Beryllium Sensitization Progresses to Chronic Beryllium Disease

A Longitudinal Study of Disease Risk

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The blood beryllium lymphocyte proliferation test is used in medical surveillance to identify both beryllium sensitization and chronic beryllium disease. Approximately 50% of individuals with beryllium sensitization have chronic beryllium disease at the time of their initial clinical evaluation; however, the rate of progression from beryllium sensitization to chronic beryllium disease is unknown. We monitored a cohort of beryllium-sensitized patients at 2-year intervals, using bronchoalveolar lavage and repeated transbronchial lung biopsies to determine progression to chronic beryllium disease as evidenced by granulomatous inflammation in lung tissue. Fifty-five individuals with beryllium sensitization were monitored with a range of 2 to 5 clinical evaluations. Disease developed in 17 sensitized individuals (31%) within an average follow-up period of 3.8 years (range, 1.0–9.5 years). Thirty-eight of the 55 (69%) remained beryllium sensitized without disease after an average follow-up time of 4.8 years (range, 1.7–11.6 years). Progressors were more likely to have worked as machinists. We found no difference in average age, sex, race or ethnicity, smoking status, or beryllium exposure time between those who progressed to chronic beryllium disease and those who remained sensitized without disease. We conclude that beryllium sensitization is an adverse health effect in beryllium-exposed workers and merits medical follow-up.

Keywords: berylliosis; beryllium; lymphocyte proliferation test; medical surveillance; transbronchial biopsy

In the late 1980s and 1990s, several population-based studies of beryllium-exposed workers in the beryllium ceramics and nuclear weapons industries resulted in the resurrected use of a blood test designed to detect beryllium-specific T cell–proliferative responses in the blood of beryllium-exposed workers (1–9). This test, referred to as the beryllium lymphocyte proliferation test (BeLPT), has been shown to have greater sensitivity and specificity than previously used medical surveillance tools to detect beryllium sensitization (BeS) and chronic beryllium disease (CBD). The test has been shown to outperform chest radiograph, simple spirometry, and clinical examination in the detection of both BeS and CBD (4, 6, 8). The blood BeLPT is now the standard of care in workplace screening and surveillance efforts (9–11) identifying both BeS and CBD. Among workers identified with BeS based on abnormal blood BeLPT results, clinical evaluation with bronchoalveolar lavage and transbronchial lung biopsy is usually necessary to confirm the diagnosis of CBD.

The percentage of those with BeS who have CBD at the time of initial evaluation varies among different workforce studies (1, 3–5, 7, 9, 10). Within these mainly cross-sectional studies, the rate of CBD among those with BeS varied from 14 to 100%. In a report of beryllium ceramic workers by Kreiss and coworkers (4), 100% of workers with abnormal blood BeLPT results had CBD on clinical evaluation, some of whom were clinically symptomatic. Beryllium was used historically in that plant, with its use ending 15 years before the surveillance project was initiated. The mean time from first exposure to screening among the study participants was 24 years. In contrast, Henneberger and coworkers (10) identified only one employee with CBD among seven sensitized short-term workers (14.3%) of a beryllium ceramics facility. In that cohort, the median time from first beryllium exposure to time of blood screening was only 1 year (range, 0.25–12.75 years). The authors speculated that a certain lung burden of beryllium may be necessary to result in CBD or that BeS progresses to disease with the passage of time, regardless of lung burden or continued exposure. Longitudinal follow-up of their cohort will be of interest to determine whether those with BeS without disease progress to CBD as the latency period from first exposure increases. As a result, when conducting blood testing for beryllium-exposed workers, it is not always possible to know whether individuals with abnormal BeLPT results have BeS alone or already have CBD.

The merits of the blood BeLPT as a biomarker of beryllium health effect hinge, in part, on whether the blood test detects a clinically significant abnormality or not. The blood BeLPT has proven utility for those patients with clinical evidence of lung disease by lending specificity to their diagnosis. However, counseling of individuals with abnormal blood BeLPT results, in whom disease signs and symptoms are not obvious, would be greatly enhanced by knowing the rate at which those who do not have CBD at the time of initial evaluation develop disease. We have previously demonstrated that BeS precedes CBD (3), but the natural history and rate of progression from sensitization to disease are not fully known (12) because the literature to date has focused on cross-sectional, and not longitudinal, study designs.

We hypothesize that most beryllium-sensitized workers will eventually develop CBD evidenced by noncaseating granulomas and/or mononuclear cell infiltrates in lung tissue. To test this hypothesis, we performed a longitudinal cohort study of a group of individuals detected through workplace medical surveillance programs as having BeS with no initial evidence of CBD. We have studied these individuals at 2-year intervals for indication of disease progression as evidenced by the new development of granulomatous inflammation detected by lung biopsy. Some of the results of this study have been previously reported in the form of an abstract (13).

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METHODS

We conducted a longitudinal cohort study of individuals who were clinically evaluated at the National Jewish Medical and Research Center (Denver, CO) between 1988 and 1998 and found to have BeS without evidence of CBD, as detailed below. Clinical reevaluation was offered every 2 years through 2002, or sooner if a patient developed symptoms. The study was approved by the center's Institutional Review Board and all participants signed informed consent forms.

We defined beryllium sensitization (BeS) as evidence of beryllium-specific immune response demonstrated by two or more abnormal blood BeLPT results, with no evidence of granulomas and/or mononuclear cell infiltrates on transbronchial lung biopsy. Chronic beryllium disease (CBD) was defined as evidence of BeS with granulomas and/or mononuclear cell infiltrates in lung tissue (14).

Blood BeLPTs were performed within 24 hours of venipuncture, using methods previously published (2). Additional detail is provided in the online supplement. Results are expressed as a stimulation index, which is the ratio of the counts per minute of radioactivity in cells stimulated with beryllium salts divided by the counts per minute for unstimulated cells. A test was considered abnormal if two or more of the six stimulation indices exceeded the normal range.

Clinical evaluation included pulmonary function testing, exercise testing, chest radiograph with International Labor Organization B reading (15), fiberoptic bronchoscopy with bronchoalveolar lavage (BAL), and transbronchial lung biopsies. FVC and FEV_1 were measured with a pneumotachograph. The single-breath method of Ogilvie and coworkers was used to evaluate the ratio of diffusion capacity of carbon monoxide ($D_{L_{CO}}$) (16). Gas exchange, maximal exercise capacity, and maximal oxygen consumption ($V_{O_2}max$) were determined with a 380 B cycle ergometer (Siemens-Elema, Stockholm, Sweden) with continuous cardiac rhythm and arterial oxygen content monitoring (17). An indwelling arterial line measured arterial blood gases at rest and after each minute of exercise. Results are reported as the arterial partial pressure of oxygen (Pa_{O_2}) and as the alveolar–arterial oxygen pressure difference [$P(A–a)O_2$] at rest and during maximal exercise. We performed BAL by methods described previously (18) and in the online supplement. We determined the percentage of lymphocytes in the recovered BAL fluid. We tested BAL cell response by performing the BeLPT in a manner similar to the blood test. Lung tissue was fixed with 10% formalin, embedded in paraffin, cut into 2-μm-thick serial sections, and stained with hematoxylin and eosin. The reviewing pathologist was unaware of clinical data or results of any prior biopsies.

Statistical analyses were performed with JMP release 5.0.1a (SAS Institute, Cary, NC) and SAS release 8.01 (SAS Institute). Continuous variables were compared by Student's *t* test. Categorical variables were compared by χ^2 or Fisher's exact test. Comparisons were considered significantly different when $p < 0.05$. All tests were two-sided. To approximate the rate of progression from BeS to CBD, we used the Kaplan–Meier method of estimating survivor functions, substituting new evidence of lung pathology as the end point. For logistic regression we used a step-down modeling approach. Variables with a significance level of 0.25 or less were entered into the model.

RESULTS

Study Participants

Of all individuals who were referred to National Jewish Medical and Research Center for clinical evaluation from 1988 through 1998 because of repeatedly abnormal blood tests from medical surveillance, 76 were found to have BeS without evidence of CBD, thus meeting our criteria for study inclusion. Study subjects were employed mainly in the nuclear weapons industry (80%) with an average of 24.2 years (range, 3.6–49.5 years) since first exposure to beryllium. Thirty-two individuals (42%) were still working under conditions of beryllium exposure at the time of their baseline clinical evaluation. Of those who were no longer exposed, average time since last exposure until BeS diagnosis was 17 years (range, 1.6 to 41.6 years). The mean age of the entire group was 52.9 years (range, 31–80 years) at baseline evaluation, with 66 males and 10 females, which reflects the sex makeup of these segments of the beryllium industry. Sixty-three individuals were white (non-Hispanic), nine were Hispanic, two were African American, and two were of Asian descent. Twenty (26.3%) were current smokers, 30 (39.4%) were former smokers, and 26 (34.2%) were never-smokers.

Longitudinal assessment 2 years after the initial assessment and every 2 years thereafter was offered to all individuals. Twelve of the 76 (15.6%) declined repeat bronchoalveolar lavage and lung biopsy, but continued to participate in medical follow-up. Two (2.6%) were unable to participate in follow-up because of other medical problems unrelated to their beryllium exposure that precluded bronchoscopy. Five (6.5%) were lost to follow-up, and two individuals (2.6%) died (cause of death unrelated to beryllium exposure). Thus, 55 of 76 (72.4%) had one or more reevaluations including repeat bronchoalveolar lavage and transbronchial lung biopsy. Follow-up clinical evaluations duplicated the testing performed at the time of initial clinical assessment. The average follow-up period from the time of initial evaluation to most recent evaluation with biopsy was 4.5 years (range, 1.0–11.6 years). Of these 55, 25 have had one reevaluation (mean follow-up time, 3.4 years), 21 have had two reevaluations (mean follow-up time, 4.8 years), 7 have had three reevaluations (mean follow-up time, 6.5 years), and two individuals had four reevaluations (mean follow-up time, 8.4 years). Because study participants were entered into the study over the course of 10 years, follow-up times and numbers of follow-up evaluations were variable.

Table E1 in the online supplement compares clinical parameters at baseline between the 55 participants and the 21 who did not have repeat bronchoscopies. Those who did not participate tended to be older at 55.9 years compared with 51.7 years for participants, although this difference was not statistically significant ($p = 0.16$). There were no differences in smoking status or estimates of beryllium exposure time. We found no differences in pulmonary function test results between those who participated in follow-up with bronchoscopy compared with those who did not. Nonparticipants had a higher $P(A–a)O_2$ gradient at rest (11.8 mm Hg) compared with participants (9.0 mm Hg, $p = 0.05$). However, we saw no differences in any other measures of exercise physiology.

Progression from BeS to CBD

Of the 55 individuals who underwent complete reevaluations, 17 (30.9%) developed CBD over a mean follow-up period of 3.8 years (range, 1.0–9.5 years). Sixteen of the 17 were diagnosed with CBD based on the development of granulomas and/or mononuclear cell infiltrates on repeat transbronchial lung biopsy (Figure 1). Eight of the 16 individuals developed interstitial granulomas. Five of the 16 developed granulomas in the bronchial wall and 3 other patients were diagnosed on the basis of the identification of mononuclear cell infiltrates in the parenchyma. One individual was also diagnosed as having CBD based on the development of a significant BAL lymphocytosis (56% lymphocytes), an abnormal BAL BeLPT, symptoms of shortness of breath and fatigue, and decrements in other measures of physiology. Biopsies in this individual were curtailed because of bleeding during bronchoscopy and follow-up biopsies were not attempted.

The follow-up period from initial detection of BeS to CBD development was 3.8 years (range, 1.0–9.5 years), resulting in a conversion rate from BeS to CBD of 8.1% per year. Thirty-eight of the 55 (69.1%) remained beryllium sensitized without evidence of progression to CBD after a mean follow-up time of 4.8 years (range, 1.7–11.6 years). There were no differences in the number of follow-up evaluations between those who progressed to CBD and those who did not progress, with both groups having an average of 2.7 clinical evaluations, including

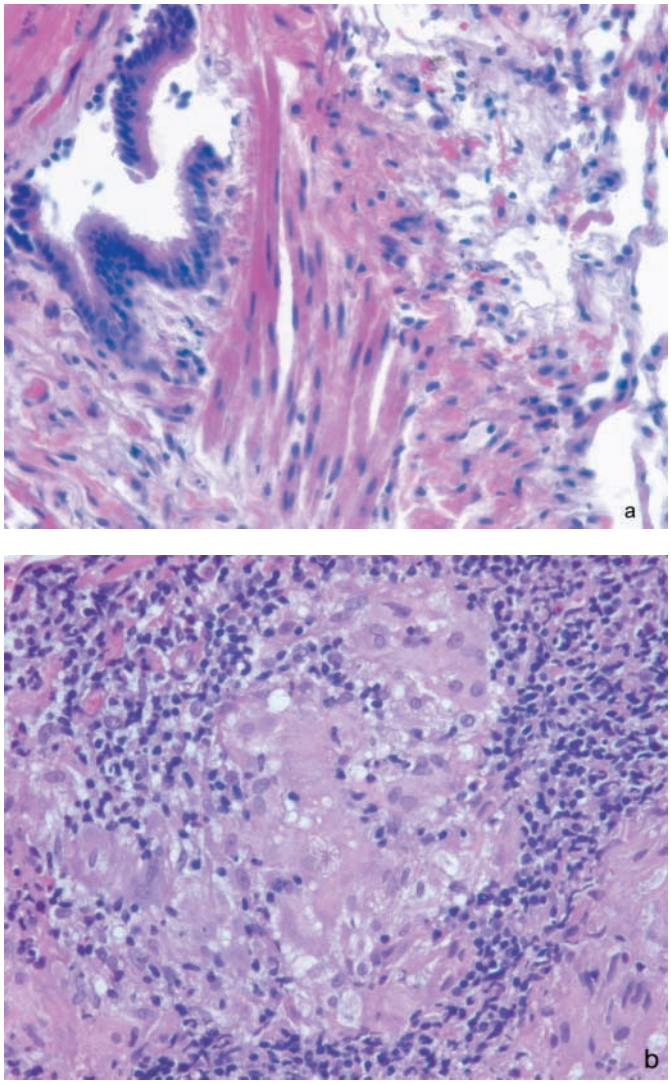

Figure 1. (*A*) Hematoxylin–eosin staining of lung tissue from a study patient with beryllium sensitization but no evidence of chronic beryllium disease at baseline clinical evaluation. Original magnification, ×400. (*B*) Hematoxylin–eosin staining of lung tissue from the same patient on follow-up clinical evaluation, 3 years after baseline, showing well formed granuloma and giant cells. Original magnification, ×400.

baseline evaluation. Using a conservative assumption that none of the 21 unevaluated patients have or will develop granulomatous lung disease, the estimated conversion from BeS to CBD would be 22.4%. Annualizing this percent conversion results in a conversion rate of 5.8%. Thus, the range for the rate of conversion is between 5.8 and 8.1%/year. Notably, in the average follow-up period of 4.5 years, 69% of all BeS subjects have not developed CBD.

To account for differing follow-up times, a Kaplan–Meier survival curve was constructed to estimate the rate of progression from BeS to CBD (Figure 2). At 2 years of follow-up, it is estimated that 13% of BeS patients will have progressed to CBD (95% confidence interval, 4–21.8%) By follow-up year 4, about 19% of the participants will have progressed (95% confidence interval, 8.4–30%). After 6 years of follow-up it is estimated that 37% of patients will have progressed (95% confidence interval, 19–55%). Estimates of progression past 6 years are too unstable to report, based on the average follow-up time of 4.5 years.

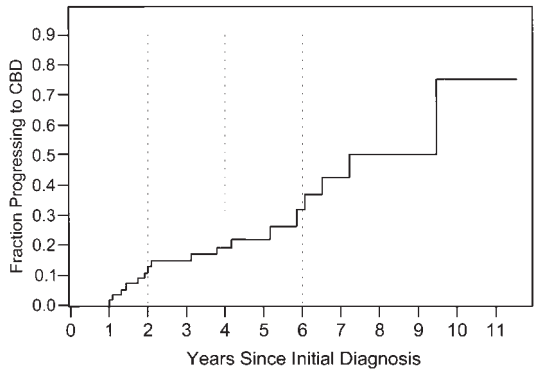

Figure 2. Kaplan–Meier estimate of individuals progressing to chronic beryllium disease over time.

Using the 6-year follow-up point on the curve, we estimate that BeS progresses to CBD at a rate between 3.2 and 9.2%/year.

Risk Factors for Progression

Table 1 summarizes the demographic and exposure factors for individuals with BeS who progressed to CBD compared with those with BeS who remain free of granulomatous lung disease. We observed no statistically significant difference in age, sex, race, or ethnicity at time of initial evaluation between those who progressed and those who remained sensitized. There were no differences in smoking status at the time of initial diagnosis, with 29.4% of those who progressed being current smokers, compared with 23.7% of those who remained sensitized. Smoking status also had no association with progression to CBD as determined on last clinical evaluation. There was a reduction in smoking rates among both the progressors and the nonprogressors from initial clinical evaluation to last evaluation. At the time of last follow-up evaluation, 17.7% of progressors remained current smokers compared with 15.8% of nonprogressors ($p = 0.95$).

Those who progressed to CBD were more likely to be employed as machinists (41.2%) compared with those who remained sensitized (16.2%) ($p = 0.05$). The two groups did not differ in latency from time of first beryllium exposure to baseline evaluation or in estimated time of beryllium exposure. There were also no differences regarding their employment in the nuclear weapons industry. Those who progressed were no more likely to have current beryllium exposure at the time of their CBD diagnosis then those who remained sensitized. Of those who were no longer exposed, there were no differences between the two groups in average years since last exposure to diagnostic or most recent follow-up evaluation.

Baseline Clinical Evaluation

Table 2 compares the baseline clinical evaluation results for progressors and nonprogressors. There were no differences in baseline chest X-ray, pulmonary function, and exercise tolerance test measures for those who remained sensitized compared with those who progressed. Those individuals who progressed from BeS to CBD had a significantly higher percentage of lymphocytes in their BAL fluid on baseline clinical evaluation. Progressors to CBD had a mean lymphocyte percent of 22.8% (range, 6–69%) compared with a mean lymphocyte percent of 15.1% (range, 0–38%) for those who remained sensitized ($p = 0.03$). Of the patients who progressed to CBD, 23.5% (4 of 17) had abnormal BAL BeLPT results on baseline evaluation compared with 7.9% (4 of 38) of those who remained sensitized ($p = 0.19$). Three of

TABLE 1. DEMOGRAPHIC AND EXPOSURE COMPARISONS FOR INDIVIDUALS WHO PROGRESSED TO CHRONIC BERYLLIUM DISEASE COMPARED WITH THOSE WHO REMAINED BERYLLIUM SENSITIZED

	Progressed to CBD (*n = 17*)	Not Yet Progressed (BeS) (*n = 38*)	p Value
Age, yr (SD)	53.7 (9.0)	50.8 (10.6)	0.32
Sex, % male	94.1	81.6	0.41
Race, % white	100.0	97.4	1.00
Hispanic ethnicity, %	17.7	13.2	0.69
Current smoker, %*	29.4	23.7	0.90
Time from initial to most recent evaluation, yr (SD)	3.8 (2.5)	4.8 (2.1)	0.11
Time since first beryllium exposure, yr (SD)*	26.3 (11.9)	25.2 (10.2)	0.72
Period of beryllium exposure, yr (SD)*	13.5 (9.7)	11.2 (7.9)	0.36
Current beryllium exposure, %†	35.3	29.0	0.65
Time since last beryllium exposure, yr (SD)†	19.8 (13.4)	19.7 (12.7)	0.98
Employed in nuclear weapons industry, %	81.3	84.2	0.40
Employed as machinist, %	41.2	16.2	0.05

Definition of abbreviations: BeS = beryllium sensitized; CBD = chronic beryllium disease.
* At time of baseline evaluation.
† At diagnostic evaluation for progressor and most recent evaluation for those remaining sensitized.

the four who progressed to CBD also had evidence of lymphocytosis (defined as more than 20% lymphocytes) in BAL fluid on baseline evaluation, whereas none of the four who remained sensitized did. All three with both abnormal BAL BeLPT results and lymphocytosis developed evidence of granulomatous inflammation on subsequent follow-up visits occurring an average of 2.6 years later (range, 1.3 to 4.2 years). Two of the three were diagnosed on the first follow-up visit after BeS diagnosis and the third individual was found to have granulomas after two subsequent follow-up visits, 2.1 and then 4.2 years later after baseline.

We constructed a multiple logistic regression model including exposure and physiologic variables from Tables 1 and 2. Using a step-down modeling approach and retaining those variables with a significance of 0.10 or less, three variables were entered into the model (*see* Table 2E of the online supplement). Having an abnormal chest X-ray on baseline evaluation had an odds ratio of 9.1 (95% confidence interval, 0.68–121.1). The wide confidence interval reflects that only two progressors and one person who remained BeS had abnormal profusion scores on baseline chest X-ray. Percent lymphocytes in bronchoalveolar lavage fluid at baseline entered the model as a continuous variable. There was an increase in risk of 5.2% for each percent elevation in lavage lymphocyte percent (95% confidence interval, 0–10.6%). Machining beryllium was the final variable to enter the model and had an elevated odds ratio of 4.4 (95% confidence interval, 1.07–17.8).

Longitudinal Changes in BAL and BeLPT

Of those who developed CBD, 15 of the 17 (88.2%) maintained an abnormal blood BeLPT response over time compared with 60.5% (28 of 38) of those who had not progressed ($p = 0.06$). Ten of the 17 individuals who progressed to CBD had developed new lymphocytosis (more than 20% lymphocytes) in their bronchoalveolar lavage at the time of CBD diagnosis, 4 of whom also developed abnormal BAL BeLPT results. Seven of the 17

TABLE 2. BASELINE CLINICAL EVALUATION RESULTS FOR INDIVIDUALS WHO PROGRESSED TO CHRONIC BERYLLIUM DISEASE COMPARED WITH THOSE WHO REMAINED BERYLLIUM SENSITIZED

	Progressed to CBD (*n = 17*)	Not Yet Progressed (BeS) (*n = 38*)	p Value
Abnormal chest radiograph, %	11.8%	2.6%	0.22
Mean peak blood BeLPT SI	15.7 (33.6)	11.4 (22.1)	0.59
Pulmonary function tests, mean (SD)			
Forced vital capacity, % predicted	92.3 (15.6)	92.5 (13.9)	0.97
FEV_1, % predicted	92.1 (19.5)	93.2 (16.1)	0.83
D_{LCO}, % predicted	100.9 (15.7)	106.5 (18.7)	0.34
Exercise tolerance testing results, mean (SD)			
Maximal workload achieved, W	177.1 (35.0)	179.1 (51.9)	0.88
V_{O_2} at maximal exercise	2.0 (0.41)	2.08 (0.59)	0.75
Pa_{O_2} at maximal exercise	79.7 (9.9)	78.4 (8.7)	0.63
$P(A–a)O_2$, rest	9.3 (5.4)	8.9 (4.9)	0.79
$P(A–a)O_2$, maximum	13.9 (6.7)	14.7 (7.5)	0.73
BAL results, mean (SD)			
White blood cells, $\times 10^{-4}$/ml	35.2 (28.9)	34.8 (36.3)	0.97
Lymphocytes (%)	22.8 (17.2)	15.1 (9.0)	0.03
Peak BAL BeLPT SI	6.2 (13.1)	2.1 (2.2)	0.08

Definition of abbreviations: BAL = bronchoalveolar lavage; BeLPT = beryllium lymphocyte proliferation test; BeS = beryllium sensitized; CBD = chronic beryllium disease; D_{LCO} = diffusion capacity of carbon monoxide; Pa_{O_2} = arterial oxygen pressure; $P(A–a)O_2$ = alveolar–arterial oxygen pressure difference; SI = stimulation index; V_{O_2} = oxygen consumption.

had normal percentages of lymphocytes at the time of their CBD diagnosis. Four of the 38 individuals who remained sensitized had BAL lymphocytosis on their most recent follow-up evaluation, but none had abnormal BAL BeLPT results or evidence of granulomas on biopsy. There were, among the 38 who had abnormal BAL BeLPT results, an additional 4 individuals without lymphocytosis or granulomatous changes in lung tissue on most recent evaluation, whom we categorized as nonprogressors.

Longitudinal Follow-up of CBD Cases

Of the 17 individuals who progressed to CBD, 11 had the opportunity to have one or more follow-up evaluations after their CBD diagnosis to determine progression of disease. Average follow-up time from CBD diagnostic evaluation to most recent evaluation was 4.7 years (range, 1.6 to 10 years). Of the 11, there were 8 individuals who showed a decline in FVC percent predicted, ranging from 2 to 23% between date of CBD diagnosis and most recent clinical evaluation. Four showed interval decreases in FEV_1 percent predicted (5 to 8% decline). Nine individuals showed declines in D_{LCO} percent predicted values, ranging from 6 to 33%. This 15.5% average decline in D_{LCO} percent predicted was statistically significant in a paired *t* test analysis ($p = 0.002$). Four individuals had a decline in workload at maximal exercise between 20 and 67 W. Nine individuals had interval declines in V_{O_2} at maximal exercise ranging from 0.005 to 1.107 L/minute. This average 0.22-L/minute decline was also statistically significant ($p = 0.04$). There were no differences from CBD diagnostic evaluation to most recent follow-up in Pa_{O_2} at rest, or Pa_{O_2} at maximal exercise for the group as a whole, nor were there differences in $P(A–a)O_2$ at rest or $P(A–a)O_2$ gradient at maximal exercise. Only five of the patients with CBD had BAL as part of their follow-up evaluation. These individuals showed a 6.6% average interval increase in percent lymphocytes in BAL fluid. One individual was administered oral corticosteroids by the treating physician 2 years after CBD diagnosis because of increasing fatigue, dyspnea, and cough, a decrease in exercise work load, and a 33% drop in D_{LCO} percent predicted.

DISCUSSION

This longitudinal clinical follow-up study demonstrates that BeS progresses to CBD over time at a rate of about 6 to 8%/year after initial diagnosis. We found that 31% of 55 individuals with BeS who had no evidence of CBD on initial lung biopsy developed CBD on subsequent clinical evaluation. However, continuing follow-up will be needed to determine whether all individuals with BeS will eventually develop CBD. Within this study, only lavage lymphocytosis at the time of baseline evaluation and being a beryllium machinist were identified as significant risk factors for progression from BeS to CBD.

Previous evidence of progression from BeS to CBD was presented in a study by Kreiss and coworkers (3), who identified six cases of BeS without CBD among nuclear weapons workers. Three of the six progressed to CBD over a 2-year time period. These six individuals are included in the cohort of individuals monitored in our study. In addition to the three individuals whose progression was described, one additional individual was found to have progressed to CBD on his fourth follow-up evaluation, 9.5 years after initial BeS diagnosis, which increases the rate of progression within this small group to 67%. Barna and coworkers (19) identified 57 individuals with repeatedly abnormal blood BeLPT results, 24 of whom had granulomatous inflammation on biopsy. Among those without granulomas, 5 of 33 (16%) had abnormal BAL LPT results. The authors reported that over a 5-year follow-up period, two of these five individuals developed granulomas, increasing the CBD rate among those sensitized to 46%. Additional longitudinal follow-up of the remaining sensitized individuals, including those without abnormal BAL BeLPT results, will be important to determine how many of the original cohort will eventually progress to disease.

In our study most of the diagnostic pathology came from the pulmonary interstitium; however, five individuals had granuloma formation within bronchial walls. Past pathology studies have described bronchial involvement in CBD (20, 21). Bronchial involvement is consistent with the obstructive changes seen in clinical beryllium disease as described by Pappas and Newman (22). Among their patients with clinically evident disease, airflow limitation was the most common spirometric abnormality. Thus, although generally thought of as an "interstitial lung disorder," CBD more accurately should be classified as a "diffuse lung disease," like sarcoidosis, and emphasizes the importance of obtaining both transbronchial and endobronchial biopsy specimens.

One potential limitation in this study is the possibility of transbronchial biopsy sampling error. Individuals who may have had normal pathology on first evaluation and who then developed abnormal pathology on subsequent evaluation may have been missed on initial evaluation because of sampling error. The physicians participating in this study consistently obtained from 9 to 12 biopsies in an effort to minimize such sampling error. In sarcoidosis, it has been determined that 10 biopsies were adequate to diagnose Stage 1 sarcoidosis, which is the stage most consistent with the early CBD seen in the patients in our study (23). Nonetheless, it is possible that if some of our CBD cases had been immediately rebiopsied, CBD might have been detected at the time of first evaluation instead of 2 to 9 years later.

Of the 55 individuals in our study, 3 individuals had both abnormal BAL BeLPT results and evidence of lymphocytosis at baseline clinical evaluation. Five additional individuals had abnormal BAL BeLPT results on baseline clinical evaluation in the presence of a normal lymphocyte percentage in BAL fluid. All three of the patients with both abnormal BAL BeLPT results and lymphocytosis developed granulomatous inflammation on follow-up evaluation, whereas only one of the five with an abnormal BAL BeLPT went on to progress to CBD. On the basis of this evidence, individuals who have both lymphocytosis and an abnormal BAL BeLPT may likely have evidence of granuloma formation on subsequent clinical evaluation. As mentioned above, this could possibly be due to sampling error on initial biopsy. However, in the case of one of our individuals with an abnormal BAL BeLPT and lymphocytosis, granulomas were not evident until his second follow-up evaluation 4.2 years later after baseline BeS diagnosis. Also of interest were four individuals who developed granulomatous inflammation in the presence of normal or uninterpretable BAL BeLPT results and showed no increase in lymphocyte percent. Notably, three of the four individuals were current smokers at the time of their diagnostic clinical evaluation. Cigarette smoking is known to increase the number and percentage of macrophages, thus potentially masking the BAL lymphocyte response, and nicotine may inhibit lymphocyte proliferation, potentially affecting the LPT response (24).

Unfortunately, this study was limited by the lack of personal exposure monitoring data for the majority of individuals, leaving us without a measure of quantitative beryllium exposure. Thus, we do not know whether individuals with more exposure will progress from BeS to CBD at a faster rate than those with lower or intermittent exposure. Most individuals in this study were exposed in the nuclear weapons industry in a time period for which we have limited access to quantitative exposure estimates. Indirectly, the observation that machinists were more likely to progress from BeS to CBD suggests that characteristics of exposure contribute to disease risk and progression to CBD. We do

know that exposures within the nuclear weapons industry were variable, including people with both active and bystander exposures. Other industries are also represented, including the ceramics industry (3.6%) and the metal machining industry (5.5%), in which we know that the exposures were probably higher and more consistent for machinists than for other employees (5, 25). It is noteworthy that two of our progressors had only incidental or bystander exposure. One individuals was a secretary who worked in a building in which beryllium was used. The other was a security guard who passed through buildings in which beryllium was used. Quantitative exposure measures are desirable in any occupational study and lack of precise exposure information makes it difficult for us to predict progression of BeS to CBD on the basis of exposure level. On the basis of the work history information we were able to collect, we conclude that although workers with possibly higher or more consistent exposures may be more likely to progress to disease (i.e., machinists), individuals with bystander exposure are also at risk of progression.

Because all participants were identified with BeS through workforce medical surveillance, we do not know precisely how long individuals had already been sensitized before undergoing their first clinical evaluation for CBD. This limits our ability to predict the course of progression from the time of first sensitization. However, when a physician evaluates a patient with newly diagnosed BeS, they often do not know how long the worker has been sensitized and need some basis for estimating the likelihood that CBD will or will not develop in future. Our study provides this information. It is possible that the rate of progression might vary if cases could be tested for disease promptly after BeS first occurs. We know from a previous study in a machining workforce that individuals can develop sensitization within weeks of first exposure or many years after first exposure (9). In our study, there is only one individual for whom we know the approximate time of sensitization. This individual first began working with beryllium in 1992. In mid-1992, two BeLPTs performed on this individual from two different laboratories were negative. This individual was found to have abnormal BeLPT responses in 1993, after an accidental skin inoculation and granulomatous skin reaction to beryllium. On clinical evaluation in 1993, this person showed evidence of BeS only and later developed CBD on subsequent evaluation in 1995. We observed no differences over time since first beryllium exposure between those who progressed to disease and those who remained sensitized. Using time since first exposure as a surrogate for sensitization time, based on the observation that some individuals are sensitized within a short time after first exposure (9), suggests that other exposure factors or individual characteristics such as genetic makeup (26–32) may influence the progression from BeS to CBD.

It will be important to monitor this longitudinal cohort to determine whether all individuals with BeS will eventually develop granulomatous disease and to expand our follow-up to those individuals identified with BeS recently, who have had more remote exposures in the beryllium industry. It is noteworthy that one of the BeS individuals who progressed to CBD has already required treatment with corticosteroids 2 years after diagnosis. We also saw statistically significant interval declines in $D_{L_{CO}}$ percent predicted and declines in V_{O_2} at maximal exercise in nine individuals progressing to CBD an average of 4.2 years after their CBD diagnostic examination. What remains to be determined is the extent to which other individuals clinically worsen in future, as all were diagnosed with CBD right after the onset of granuloma formation. Although we cannot identify when BeS initially occurred, the time from first exposure to the development of CBD ranged from 3.5 to 44.5 years in this study, indicating that those with BeS remain at lifelong risk of progressing to CBD. Medical follow-up should be provided and counseling should convey this information to all individuals undergoing beryllium medical surveillance.

Conflict of Interest Statement: L.S.N. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; M.M.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; R.B. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; L.A.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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