estimates of the ratio of two probabilities of death from lung cancer. The approach was that suggested by Cole and MacMahon (*9*). The estimated excess relative risk of death from lung cancer among nonsmokers who were gassed (col 3) was virtually zero, though sampling variability produced a value of −0.1. The corresponding estimate for smokers who were not gassed was 3.4. For men exposed to both factors, the estimated relative risk was 4.3. The size of the corresponding 95% confidence limits on each of these three estimates clearly indicated that, while 4.3 exceeded the sum of 3.4 and −0.1, the difference was insignificant. Consequently, there was no evidence that these two factors acting together produced either a smaller or larger relative risk of death from lung cancer than the sum of their separate effects.

Possibly, cigarette smoking was considerably curtailed among the members of the mustard-gas roster because of the respiratory symptoms and discomfort induced by the gas. The smoking histories of 234 men obtained from the Dorn files provided for each roster estimates of the proportion of cigarette smokers, ex-cigarette smokers, men who stopped smoking cigarettes before age 40, and the number of person-years of cigarette smoking. Respondents to the Dorn questionnaire on the mustard-gas, pneumonia, and control rosters numbered 96, 49, and 89, respectively. (This order will be followed throughout the following statement of findings.) The percentages of cigarette

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smokers at the time of the survey were 44, 39, and 49, whereas the percentages of ex-cigarette smokers were 26, 22, and 19. For those men stopping before age 40, the percentages were 13.5, 6.1, and 6.7. None of these values indicated any significant ($P<0.05$) variation between rosters in the standard chi-square test. Nevertheless, early cessation of cigarette smoking appears to have been somewhat more common among men who were gassed. The average number of years smoked by 65, 30, and 59 men on the three rosters were 34, 37, and 37 years, respectively, figures somewhat unreliable due to grouped coding of responses. For those ex-smokers who gave a specific reason for stopping, the ratios for those citing "doctor's orders" were 1 of 23, 4 of 11, and 1 of 15; physical discomfort was the motivation for 15 of 23, 5 of 11, and 9 of 15.

The available data on the smoking habits of the men did not show that roster differences in the use of tobacco lowered the observed risk of lung cancer for men on the mustard-gas roster relative to those among the controls.

DISCUSSION

Japanese factory workers with prolonged exposure to mustard gas experienced a highly significant excess lung cancer mortality, whereas only a marginal increase in deaths from this cause has been found in a 47-year follow-up of men who received a single combat exposure. This suggests the existence of a dose-response relationship. It seems that the men in this study received a relatively light dose. Case and Lea (*3*) suggested that mustard gas is not specifically carcinogenic but leads to respiratory tract cancer indirectly by way of a variety of pulmonary disorders, especially bronchitis. This was based on a twofold excess mortality for lung cancer in each of two samples of World War I veterans pensioned as of January 1, 1930, and followed through 1952. The first group was pensioned for the effects (usually bronchitis) of mustard-gas poisoning; the second had no gas exposure but the men were listed as having bronchitis. Several observations cast doubt on their hypothesis. 1) Beebe's study (*1*) indicated that while bronchitis was more common among victims of mustard-gas poisoning, it was no more common among men who died of respiratory neoplasms than among those dying of other causes or surviving to 1956. 2) It has recently been noted (*10*) that British coal miners have experienced a 56% excess mortality from bronchitis but a 20% deficit in lung cancer mortality. 3) Since the incidence rate of bronchitis among cigarette smokers is several times that for nonsmokers, it seems likely that the second group of British pensioners was (unintentionally) selected for cigarette smoking rather than for their bronchitis, which could account for their excess lung cancer mortality.

An interesting, possibly significant, pattern occurs in the age-at-death distribution of the difference between cumulative observed and expected deaths from lung cancer among the rosters of both British and U.S. veterans with mustard-gas injury. As table 6 indicates, the observed excess mortality in

TABLE 5.—*Estimates of relative risk of death from lung cancer according to exposure to mustard gas and cigarette smoking*

Mustard gas exposure	Cigarette smoking	Lung cancer deaths	All others	Relative risk	Excess relative risk	95% confidence limits
1. No	No	4	34	1.0	0.0	—
2. No	Yes	35	68	4.4	3.4	0.4–10.0
3. Yes	No	2	20	0.9	−0.1 [a]	−0.8–3.3 [a]
4. Yes	Yes	28	45	5.3	4.3	0.7–12.7
Total		69	167			

[a] Negative estimate reflects small sample fluctuation.

TABLE 6.—*Cumulative observed and expected deaths from lung cancer by age for British [a] and U.S. rosters of men injured by mustard gas*

Age at death	British group (N=1,267)			U.S. group (N=2,718)		
	Cumulative observed deaths	Cumulative expected deaths	Cumulative difference	Cumulative observed deaths	Cumulative expected deaths	Cumulative difference
≤44	1	0.7	0.3	1	1.1	−0.1
≤49	8	2.1	5.9	6	2.9	3.1
≤54	16	5.1	10.9	9	6.7	2.3
≤59	22	9.0	13.0	22	14.4	7.6
≤64	28	11.9	16.1	37	26.9	10.1
≤69	29	13.5	15.5	51	43.4	7.6
≤74	29	14.0	15.0	65	57.1	7.9

[a] From data of Case and Lea (*3*).

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each group first appears among men age 45–49, rises to a maximum in the age group 60–64, and thereafter declines. The same pattern does not appear on any of the other rosters among men dying of lung cancer in either this or the British study. Since the median age of both mustard-gas groups in 1917 was about 25, estimates of the minimum and maximum length of the latent period for a carcinogenic effect would be 22 and 37 years, respectively.

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