Chronic Beryllium Disease in the United States

Mark R. Cullen, M.D., Martin G. Cherniack, M.D.,† and John R. Kominsky, C.I.H., M.S.‡*

Chronic beryllium disease (CBD), sometimes called berylliosis, has been recognized as an industrial disease in the United States since the early 1940s.[1] During the past four decades, a considerable wealth of information has been accumulated to aid clinicians and public health officers in the control of this disabling, often lethal disorder. Yet, despite application of this knowledge and predictions that the problem had been eradicated,[2] new severe cases continue to occur[3,4] and thousands of workers remain at risk.[5]

The purpose of this review is threefold. First, we shall attempt to summarize the current state of knowledge regarding the clinical spectrum of CBD, the settings in which it has occurred, and present diagnostic strategies. In the second segment, we shall discuss and analyze some of the more recent experience with the disorder in order to highlight the serious limitations of the present understanding. Finally, we shall describe several new lines of investigation that offer the prospect of better control, perhaps even eradication, in the foreseeable future.

THE PRESENT STATE OF KNOWLEDGE

CLINICAL SPECTRUM OF CHRONIC BERYLLIUM DISEASE

Ever since the first recognized American cases were initially misdiagnosed as idiopathic sarcoidosis,[6] the single most striking clinical feature of CBD has been its close resemblance to that more prevalent disease.[7] Although many of the earliest cases, associated with extremely high exposures to beryllium compounds, presented with a nonspecific fibrosing pneumonitis, most cases reported since 1960 have shown typical sarcoidlike epithelioid granulomas on biopsy of involved tissues.[8,9] The resemblance to sarcoidosis is not limited to this apparently common histopathologic expression. CBD, like sarcoidosis, is a systemic disorder, pathologically involving not only the lung, but also lymphatics, liver, skin, and occasionally remote organ targets. As in sarcoidosis, patients with CBD have evidence of disturbed T-lymphocyte function with anergy,[9] depressed helper-supressor T-cell ratios in the peripheral blood, and massive accumulations of helper T-cells in the lung.[10,11] Radiographically, symmetric reticulonodular infiltrates, with or without hilar adenopathy, are typical in both disorders, as are fibrocystic changes in the late, irreversible stages.[12] Physiologically, restrictive ventilatory impairment and abnormal measurement of diffusing capacity predominate in both as well.[12] Therapeutically, although comparable data bases are not available, long experience indicates that CBD responds beneficially to corticosteroid administration, as in sarcoidosis, although long-term efficacy is not proved in either disease.[9]

To be sure, there are differences in the clinical spectrums of the two diseases, at least when series of patients are compared (Table 1). Not surprisingly, given the composition of the work force, patients with CBD are typically older and more commonly white and male than those with idiopathic sarcoidosis. Cases of CBD rarely present with stage I radiographic changes, that is, bilateral hilar adenopathy without parenchymal involvement. Symmetric reticulonodular of fibrocystic changes are

*Yale-New Haven Occupational Medicine Program, Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut. Dr. Cullen is a Henry J. Kaiser Family Foundation Faculty Scholar in General Internal Medicine

†Department of Internal Medicine, University of California, Irvine, California

‡Health Evaluation Technical Assistance Branch, National Institute for Occupational Safety and Health, Cincinnati, Ohio

Reprint requests: Dr. Cullen, Yale-New Haven Occupational Medicine Program, Dept. of Internal Medicine, Yale University School of Medicine, 333 Cedar St., New Haven, CT 06510

Publisher: Thieme Inc., 381 Park Avenue South, New York, NY 10016

Table 1. Clinical Differences Between Chronic Beryllium Disease and Sarcoidosis

Sarcoidosis	*Chronic Beryllium Disease*
Hilar lymphadenopathy without parenchymal lung involvement, radiographically or functionally, is common	Lung parenchyma almost always involved, radiographically and functionally
Extrapulmonary manifestations common and may predominate illness	Clinical extrapulmonary involvement uncommon, rarely prominent
Kviem test positive in about 80%	Kviem test negative
Spontaneous remission frequent; permanent sequelae uncommon; mortality rare	Spontaneous remission rare; permanent sequelae the rule; mortality fairly common

usually evident at diagnosis.[7,12] The extrapulmonary manifestations of CBD, although comparable to those seen in idiopathic sarcoidosis, are rarely prominent, and certain features, such as iridocyclitis and central nervous system, cardiac, and endocrine dysfunction, have virtually never been reported.[7] Reactivity to Kveim antigen, positive in 80% of patients with sarcoidosis, has been negative in all CBD cases tested.[7,9] The disease course is also different; the natural history of CBD appears in general to be consistently less benign than that in most cases of sarcoidosis. Irreversible pulmonary fibrosis is the rule in CBD,[9] although a handful of patients have been reported to remit after removal from beryllium exposure.[13] Mortality may be as high as 30%.[9,14]

EPIDEMIOLOGY OF CHRONIC BERYLLIUM DISEASE

The close similarities between CBD and idiopathic sarcoidosis would likely have obscured the differences were it not for Hardy's recognition of the epidemic disease in the fluorescent light bulb industry due to widely used beryllium-containing phosphors.[6] Subsequently, more than 600 chronic cases have been reported to the Beryllium Case Registry, the vast majority being workers in a few high-risk industries: beryllium extraction and smelting, lighting tubes, electronics, ceramics, and beryllium allow-forming and machining.[12] Occasionally, "neighborhood" cases have also been documented, such as spouses and children of workers and residents living near factory stacks and effluent.[15] Based on study of these cases and analysis of the major industries involved, certain epidemiologic conclusions can be drawn.

First, it is now established that CBD is an idiosyncratic disorder, requiring some "host" factor as well as beryllium exposure. This is clear because even in the most heavily exposed worker groups, no more than 1 in 20 has ever been affected (Table 2). Furthermore, the host factor is illustrated by the remarkable variability in the time of onset relative to exposure. Although in about half of known cases, the persons became ill during the time they worked with beryllium or its compounds, many developed first manifestations months, even years later.[12] This variability is in distinct contrast to the major pneumoconiosis, such as silicosis and asbestosis, in which all workers are susceptible, although perhaps to varying degrees, and in which the time course is a predictable function of the exposure intensity.

A second conclusion is that the form of exposure to beryllium determines, in part, the attack rate. The beryllium-containing phosphors historically caused a rate of disease comparable to that in beryllium production, despite apparently much lower levels of exposure[2] (Table 2). Furthermore, very few cases of disease have been seen in workers who have machined beryllium-containing metals at low temperature; most cases of metal processors have occurred in those who worked around the furnaces.[2] Whether these observations can be attributed to the chemical form of inhaled beryllium, to the particle sizes, or to other factors remains unknown.

Finally, host idiosyncrasy and exposure "form" not withstanding, dose of exposure does seem to be a determinant of the attack rate. Two lines of

Table 2. Incidence of Berylliosis and Estimated Level of Severity of Exposure*

	No. Exposed	*No. Cases*	*Incidence (%)*	*Estimated Level of Exposure*
Residents living within 0.25 mile of the Lorain plant	500	5	1.0	1
Fluorescent lamp manufacturing				
Massachusetts	15,000	175	1.16	100
Ohio	8,000	32	0.4	100
Machine shop	225	11	4.9	500
Beryllium-copper foundry	1,000	13	1.3	500
Beryllium extraction				
Lorain, OH	1,700	22	1.3	≥1000
Painesville, OH	200	0	0.0	≥1000
Reading, PA	4,000	51	1.3	≥1000

*Modified with permission from Flourney.[30]

evidence support this conclusion. There has been a dramatic decrease in the number of cases of CBD occurring in workers first exposed after the widespread introduction of industrial hygiene controls in 1950.[2,12] Only 10% of all United States cases were first exposed after this date. Although this may be a reporting artifact (see later), the decrease in rate within major plants after this time[16] should not be so biased. There are, to be sure, some conflicting data, especially the unexpectedly very high rate of neighborhood cases outside one Ohio plant equaling the attack rate of workers inside.[2] However, in general, the data available at present do support some positive association between dose and incidence for a given form of beryllium exposure.

DIFFERENTIAL DIAGNOSIS OF CHRONIC BERYLLIUM DISEASE

Until, recently, a specific test to differentiate CBD from idiopathic sarcoidosis has not been available, the once highly tauted beryllium patch test having proved too dangerous for general use.[17] For this reason, the criteria for diagnosis have indirectly relied heavily on epidemiologic data: since CBD occurs with a cumulative prevalence of up to 5% in exposed populations, whereas sarcoidosis is much rarer (no higher than 1 per 1000 in high-risk populations[11]), proof of exposure has been the hallmark and *sine qua non* of diagnosis of CBD. Thus, the combination of pathologically confirmed noninfectious granulomatous lung disease associated with sarcoidlike radiographic and physiologic abnormalities in an exposed patient has been considered diagnostic of CBD.[7]

Because of the frequent difficulty of obtaining a clear history of beryllium exposure in some patients, new biologic strategies were developed to aid the clinician. Measurement of beryllium in urine, although insensitive when exposure is remote, can confirm ongoing exposure. More helpful is quantification of beryllium in lung or lymph node tissue; since beryllium is retained in these sites for many years, significant levels persist irrespective of when exposure occurred, and normative data are available for comparison.[7,12] Importantly, however, neither of these methods in any way differentiates healthy from diseased subjects, but only serves to document that exposure has occurred. Clinical and pathologic demonstration of characteristic disease is still necessary for diagnosis.

In the past decade, suspicion of an immunologic basis for CBD prompted study of two new in vitro tests. First, it was demonstrated that lymphocytes from affected patients or sensitized guinea pigs would secrete large amounts of macrophage inhibition factor (MIF) when cultured with beryllium salts.[18,19] More reproducibly, culture of lymphocytes with beryllium led to rapid blast transformation, measurable by the uptake of tritiated thymidine.[20,21] This test, the lymphoblast transformation test (LTT), proved positive in 60 to 70% of clinically diagnosed CBD patients, whereas patients with idiopathic sarcoidosis or beryllium-exposed but healthy controls reacted rarely.[22,23] Thus LTT, with its demonstrated specificity, potentially provides a strategy for diagnosis of CBD independent of exposure history. Unfortunately, two factors have limited its usefulness. Because it is insensitive (only 60 to 70% of clinically suspected CBD cases are positive), a negative test is difficult to interpret. More importantly, the availability of the test has been extremely limited, so that most clinicians have not been able to use it at all. Therefore, the traditional strategy, histologic demonstration of granulomas combined with historic or biologic proof of exposure, remains the basis for the diagnosis of CBD.

LIMITS TO OUR PRESENT KNOWLEDGE OF CHRONIC BERYLLIUM DISEASE

The apparent reduction in the basic beryllium industries of incident cases first exposed after the institution of industrial hygiene controls has led some observers to conclude that CBD as a public health problem had been largely resolved.[2] Were this true, it would not be necessary critically to reassess the state of the art. Unfortunately, scattered reports of new cases and outbreaks occurring in nontraditional settings[3,4,24] combined with enormous changes that have occurred in the industrial applications and handling of beryllium require a close second look to determine if the disease is in fact to be successfully controlled.

Currently, there are three major gaps in our understanding that preclude effective control.

First, the quantity and form of beryllium exposure in modern industrial settings is virtually unknown. Although production of beryllium has not increased in the United States during the past two decades, the number of uses has expanded and the number of settings has diversified. Beryllium use has become particularly important in the solid state industry, including computers and communications, and the aircraft and aerospace industries. Combined with applications in automotives, dental materials, and tool and die making, more than 800,000 workers are now potentially exposed, the vast majority being outside the primary beryllium refining industry or its direct customers[5] (Table 2). Beyond the manufacturing industries that use beryllium, there is also concern for the growing industry in which materials are recycled and

Table 3. Industries and Trades with Potential Beryllium Exposure

Ceramics
Electrical connectors
Nonferrous foundries
Nonferrous smelters
Sandblasting
Aerospace
Nuclear control equipment
Electronics
Solid state
Refractories
Beryllium smelting or fabrication
Hazardous waste processing
Dental equipment and supplies
Engineering and scientific equipment
Mechanical measuring devices
Tool and die making
Soldering
Welding or flame cutting
Metal plating
Automotive parts
Telecommunication equipment

processed, a source of one recent outbreak.[4] Nonsiliceous mineral slag used for sand blasting is also frequently contaminated with beryllium.[25] Potential exposure settings are summarized in Table 3.

Unfortunately, scientific attention to industrial hygiene has not followed expansion of the industry. Few data characterizing the intensity and form of exposure in the "new" industries have reached the published literature, despite the fact that both the Occupational Safety and Health Administration (OSHA) and the National Institute for Occupational Safety and Health (NIOSH) have recorded levels in excess of the OSHA 2 $\mu g/M^3$ permissible exposure limit in various settings[26] (Table 4). Hence, we cannot at present define precisely the populations at risk for CBD, nor estimate the extent of exposures given a particular suspicious work history.

Second, the dose-host-response relationship is obscure, especially at low levels of exposure. Even if we knew the form and intensity of exposure in a given patient or population, it would still be impossible at this time to translate this into risk for CBD. The reason is that the dose-response curve for beryllium and its compounds is still largely unknown, especially in the range of low-level exposure. Moreover, there is no clue yet as to what host factors might influence risk, as there is for idiopathic sarcoidosis in which race and sex, for example, are major determinants.

Why is the dose-response curve so obscure after the study of more than 600 cases and several large industries? Part of the problem rests with the incompleteness of the data from the classic studies, especially in terms of industrial hygiene data. Specifically, the absence of careful air level measurements, particle size analysis, and determination of the chemical state of beryllium associated with disease clusters accounts for much of the uncertainty about dose-response, especially in the high-dose range.

A potentially more serious problem lies with the difficulty in case recognition with almost certain underreporting of cases exposed to relatively low doses. This is understandable, even predictable, when, as noted before, diagnosis has been contingent on the evidence for exposure, historic or biologic. Hence, if incidental doses of some forms of beryllium do indeed cause disease (this possibility is suggested by some of the neighborhood cases), how would cases be distinguished from idiopathic sarcoidosis? Certainly, the usual reasoning based on likelihood estimates derived from epidemiologic data breaks down in the low-risk setting. Even 1000 cases among the widely dispersed exposed American workers (1.2 per 1000) could easily be "lost" as an epidemic. Recent case reports, almost all previously misdiagnosed as sarcoidosis, lend credence to the importance of this phenomenon.[3,4,24]

Therefore what is necessary is quite clear. First, new cases and especially clusters must be carefully investigated to ascertain and quantify the environmental circumstances of exposure. Second, there is an obvious need for an available, sensitive, and specific test that can readily distinguish idiopathic sarcoidosis from CBD and that is independent of the exposure history. As long as dose is used as a differential criteria, we will be tautologically locked

Table 4. OSHA Inspection Summary for Beryllium Compounds (6/1/79 to 1/31/84)

Type of Industry	*Beryllium Detected*	*≥0.5 $\mu g/M^3$ (NIOSH Criterion)*	*≥2. $\mu g/M^3$ (OSHA Standard)*
Traditional*	25	16	9
High technology†	3	3	2
Secondary process‡	5	1	0
Dental laboratory	1	0	0
	34	20	11

*Traditional sources include particulate blasting, shipbuilding and repair, nonferrous foundries, nonclay refractories, beryllium machining and fabrication, and metalworking.
†High technology includes the semiconductor industry, precision electronics industry, and spacecraft and missile manufacture.
‡Secondary processing includes secondary nonferrous smelters, nonferrous foundries, and hazardous waste reclamation.

into the (probably wrong) view that low doses of beryllium cannot cause CBD.

Third, there is no currently known means for secondary prevention. Since we do not yet know the lowest dose that may be associated with risk and therefore cannot eliminate CBD by primary prevention short of eliminating beryllium from the workplace altogether, there is a need to develop and evaluate means for early recognition of cases at a point where the natural history can be altered. Although a few apparent cases have been reported that remitted after recognition and removal from exposure,[13] the general experience has been overwhelmingly poor in this regard; once radiographic and clinical manifestations are present, the natural history almost invariably entails permanent functional loss or progressive deterioration, the therapeutic benefits of corticosteroids not withstanding.[8,9] Unfortunately, there are not yet convincing data that routine medical surveillance tools, including questionnaires, physical examination, radiographs, or spirometry, offer promise as a means for clinically meaningful early detection, however frequently or carefully applied.

INVESTIGATIONS IN PROGRESS: PROSPECTS FOR FUTURE CONTROL OF CHRONIC BERYLLIUM DISEASE

DEFINING CONTEMPORARY BERYLLIUM EXPOSURES

Some of the most important work currently being conducted in CBD research is the characterization of the "new" exposure settings already described, including the aerospace industry, dental laboratories, secondary refineries, and shipyards. Although the sampling methods are not new, awareness of inadequacies in the existing data base has prompted a new and timely attention to detail.

This is best illustrated by the recently reported industrial hygiene data from a metal recycling facility where four cases were reported by us.[27] Although all of the patients had worked as furnace tenders, all six job categories with potential exposure were sampled. Furthermore, numerous samples were obtained during 18 shifts at each site.

Although this extensive sampling may appear exorbitant at first glance, the investigators achieved three important experimental breakthroughs. First, although concentrations of airborne beryllium in many parts of the shop exceeded the 2 $\mu g/M^3$ allowable exposure for an 8-hour shift, none of the samples obtained in breathing zones of the furnace tenders were this high. Also, the finding of high beryllium levels in dust from the cold-crushing and sorting of beryllium (in areas with no disease) in combination with much lower levels in the fume from the refining furnace (where the attack rate has been in excess of 2 per 100) provides strong corroboration of prior suspicions regarding the importance of type and form of exposure. Thirdly, the investigators demonstrated that in batch operations that may be common in many exposure settings, the variability among samples may be many orders of magnitude. For this reason, multiple samples are necessary to characterize the distribution of exposures.

DISCOVERING AND VALIDATING A SENSITIVE, EXPOSURE-INDEPENDENT, CLINICALLY AVAILABLE DIAGNOSTIC TEST

The second major advance derives from the recent discovery by Epstein and coworkers at the University of Pennsylvania that lymphocytes obtained from bronchoalveolar lavage in a patient with CBD were more immunologically reactive in vitro to beryllium salts than peripheral blood lymphocytes.[28] This observation has now been confirmed in other patients, including several from the metal reclamation study alluded to previously,[10] and reported from Japan as well.[11] Another important contribution by Epstein's group has been development of a reproducible and simple technique for overnight transport of lavage fluid, potentially rendering the test available to virtually any bronchoscopist in the United States.[10]

Based on biologic considerations and the limited available experience, it seems likely that the LTT on lymphocytes from bronchoalveolar lavage will become the primary diagnostic technique for differentiation of CBD from sarcoidosis. Although its sensitivity is unknown and, for lack of a true gold standard, difficult to measure, this new test is clearly more sensitive than peripheral blood testing, which already showed promise (see before). The specificity, both vis a vis (never-beryllium-exposed) sarcoidosis patients and exposed but healthy workers, is presently being tested by us in collaboration with Epstein's group. Barring unexpected findings in this phase, the long sought-after test may soon be at hand, allowing solution to the dose-response question.

STRATEGIES FOR SECONDARY PREVENTION

Despite these efforts, we remain years from defining and controlling all the exposure factors that produce risk. Furthermore, beryllium is not likely to be replaced in the forseeable future in its new roles in high-technology industries. Therefore

it remains imperative to find alternative strategies for control of CBD in the interim.

Although this area has not yet proved very fertile, a theoretically promising approach has been conceived and subjected to an initial experimental evaluation. The concept is as follows: from a strictly biologic point of view, it is likely that a window in time exists between the first "sensitizing" event, when specific immunologic reactivity to beryllium begins and the onset of overt clinical disease. It is at least plausible that some intervention during this time period may influence the outcome, even if interventions after clinical onset do not.

Following this logic, Rom and colleagues[29] have retrospectively examined data from serial LTT on blood lymphocytes from workers in the primary industry. From this survey, they made the provocative observation that some healthy workers with false-positive tests early in 1979 had reverted to negative by 1982, coincident with reductions in their exposures to beryllium. Although there are many possible interpretations of these data, one possibility is that healthy but sensitized workers have lost their sensitivity by virtue of environmental reduction during a hypothetical preclinical window.

Of course all of the assumptions implicit in this conclusion—that a positive test in a healthy work implies sensitization, that sensitization implies risk for disease, and that sensitization status or risk per se can be modified—must be carefully tested before this approach can be meaningfully applied to the exposed work force. Conceptually, at least, the strategy does offer new promise as a means for secondary prevention of CBD.

CONCLUSION

Recent recognition of new cases and clusters of CBD has necessitated reexamination of the notion that the disease has been eradicated and a reevaluation of industrial practice of control. Although investigations of early major outbreaks have provided a firm point of take-off, many crucial issues remain unresolved. Neither the absolute safe levels of exposure, nor the risks to individuals in modern industrial settings are known. Therefore solutions will require renewed research efforts in industrial hygiene, immunology, and clinical epidemiology. Fortunately, many productive investigations are well under way, offering clinicians new means for differentiating CBD from idiopathic sarcoidosis and providing industrial hygienists and regulators new insight into primary control strategies. However, only by rigorous application of these advances and further investigations can ultimate control of this highly morbid occupational disease be anticipated.

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