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Epidemiological Study of the Beryllium Industry

Cohort Methodology and Mortality Studies

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FOLDER 2.42 BERYLLIUM FILE #1 YEAR 1978

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The study of harmful effects relative to "in plant," "neighborhood," and "contact" exposure to beryllium has been beset with difficulties.[1-18] For the interval 1937-1943, the recognition of beryllium disease, its complications, or cause of death, was non-existent because little attention was paid to early reports of harmful effects. Over the years, there has been a gradual extension of observations pertaining to harmful effects on employee and neighborhood groups exposed to varying amounts of beryllium. The methods of study have been necessarily retrospective. Sources of information were derived principally from case studies, hospital records, and a U.S. Beryllium Case Registry established in Boston, Massachusetts, in 1952.[2,19-39]

The clinical reports of Hardy, among others, emphasizing the systemic nature of beryllium disease, as expressed by characteristic pathologic changes identified in spleen, kidney, liver, myocardium, lymph nodes, striated muscle, subcutaneous tissue, and skin, as well as in lung and pleura, are of importance. The presence of beryllium in various extrapulmonary organs, and experimental animal findings of harmful effects on bone, thyroid, adrenals, and pancreas, as well as lung, have added new significance to the study of toxic beryllium effects.[2,25,33,35,40-76] Vorwald induced lung cancer in rats, and Gardner described osteogenic sarcoma in rabbits exposed to beryllium-containing phosphors. These findings have raised the question as to whether there would be a human counterpart to the findings of the animal experiments.

The present study is the first phase of an epidemiological approach to explore the mortality pattern of beryllium workers for an indication of which organs or systems may be involved.

The authors have been interested for some time in the epidemiological method of successive cohorts.[77-79] In this approach, employees are classified according to the year of their first employment in the beryllium industry. Each group employed in the same years constitutes a separate cohort, e.g., 1937-1939. The utilization of the successive cohort approach provides a means of identifying and confirming an environmental problem by the consistancy with which an identical biologic effect follows exposure to the same environmental agent, over the same period of time. It would also be possible to ascertain whether one cohort in a given year was exposed to a carcinogenic agent, and successive cohorts were not so exposed. In addition, the successive cohort method can serve as a biological index of the effectiveness of environmental control.

The purposes of the present study can be stated as follows:

1. To determine the limitations peculiar to a study of beryllium workers based on mortality data only.

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2. To explore the question (as of 1966) as to whether there is a developing relationship of malignancies in humans who have been exposed to beryllium and its compounds.
3. To determine whether there is a difference in mortality patterns between Company *A* and Company *B* within the limitations of the data available.

Our epidemiological approach is based upon cohort studies of the total population of each of the two major beryllium extraction plants, as derived from Social Security data. No accurate and complete resource was available for definition by departments and processes of the employee populations in the early years for the respective plants. Further, it is recognized that the mortality pattern of the total plant population reflects the influence of the total environmental complex. Although beryllium does constitute the common denominator and principal prevailing exposure, it is important to emphasize that other factors, both in work exposure and in the host, may have been present, and directly, or in conjunction with beryllium, influenced the recorded causes of death.

Method of Study

This study consists of employment histories of the 1937-1948 series of cohorts of workers, derived from data of the Social Security Administration (SSA), who shared a common-risk experience of varying duration, since 1937, in the two companies manufacturing beryllium products.

In this successive cohort approach, employees are classified according to their year of first employment, and each group constitutes a separate cohort. The successive cohorts were 1937-1939, 1940-1942, 1943-1944, and 1945-1948. In order to arrive at comparable successive cohorts, each cohort was followed for the same latent period, equal to 22 years, starting from the first year of follow-up (i.e., 1940 and/or year of first employment).

Each successive cohort was classified into ten-year age groups, as of the year of first employment. The age at first employment was calculated for each employee, based on his year of birth and year of first employment in the beryllium company. The average annual mortality rate was computed by age at first employment, by dividing the number of deaths by the corresponding person years during the 22 years of follow-up for each age group.

In the present paper, the basic comparisons are between the individual Companies, *A* and *B*, each extracting beryllium products, based on the average annual mortality rates for each company. An industrial cohort is included as a point of reference, providing rates for corresponding causes of death. The industrial cohort for this purpose consists of a series of rubber cohorts, which were made available, through SSA, by applying the same method used for the industrial beryllium cohorts. Employees of rubber cohorts, who were employed during 1937, 1938, or 1939, and who had cumulative employment experience, in the company under study, of two years or less during the period 1937-1964, were selected for industrial comparison. This industrial cohort was classified by age at first employment (ten-year age groups), and followed for 22 years, starting from the first year of follow-up (i.e., 1940). The average annual mortality rate was calculated by the same method used for successive cohorts of the beryllium study. It is recognized that the health risks in the rubber industry are not known. Should a carcinogenic risk be associated with employment in the rubber industry, the comparisons in this study would then constitute a conservative estimate of risk for the Beryllium plants.

Findings

There were 3,685 white male employees, identified during 1937-1948, in the two plants manufacturing beryllium products. The number of white male employees were classified by age and by successive cohort based on year of first employment in the two companies (Table I).

The employment pattern of the cohort under study was unique. Among the total of 3,685 white males, in 1937-1948 cohorts inclusive, there were 2,863 employees (77.7%) who had worked in the beryllium companies under study for two years or less, and only 822 employees (22.3%) who had worked for more than two years. This fact of rapid turnover implies several points of critical importance in the study of industrial beryllium disease. By implication, the relatively short exposure periods may mean intense exposure, causing illness and leading to a so-called medical discharge. Or, if the proposal of Sterner and Eisenbud proves correct, the rapid turnover may allow the conclusion that there is a population of workers who have been made sensitive to beryllium, and their further exposure at levels considered safe may precipitate beryllium poisoning.

Underlying Causes of Death; Limitations of Mortality Data

Table II describes the number of deaths for all causes, and selected underlying causes of death, and the total population, classified by sex and color, for the combined cohorts (1937-1948) of beryllium workers followed to 1966. There was a total of 834 deaths: 729 males, white; 45 males, non-white; 49 females, white; and eleven females, non-white; due to all causes.

In such a mortality study, it must be emphasized that the death certificate does not, necessarily, reflect any previous disease which ended in clinical recovery. This

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TABLE I

NUMBER OF WHITE MALE EMPLOYEES* CLASSIFIED BY COMPANY, AGE AT FIRST EMPLOYMENT, SUCCESSIVE COHORT AND THOSE LIVING AND DECEASED DURING 1940 to 1966 IN COMPANY "A" MANUFACTURING BERYLLIUM PRODUCTS

Year of First Employment	1937-1939			1940-1942			1943-1944			1945-1948		
Age at First Employment	L	D	T	L	D	T	L	D	T	L	D	T
					A. Company "A"							
15 – 24	22	1	23	204	16	220	92	8	100	213	7	220
25 – 34	16	5	21	92	15	107	50	8	58	245	16	261
35 – 44	7	1	8	29	13	42	33	10	43	89	21	110
45 – 54	4	1	5	20	17	37	12	13	25	23	17	40
55 – 64	1	1	2	5	14	19	2	14	16	7	3	10
65 & Over	-	-	-	3	6	9	4	4	8	-	4	4
All Ages	50	9	59	353	81	434	193	57	250	577	68	645
					B. Company "B"							
15 – 24	56	3	59	335	18	353	171	10	181	194	4	198
25 – 34	51	13	64	222	34	256	97	15	112	157	14	171
35 – 44	26	12	38	108	41	149	101	31	132	63	16	79
45 – 54	11	11	22	71	52	123	47	65	112	17	15	32
55 – 64	2	8	10	18	35	53	24	89	113	3	5	8
65 & Over	-	1	1	2	4	6	5	18	23	2	-	2
All Ages	146	48	194	756	184	940	445	228	673	436	54	490

*Exclude deaths due to war casualty
L = Living, D = Deceased, T = Total

was illustrated by the reversible nature of some cases, with severe clinical characteristics of a disease, and the development of complications, known to have been observed among members of the cohort, which would not be reflected on the specific death certificates. Such diagnoses in cases of ill beryllium workers include pneumonitis, pneumothorax, kidney and liver changes, and possible involvement of the pancreas and adrenal. Further, there was not only a delay in recognition of beryllium disease and its association with specific causes of death during the early years, but also there was a combination of limitations imposed by SSA data, a lack of information in the Beryllium Registry, and the failure of many death certificates to reflect important pathologic changes.

Table III, although relating to a selected sample of beryllium disease cases for one company *(A)* illustrates the interrelation of these sources of data.

There was some under-reporting of deaths to SSA through a lack of awareness of Social Security death benefits among the general population, a lack of information among survivors, and for other reasons. Such under-reporting is evident by the nine deceased cases which were not reported by SSA for company *A* but were available from the Beryllium Registry (Table III). This has some bearing on the interpretation of the findings, since the Beryllium Registry is readily acknowledged to be incomplete because of factors beyond the control of the Beryllium Registry, and because of the usual difficulties in tracing persons during a number of years. Although this appears to be a small number, within this group of nine made available from the Beryllium Registry data, there was one lung cancer. It is not known how many other deaths were not reported.

An indication of the incompleteness of follow-up of the Beryllium Registry, pertaining to the deceased for these companies, is reflected in the group of 43 cases in the Beryllium Registry, which represented only those who could be matched with the cohort for Company *A* through death records (Table III). Of this group, 14 (33%) were not known to the Beryllium Registry as deceased, but were so determined in this study through SSA. For 20 of the 43 deaths (46%) for Company *A*, the deaths were reported by both SSA and the Beryllium Registry. The causes of death are shown in Table III.

The limitations pertaining to the death certificates were further illustrated by the number of workers with beryllium disease, known to the Beryllium Registry, whose underlying cause of death, as recorded on the death certificate, was specified as some other cause, with no mention of beryllium disease, and neither autopsy nor microscopic review was available. For Company *A* alone, among the 43 cases of beryllium disease which were recorded on the Beryllium Registry, and which were also part of our cohort for whom death certificates were obtained, only eleven deaths were recorded on the death certificates as being related to beryllium disease; 32 (74%) were recorded as deaths due to other causes on

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TABLE II

NUMBER OF DEATHS FROM ALL CAUSES AND SELECTED UNDERLYING CAUSES OF DEATH AND THE TOTAL POPULATION CLASSIFIED BY SEX AND COLOR FOR 1937-1948 COHORT OF BERYLLIUM WORKERS FOLLOWED TO 1966

CAUSE OF DEATH AND CODE		Male		Female	
	All	White	Non-White	White	Non-White
All Causes of Death*	834	729	45	49	11
Tuberculosis (001-019)	19	16	1	1	1
All Malignant Neoplasms (140-205)†	134	113	5	14	2
Oral Mesopharynx (145)	1	1	-	-	-
Digestive Organs & Peritoneum (150-159)	45	40	2	3	-
Oesophagus (150)	3	3	-	-	-
Stomach (151)	9	9	-	-	-
Large Intestine except Rectum (153)	15	12	1	2	-
Rectum (154)	8	8	-	-	-
Liver and Biliary Passage (155-156)	8	6	1	1	-
Pancreas (157)	2	2	-	-	-
Respiratory System (160-165)	34	31	2	1	-
Bronchus, Trachea & Lung (162-163)	34	31	2	1	-
Breast and Genitourinary Organs (170-181)	26	16	1	9	-
Breast (170)	5	-	-	5	-
Female Genital Organs (171-176)	4	-	-	4	-
Prostate (177)	8	7	1	-	-
Urinary Bladder (181)	9	9	-	-	-
Other & Unspecified Sites (190-199 & 237)†	16	14	-	1	1
Brain & Other Parts of Nervous System (193-237)†	9	7	-	1	1
Bone (196)	1	1	-	-	-
Lymph Nodes - Unspecified (198)	1	1	-	-	-
Unspecified Sites (199)	5	5	-	-	-
Lymphatic & Haematopietic Tissue (200-205)	12	11	-	-	1
Lymphosarcoma & Reticulosarcoma (200)	2	2	-	-	-
Hodgkin's Disease (201)	4	4	-	-	-
Lymphoma (202)	1	1	-	-	-
Multiple Myeloma (203)	1	1	-	-	-
Leukemia (204)	4	3	-	-	1
Diabetes Mellitus (260)	12	9	-	1	2
Diseases of the Blood & Blood Forming Organs (290-299)	3	3	-	-	-
Diseases of the Nervous System and Sense Organs excluding Vascular Lesions Affecting Central Nervous System (300-329 & 335-398)	14	13	-	1	-
Diseases of the Circulatory System including Vascular Lesions Affecting Central Nervous System (330-334 & 400-468)	397	370	18	6	3
Vascular Lessions Affecting the Central Nervous System (330-334)	58	55	1	2	-
Diseases of the Cardiovascular System (400-468)	339	315	17	4	3
Arteriosclerotic Heart Disease including Coronary Disease (420.0 - 420.9)	257	242	12	2	1
Hypertensive Heart Disease (440-447)	23	16	5	1	1
Diseases of the Respiratory System (470-527)	62	47	5	8	2
Pneumoconiosis and Pulmonary Fibrosis (523-525)	27	17	2	6	2
Diseases of the Digestive System (530-587)	36	32	1	3	-
Diseases of the Liver, Gall Bladder & Pancreas (580-587)	23	19	1	3	-
Diseases of the Genitourinary System (590-637)	16	12	1	2	1
Accidents (E800-E965 & E980-E985)	90	74	7	9	-
Suicides (E970-E979)	18	17	-	1	-
Other Causes of Death	33	23	7	3	-
Total Population Living and Deceased*	4,624	3,685	196	684	59

*Excludes 26 deaths due to War Casualty and 9 living cases whose color and/or birth date was not identified.

†All neoplasms were of malignant type (140-205) except one death due to unknown type of brain tumor (237) of an employee who worked for 16.25 years in beryllium industry and death certificate indicates silicosis of both lungs.

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TABLE III

NUMBER OF DEATHS IN COHORT OF COMPANY "A" AMONG SELECTED EMPLOYEES REPORTED TO THE BERYLLIUM REGISTRY CLASSIFIED BY SOURCE OF INFORMATION AND UNDERLYING CAUSE OF DEATH

CAUSE OF DEATH AND CODE	Death Reported by:			Beryllium Disease on Death Certificate	
	Both	BR* only	SSA† only	Yes	No
All Causes	20	9	14	11	32
All Neoplasms	3	1	2	-	6
Malignant Neoplasms of the Trachea,	2	1	1	-	4
Bronchus & Lung (162-163)	2	1	1	-	4
Vascular Lesions Affecting CNS and Cardiovascular Disease (330-334 & 440-468)	8	-	6	-	14
Vascular Lesions Affecting CNS (330-334)	2	-	1	-	3
Diseases of the Cardiovascular System (400-468)	6	-	5	-	11
Arteriosclerotic Heart Disease including Coronary (420)	6	-	4	-	10
Diseases of the Respiratory System (470-527)	5	6	1	11	1
Pneumoconiosis and Pulmonary Fibrosis (523-525)	5	3	-	8	-
Diseases of the Digestive System (530-587)	-	-	1	-	1
Other	4	2	4		10

*Beryllium Registry
†Social Security Administration

the death certificates (Table III). This demonstrated, for one group of employees of one company, the wide divergence between preexisting disease, as it relates to exposed beryllium workers, and what is recorded on the death certificate.

Another limitation to the mortality study was the question of competing risks, whereby one or more predominant diseases or causes of death, with a shorter latent period, may severely affect the cohort with large numbers of earlier deaths, and influence the number of the remaining group of the cohort who could survive a sufficient length of time to meet the requirements of the long latent period for the specific cancers or other pathologic changes. This was illustrated by deaths due to respiratory diseases (63 workers) and the competing causes of death: 257 deaths due to arteriosclerotic heart disease; 90 deaths due to accidents; 18 deaths due to suicides; and 26 deaths due to war casualties (Table II). Consequently, the factor of competing causes of death adds to the difficulties of studying the long-term harmful effects among beryllium workers.

There was a further limitation, due to an inability to ascertain, through follow-up, any further information on five deaths, specified as "malignancy, primary site unknown." In addition, four deaths were attributed to ill-defined causes of death, and there were nine deaths for which death certificates were unavailable. In our previous study, with a similar limited follow-up, the subsequent microscopic review of malignancies among asbestos workers uncovered six additional lung cancers which would not otherwise have been recognized.[80]

Such detailed consideration of the limitations involved in the conduct of a study directed principally at mortality and the primary cause of death, in which the sources of information are death certificates, are required before interpretations of our findings is justified.

Mortality Rates by Selected Underlying Cause of Death

The purpose of this analysis is to provide a comparison between various successive cohorts within the same company, and between the two companies, within a specified successive cohort; and to provide a comparable control for these successive cohorts, using the specified cause of death as a point of reference. Results of these analyses are confined to the age groups 15-24, 25-34, 35-44, and 45-54. Age groups 55 and over were deleted in view of the small number of employees in each respective cohort and in the industrial control, and because of

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TABLE IV

NUMBER OF DEATHS AND AVERAGE ANNUAL MORTALITY RATES PER 100,000 POPULATION DUE TO SELECTED UNDERLYING CAUSE OF DEATH AMONG WHITE MALES EMPLOYED BY BERYLLIUM INDUSTRY CLASSIFIED BY AGE OF FIRST EMPLOYMENT, COMPANY AND SUCCESSIVE COHORTS FOLLOWED FOR 22 YEARS

Age at First Employment		Industrial Control	Successive Cohort and Company							
			1937-1944		1937-1939		1940-1942		1943-1944	
			A	B	A	B	A	B	A	B
						ALL CAUSES				
15 – 24	No	43	21	26	1	3	12	14	8	9
	R	390	288	204	206	242	257	183	377	232
25 – 34	No	37	22	434	3	9	12	22	7	12
	R	478	568	470	698	673	534	404	587	510
35 – 44	No	50	18	70	1	9	8	33	9	28
	R	1346	946	1083	571	1160	950	1092	1016	1050
45 – 54	No	37	27	108	1	6	16	44	10	58
	R	3304	2118	2295	935	1425	2367	1926	2032	2900
						DISEASES OF CARDIOVASCULAR SYSTEM (400-468)				
15 – 24	No	9	2	6	-	1	1	1	1	4
	R	82	28	47	-	81	21	13	47	103
25 – 34	No	15	3	18	1	1	1	10	1	7
	R	194	78	197	233	75	44	184	84	298
35 – 44	No	21	8	36	1	6	3	17	4	13
	R	565	420	557	571	773	356	562	452	487
45 – 54	No	13	14	44	-	2	9	14	5	28
	R	1161	1098	935	-	475	1331	613	1014	1400
						DISEASES OF RESPIRATORY SYSTEM (470-527)				
15 – 24	No	2	3	-	-	-	2	-	1	-
	R	18	41	-	-	-	43	-	47	-
25 – 34	No	2	3	1	-	-	1	-	2	1
	R	26	78	11	-	-	44	-	168	42
35 – 44	No	3	1	2	-	-	-	1	1	1
	R	81	52	31	-	-	-	33	113	38
45 – 54	No	4	4	6	1	1	2	2	1	3
	R	357	314	128	935	238	296	88	203	150
						ALL NEOPLASMS (140-239)				
15 – 24	No	3	1	1	-	-	1	1	-	-
	R	27	14	8	-	-	21	13	-	-
25 – 34	No	7	2	7	1	3	1	4	-	-
	R	90	52	77	233	224	44	73	-	-
35 – 44	No	5	2	11	-	1	-	4	2	6
	R	135	105	170	-	129	-	132	226	225
45 – 54	No	8	3	22	-	2	1	10	2	10
	R	714	235	468	-	476	148	438	406	500
						MALIGNANT NEOPLASMS OF DIGESTIVE ORGANS (150-159)				
15 – 24	No	1	-	-	-	-	-	-	-	-
	R	9	-	-	-	-	-	-	-	-
25 – 34	No	5	-	1	-	1	-	-	-	-
	R	65	-	11	-	75	-	-	-	-
35 – 44	No	3	-	2	-	-	-	1	-	1
	R	81	-	31	-	-	-	33	-	38
45 – 54	No	3	2	11	-	2	1	6	1	3
	R	268	157	234	-	476	148	263	203	150
55 – 64	No	-	3	7	1	2	1	1	1	4
	R	-	490	252	2564	1005	332	116	368	238
						MALIGNANT NEOPLASMS OF BRONCHUS, TRACHEA & LUNG (162-163)				
15 – 24	No	-	1	-	-	-	1	-	-	-
	R	-	14	-	-	-	21	-	-	-
25 – 34	No	1	-	3	-	1	-	2	-	-
	R	13	-	33	-	75	-	37	-	-
35 – 44	No	1	2	4	-	-	-	1	2	3
	R	27	105	62	-	-	-	33	226	112
45 – 54	No	1	1	7	-	-	-	2	1	5
	R	89	78	149	-	-	-	88	203	250

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the much greater number of years of prior employment (Table I). The successive cohorts at this phase of the study have been confined to 1937-1939, 1940-1942 and 1943-1944, since the 1945-1948 cohort could not be followed for the same period of 22 years (Table IV).

Malignant Neoplasms of Digestive Organs (150-159)

Table IV demonstrates a higher mortality rate among Company *B* than Company *A* for each age group: 25-34, 35-44, and 45-54. This observation is consistent for each successive cohort excepting 1943-1944, when Company *A*, for age 45-54, with one case is higher (203 vs 150). When the comparisons of Company *A* and Company *B* are extended to age group 55-64, there is an excess for Company *A*, which may be due to the small population in that age group. Among successive cohorts of beryllium workers, the 1937-1939 cohort demonstrates the highest mortality rate, specifically for ages 25-34, 45-54, and 55-64.

In reviewing the specific cancer sites which comprise the malignant neoplasms of the digestive organs, it was noted that seven of the eight deaths due to carcinoma of the liver and biliary passages observed for the 1937-1948 combined cohort occurred among employees of Company *B* (four of whom where employed in 1943). There were six white males and one non-white male (from a total of five non-white cancer deaths) and one white female (from a total of 14 white female cancer deaths). Cancer of the liver for Company *B*, white males, occurred in age group 35-44 and 45-54 and 2 in age group 55-64. Pathologic diagnosis was available for three cases; two due to carcinoma of the biliary duct; and the third due to intrahepatic malignant cholangioma.

Malignant Neoplasms of Lung, Trachea and Bronchus (162-163)

Of the 34 deaths due to malignant neoplasms of the bronchus, trachea, and lung, that had been observed in combined 1937-1948 cohort, ten occurred among Company *A* and 24 among Company *B*. Of the nine lung cancer cases among the ten for Company *A*, in our study, who had autopsies or biopsies and microscopic review, three had associated beryllium disease demonstrated in the lungs. In Company *B* with 24 lung cancer cases, only seven were identified as having biopsy or autopsies, none of which was reviewed for beryllium disease. The absence, therefore, of similar microscopic reviews, for the combined study of the two companies, of other lung cancer cases (18 deaths) and of those in our cohort with beryllium disease (59 deaths) that belong to 1937-1948 combined cohort, in both companies *A* and *B*, according to the Beryllium Registry (which matched our cohort), would indicate that other cases of lung cancer associated with beryllium disease may have occurred and have not been recognized.

Table IV, confined to the three successive cohorts for 22 years, shows a higher mortality rate, by age at first employment, for age 15-24 for Company *A*, representing the only death for either company which occurred in the 1940-1942 cohort, and a higher rate for age 35-44, which is due principally to the contribution of the 1943-1944 cohort (226 *vs.* 112).

Company *B* showed an excess in rate over Company *A* for age 25-34 (since no deaths were observed for Company *A* in this time period). Company *B* also had a higher rate than Company *A* for age 45-54 in the combined cohort 1937-1944 (149 vs. 78).

When either Company *A* or Company *B* is considered independently, in reference to the industrial cohort, either Company *A* or Company *B* shows a slightly higher rate for each age group, whenever cases of lung cancer are observed. The strongest contributions occur in the 1943-1944 cohort, in both companies *A* and *B*, for the age groups 35-44 and 45-54.

Neoplasms of Central Nervous System (193 & 237)

The unusual observation of pathologically confirmed malignant neoplasms of the CNS, although small in number, provides a possible epidemiological lead which warrants further investigation. The observed deaths due to brain tumor, during the 22 years of follow-up for age 25-34, was one death in Company *A*, which was the only neoplasm observed for the 1937-1939 cohort, and one death, out of six deaths due to malignant neoplasms, for the 1940-1942 cohort of Company *B*. For the 1943-1944 cohort of Company *B*, age 45-54, there were ten deaths due to all neoplasms, of which two deaths were due to malignant neoplasms of the CNS.

Diseases of the Cardiovascular System (400-468)

Among the successive cohorts, Company *B* has a higher mortality rate than Company *A*, in the 1937-1939 cohort, for ages 15-24, 35-44 and 45-54; in the 1940-1942 cohort for ages 25-34 and 35-44; and in the 1943-1944 cohort for all ages (Table IV). Among Company *B* employees, the mortality rate was higher among the 1943-1944 cohort than in any of the preceding successive cohorts for all ages except 35-44 (Table IV).

Diseases of the Respiratory System (470-527)

There were 18 deaths due to pulmonary tuberculosis, and one due to tuberculosis of the sigmoid colon. Among deaths due to tuberculosis, three were reported by the physician to the Beryllium Registry as having beryllium disease, but this diagnosis was not recorded on the death certificate. These findings support the view that an unknown number of cases of beryllium disease were considered, among other diagnoses, as cases of tuberculosis.[6] Beryllium Registry data appear to indicate no evidence that beryllium disease increases the susceptibility of the patient to acid fast infection.[81]

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Among the 63 observed deaths for both companies due to diseases of the respiratory system (Table II), there were ten deaths due to emphysema (eight white males; and two non-white males); there were 21 cases reported to the Beryllium Registry as having beryllium disease. On the other hand, as mentioned previously, 32 of the sample of 43 known cases of beryllium disease for Company *A* (Table III) had no mention of beryllium disease on the death certificate, and only one of the 32 referred to some category (470-527) of respiratory diseases on the death certificate.

Table IV, which reflects the 22 years immediately following first employment, demonstrates a consistently higher mortality rate for Company *A* than Company *B*. In the consideration of the successive cohorts, the observed mortality rates among Company *A* were higher than those of Company *B* for all ages for which deaths were observed.

Other Causes of Death

Suicides and homicides showed a difference between Company *A* and Company *B*, which warrants further exploration. Although Company *A* had a considerably smaller population, nine deaths occurred due to suicides, in comparison to three deaths for this cause for Company *B*, among the white males in the combined cohorts 1937-1944. Among cohorts 1937-1944 inclusive, the average annual mortality rates, by age at first employment, for ages 15-24 and 25-34, were 41 and 104 in Company *A* as compared to zero and eleven in Company *B*, respectively. In both companies, for 1937-1948 cohorts inclusive, there were 18 deaths due to suicides (twelve among Company *A* and six among Company *B*); all except one died after leaving employment in the beryllium companies. Within Company *A*, seven of the twelve deaths occurred within a latent period of 18-21 years, and within Company *B*, three of the six deaths occurred within a latent period of 17-23 years. An unusual coincidence, relative to the latent period of suicides of employees of Company *A* was observed. Two individuals, employed in 1942 at ages 30 and 35, died 21 years later, approximately one month apart (27 days); and two individuals, employed in 1943 at ages 16 and 19, died 21 years later, approximately one month apart (40 days).

A total of seven homicides (five white males, one non-white male, and one white female) was observed in the combined cohort 1937-1948 within Company *A*. Six of the seven deaths occurred after the individuals had left the company. No homicides occurred for Company *B* for the 1937-1948 cohort. Possible contributing factors, such as cultural, socio-economic, and medical care of the different communities, cannot be explored at the present time.

Selected Case Studies Derived from the Cohorts

The following two case histories illustrate unusual types of tumors and histological observations.

Case No. 11259. This death due to chondromyxosarcoma of the right ileum, was observed, and confirmed by autopsy, among the white male employees of Company *B*, in which a number of other cases of beryllium disease had been established clinically and confirmed by pathological study over a period of years. The patient had been employed as a chemical engineer for Company *B* from 1937 to 1940, and died in 1954 at the age of 61, according to his death certificate and SSA data. In the initial microscopic study of the lungs and the subsequent review, no changes characteristic of chronic beryllium disease of the lung were seen. Information pertaining to chemical analysis indicated the lung contained 7.2 micrograms, and the bone less than 0.1 microgram, of beryllium. ("The bone may have weighed about 50 Gm., and the lung somewhat less. There was a problem in the referral laboratory.")[82]

The interpretation in this case, as to whether the neoplasm was induced by beryllium or one of its compounds, is of course impossible to resolve. Importance is attached to the case, since this was the first cohort study of beryllium workers, and no other primary tumors of the bone had been observed in another comparable industrial cohort of asbestos workers, conducted in the same manner and observed for the same period of time. There was evidence of exposure to beryllium for a sufficient period of employment, with chemical evidence of beryllium retention in the lungs; the histologic type of tumor, chondrosarcoma, has been produced experimentally in rabbits; and evidence exists for the extrapulmonary deposition of beryllium, including rib and vertebrae. The reasons expressed against such a causal relation to beryllium are the lack of evidence of beryllium disease in the lungs, or in other organs of the body, and the singular nature of the observation. However, the overwhelming involvement of the lung with metastatic disease may have made impossible the discovery of other pathologic lesions characteristic, according to present knowledge, of toxic beryllium effect. It is known, for example, that asbestos-induced mesotheliomata of the pleura have been found, with and without the pulmonary fibrosis of asbestosis. Inclusion of this case report is intended to encourage other observations, in view of bone tumors found in experimental animals exposed to industrially used beryllium compounds.[60-71,76]

Case No. 11196. This is another case which was observed in our cohort study, and concerns a white male who had been employed at Company *B* for one year. The cause of death (at age 33) as reported on the death certificate was: Cancer, primary site and type undetermined, involving lung, liver, spleen, pleura, peritoneum, and skeleton. An autopsy was performed and, because of the bizarre histologic findings, is reported here.

Excerpts from the pathological diagnosis and microscopic examination are as follows: " Carcinoma, with myxomatous, fibrous, and osteoid metaplasia, primary site undetermined; metastases to lungs, liver, spleen, lymph nodes, kidney, and bone. Tumor tissue from various sites presents great histologic variation, and produces some bizarre microscopic fields. In some instances, notably in the lung, closely packed, neoplastic cells, strongly sug-

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gesting an epithelial origin, form syncytial masses. Nodules in spleen and liver frequently appear as large masses of myxomatous-appearing material, with a scattering of tumor cells at the margin and in the central portion. Particularly in the liver, some of these nodules are associated with heavy strands of collagen fibers, cholesterotic change in the connective tissue, and, in places, osteoid change. No clearly defined chondromatous areas are seen. In some portions of the liver, lymph nodes, and spleen, the growth appears to be infiltrative rather than invasive."

Schepers has referred to the multifocal origins and histologic pleomorphism of tumors in animals exposed to various beryllium compounds.[55,71]

During the course of the study, other histologically interesting cases have come to our attention. Two cases of reticulum cell sarcoma (one diagnosed from the bone marrow) occurred, similar to Schepers' experimental observations with beryllium.[71] Another case technically did not fall within the specified period of the cohort (1937-1948): a white male, employed in 1949 in Company *A* for a period of 14 years as a mechanical engineer, died at age 49 of papillary adenocarcinoma of the thyroid, with extensive metastases. This is mentioned because of the rarity of the malignancy among males, and because of Schepers' observation of the experimental toxicological effect on the thyroid.[71]

Discussion

It is recognized, in the development of the successive series of cohorts, that the observations and findings of the total populations of each of the two companies would impose definite limitations, reflecting to a certain extent the overlapping differences of its components. There were different factors affecting production at each of the companies, and, although they were engaged in beryllium production, the companies were not comparable on a yearly basis until the war years, when the demand for production was common to both. The two companies not only had different production curves and methods of production, but differed as well in control measures, and, further, in the manner of selection of the employees and the nature, extent, and availability of medical surveillance programs for the recognition of beryllium disease and other illnesses which occurred among the employees. For both companies, there has been direct concern with the economic effect of any health problem. As a result, information and medical follow-up was very limited during this period.

Certain environmental differences which existed in the nature and extent of exposure at Company *A* and Company *B* throughout the years might have influenced the distribution of the specific causes of death. Since no employment data were available for the cohorts, by department or occupation, it was not possible to define further the areas of higher risk. Consequently, the observations made are related to the entire company population, and represent, therefore, an "over-view" for each Company studied. In our experience, only when a specific cause of death is overwhelming would the total company rate be expected to be affected, because of the dilution factor involved in utilizing the total company, rather than departmental populations, at risk. Consequently, the findings at this stage of the investigation must be considered as conservative estimates of risk. There has been considerable interest in the question of harmful effects of different forms of beryllium. However, this question in our study could not be approached realistically.

It must be realized, too, that, before 1943, beryllium disease was not recognized in the United States, and for some years recognition of beryllium disease was confined to a few doctors especially interested in the problem. Recognition was very gradual among the physicians of the communities in which the companies were located, because of the trade secrecy associated with the processing of beryllium. Consequently, cases of beryllium disease, or individuals who had been exposed and subsequently developed, by 1947-1949, the identified disease or any other toxic effects, were rarely correctly diagnosed. Since a number of employees had moved out of the community, this lessened further the recognition of a job-related disease, or the association with previous exposure to beryllium.

In the comparative observations, and from the records of our present study relative to Company *A* and Company *B*, it is also evident that awareness of the disease, in its acute and chronic form, and the extent of the medical programs and surveillance were decidedly different in the years prior to 1949, as well as after 1949, for Company *A* and Company *B*. This undoubtedly is reflected in the variation and limitations in the recordings of beryllium disease and deaths for the respective populations of the two companies.

If one assumes the same relative percentage (74%) for Company *A*, of beryllium disease (Table III) not reported on the death certificate, to be applied to the deaths which have undoubtedly occurred and not been reported to the Registry nor recognized by the physician in attendance at death, then the under-reporting of beryllium disease on the death certificates is substantial. The consequences of this are the shift to other causes of death, and the concomitant influences on the underlying cause of death, and on the analysis of the mortality pattern of beryllium workers.

It became apparent during the course of our study that clinical and hospital data are highly important and necessary in any epidemiological study of beryllium workers. Unfortunately, other than from the Beryllium Registry, such data were limited or not available. There has been as yet no system of prospective medical surveillance developed, by the beryllium industry or by official agencies, relative to the progress and health status of those (affected and not affected) who had separated

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from employment over the years. Consequently, there has been no adequate mechanism to recognize beryllium disease which may occur years after exposure, nor any association of previous employment with a malignancy over a much longer latent period.

In the present study, there was a higher mortality rate due to diseases of the respiratory system among employees of Company *A*, especially in the 1943-1944 successive cohorts for ages 15-24, 25-34, 35-44, and 45-54, than among Company *B* or any of the previous successive cohorts (Table IV). An indication of a similar developing trend was noted for Company *A* for deaths due to malignant neoplasms of the respiratory system, for the same successive cohort 1943-1944, age 35-44 at first employment (Table IV). If one assumes that the deaths due to respiratory diseases could be associated with the degree of beryllium exposure, then this would suggest that there was a peak exposure to beryllium at Company *A* during the period 1943-1944. Such a peak exposure, in fact, had occured, as reflected in the clinical cases observed. Of the 23 cases of chronic occupational pulmonary disease, clinically observed by DeNardi for the period 1940-1953, twelve occurred among employees who started employment in 1943, and one in 1944, all of whom would be part of our cohort study.[20] Among the 1943-1944 successive cohort, a higher mortality rate due to neoplasms of trachea, bronchus, and lung occured among Company *A* than among Company *B* for the age group 35-44. This possible relationship of clinical disease and mortality due to respiratory disease, environmental exposure, and malignancy of the respiratory system, warrants continued observation.

When each of the early successive cohorts is viewed within the framework of the combination of limitations referred to previously, it becomes apparent that the observed findings would constitute an under-estimate of the potential and actual pathologic damage due to beryllium exposure.

A number of investigators have reported deposition of beryllium in tissues of various organs of the body, with the greater deposition occurring in the lung, bone, and liver.[2,25,33-34,43,45-46,53-54,57-58] Of particular interest to us, however, were observations relative to employees of Company *A* and Company *B*. DeNardi and Van Ordstrand studied tissues obtained at autopsy of former workers of Company *A* who died of causes other than beryllium poisoning 20 years after their last exposure, and found that there was as much beryllium in the normal pulmonary tissues of beryllium workers from Company *A* as in those who had chronic beryllium disease.[83] They concluded that beryllium is stored in the body for long periods without causing evident disease. This seems to correlate with the animal experiments of Schepers, who observed that, after cessation of exposure to beryllium, the rate of accumulation of beryllium in the lung tissue increased at an even greater pace, signifying redeposition from extrapulmonary sites.[55-71] It is evident, in view of the deposition of beryllium in the lung, that the toxic effects, including the carcinogenic potential of beryllium, remain for an unknown number of years in the tissues of exposed workers. Clinical experience demonstrated the progression of chronic beryllium disease, despite cessation of exposure, as further evidence of the toxic effect of retained beryllium.[83] It cannot be assumed that, if malignancy is going to develop, it will occur only in those patients who have previously demonstrated granulomatous lesions in beryllium disease. Experience with asbestos-related malignancy without pulmonary fibrosis is an example that is parallel.[79] At present, the carcinogenic challenge, in terms of quality and/or quantity of beryllium exposure, is unknown.

The necessity and advisability of the continuation of the study was indicated by the occurrence of three lung cancer cases after the 22 year period of observation, one in the 1937-1939 cohort, and two in the 1940-1942 cohort.

In our beryllium study for whatever factors may be involved, pertaining to the latent period, in terms of type of exposure, concentration, duration of exposure, and host factors, it will be important to continue the observations on the successive cohorts for comparable periods of time.

Summary

A cohort study of 3,685 white males, 196 non-white males, 684 white females, and 59 non-white females, who were employed, during 1937-1948, in two companies manufacturing beryllium products, was established through Social Security Administration data, and was observed to 1966. The cohort study represents a series of refinements in methodology pertaining to prospective epidemiological study of industrial populations. Successive cohorts were established for the periods 1937-1939, 1940-1942, and 1943-1944; and employees were classified by age at first employment.

The principal limitations and difficulties recognized during the conduct of the prospective study of beryllium workers, which influenced the nature and extent of the observations and findings, were as follows: (1) There is an indication of some under-reporting of deaths from Social Security, particularly for the early years; (2) Observations pertaining to the combined total populations for the two companies reflect the overlapping difficulties and factors pertaining to production, employment, and medical surveillance at each of the companies; (3) Marked influence of labor turnover on duration of employment and the population available for study; (4) Dilution factor—the lack of resource data to define the specific populations by department, process, type, or form

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of beryllium exposure; (5) Problem of competing causes of death; (6) Wide divergence between preexisting disease as it related to beryllium workers and what is recorded on the death certificate; (7) Incompleteness or absence of autopsy, biopsy, and microscopic reviews of malignancies, beryllium disease, and other causes of death; (8) Problem of small numbers of deaths observed in respective cells of successive cohorts characterized by age group; (9) Need for a longer period of observation for each successive cohort for the recognition of environmental cancer; and (10) Nature and characteristics of an appropriate cohort for comparison.

The combination of these factors, and lack of information as cited in this mortality study, severely limited the approach to the question of carcinogenic risk. Consequently, no such determination could be made, at this time, with the data available.

Some differences were observed in the causes of death between Company *A* and Company *B*, which may be due to differences in environmental exposure, the nature of medical surveillance of the employees, and community factors. (Noted among the cohorts were two cases of malignant neoplasms of rare occurrence, one chondrosarcoma of right ileum, and one carcinoma with myxomatous, fibrosis and osteoid metaplasia, primary site undetermined.)

The present study has established the foundation for the further development and continuation of epidemiological observations relative to the long-term pathologic effects of beryllium.

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