Commentary and update: Chemical pneumonia in workers extracting beryllium oxide[1]

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Nearly 1,000 cases of beryllium-related disease have been reported in the United States since the first three cases were reported by VanOrdstrand and his associates in 1943. In addition to acute chemical pneumonitis, beryllium exposure has also resulted in berylliosis, a chronic granulomatous disease. The largest number of berylliosis cases was reported in the fluorescent lamp industry where beryllium was used in phosphors until 1949. Other cases occurred due to air pollution in the vicinity of beryllium-producing factories and exposure of family members to beryllium dust brought home on contaminated work clothes. Many of the peculiar epidemiologic features of both the acute and chronic forms of beryllium disease can be explained by its sensitizing characteristics. The standards that were established for the control of beryllium disease in the later 1940s have been remarkably effective and have now been adopted worldwide.

Index terms: Beryllium, adverse effects • Occupational diseases

Cleve Clin Q 51:441–447, Summer 1984

With the opening sentences of a paper written more than 40 years ago, H. S. VanOrdstrand, Robert Hughes, and Morris G. Carmody raised the curtain on a new medical drama that would attract the attention of occupational disease specialists for decades to come. As this drama unfolded, the Cleveland Clinic became a worldwide center for clinical consultation and research, leading to much published information dealing with the many ramifications of beryllium disease. Although similar subject material in the European literature had called attention to the occurrence of a disease resembling chemical pneumonitis among workers employed in the extraction of beryllium,[1] the reports lacked continuity and the etiologic factors given to explain the disease were problematic. The publication in the January 1943 issue of the CLEVELAND CLINIC QUARTERLY was the first published in the United States and was followed by publications in other journals, not only by VanOrdstrand and his associates, but also by investigators from other parts of the United States and Europe. Interest developed so rapidly that the Sixth Saranac Symposium, which was held at the Trudeau Foundation in 1947, was devoted almost completely to "the beryllium problem" and attracted approximately 200 physicians and scientists.[2]

Beryllium is the lightest of the metals and, with an atomic weight of 9.01, is the top element in group II of the periodic table. It was discovered in 1797 and given the name "glucinum" because of the sweet taste of some of its salts. Until recently, beryllium was obtained from the mineral beryl, a beryllium aluminum silicate, of which the gems aquamarine and emerald are varieties. During the past decade, bertrandite, a silicate mineral, has also become an important source for this element.

Beryllium has proved to be useful in science and industry. Its most widespread use is as a copper alloy, containing about 2.5% beryllium, which is used for springs and diaphragms. Beryllium metal has a number of interesting nuclear properties and, because it is practically transpar-

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0009-8787/84/02/0441/07/$2.75/0

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ent to x rays, is widely used for x-ray-tube windows. Neutron sources can be produced from capsules containing mixtures of beryllium and alpha-emitting radionuclides such as radium 226 or polonium 210. The metal can also be used to moderate or reflect neutrons and, for these reasons, has found limited application in certain types of nuclear reactors. It has a high melting point (1,285° C) and also has useful structural properties that have led to its use in the aerospace industry. Additionally, beryllium oxide has excellent refractory properties.

During the early 1940s, when the first cases of beryllium disease were reported, one of the most important uses of this element was as a component of fluorescent lamp phosphors. This use was discontinued in 1949 because of the toxicity of the phosphors.

The three cases of acute chemical pneumonitis that were reported by VanOrdstrand et al in 1943 proved to be only a glimpse of a widespread problem that was not fully understood for many years. At about the same time, two women complaining of severe and disabling dyspnea were admitted to a tuberculosis sanitarium in Massachusetts. An initial diagnosis of miliary tuberculosis was discarded after about two months of study in lieu of a new diagnosis: pulmonary sarcoidosis. The fact that the two women worked in the same building of a plant manufacturing fluorescent lamps did not appear particularly important at the time. A postmortem examination of one patient seemed to confirm a diagnosis of Boeck's sarcoid. As pointed out by Shipman[3] in an early review of the history of beryllium disease, the matter would have been concluded then had not a third patient been admitted to the same sanitarium with an identical history. A fourth and fifth patient were soon treated, and upon investigation, the Division of Occupational Hygiene of the Massachusetts Department of Labor and Industries reported that the only unusual material used in the fluorescent lamp manufacturing process was a compound of beryllium—a metal about which little was known. Thus, at the same time that the VanOrdstrand group was reporting the occurrence of acute chemical pneumonitis among beryllium workers, the Massachusetts investigators were reporting a chronic debilitating sarcoid-like lung disease among workers who were also exposed to this metal.

When the first report of the Massachusetts cases was published by Hardy and Tabershaw[4] in September 1946, 17 cases of this disease, which the authors called "delayed chemical pneumonitis," were known. They noted that "the distinctive feature that separates the present group [of cases] from previous reports in the literature is the usual delay in onset following common exposure—and progression of the disease in spite of change in environment." By this time, although the Hardy and Tabershaw paper was the only report of the chronic form of beryllium disease, now generally known as "berylliosis," a number of other reports of acute chemical pneumonitis had been reported among beryllium workers in Pennsylvania, New Jersey, and Ohio. The Pennsylvania cases, which were described by the State's Director of Industrial Hygiene and which, like the first of the VanOrdstrand cases, also occurred among workers in a beryllium extraction plant, were believed by the authors to be due to the acid radicals associated with beryllium rather than to the beryllium ion itself.[5] This was not an unreasonable position to take at the time because the early European cases had been attributed to fluoride salts of beryllium. Moreover, a 1943 report on the toxicity of beryllium oxide in the rat, published by the U.S. Public Health Service, had not considered that compound to be toxic.[6]

Even as late as 1946, people had difficulty accepting the fact that beryllium was harmful. An element situated with magnesium and calcium in group II of the periodic table was not expected to be toxic. Some specialists continued to believe that the acute conditions were caused by the anions with which beryllium was associated, and one prominent pathologist, LeRoy Gardner, who was a specialist in the etiology of the pneumoconioses, even proposed that the chronic disease might be due to some infectious organism that somehow thrived in an environment that contained beryllium.[7] Moreover, general acceptance of the element's toxicity was made more difficult by the unusual clinical and epidemiologic features of the cases that were being reported.

The etiology of new industrial diseases is generally elucidated by epidemiologic studies that provide an understanding of the clinical and environmental factors involved. One essential requirement for environmental studies is techniques to sample the air in the workroom atmosphere to establish the relationships between the degree of exposure and the observed effects. After 1947, methods for the analysis of the trace amounts of beryllium in air samples had been developed, and the Atomic Energy Commission then sponsored epidemiologic and environmen-

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tal studies which led quickly to the gaining of information needed to control the disease.

The acute disease

The first three cases described by the Cleveland Clinic physicians involved workers from the Clifton Products Company, a small beryllium refinery in Painesville, Ohio; these cases were followed by additional ones involving patients both from that plant and the Brush Beryllium Company plant in Lorain, Ohio, which used a different extraction process. Cases from the Pennsylvania refinery, as noted previously, and from a plant that manufactured the phosphors used in fluorescent lamps were also reported. No acute cases were recorded from the lamp manufacturing plants themselves.

The severe form of the disease was proving to be more virulent than had been appreciated when the first cases were described. By 1948, 12 patients with acute pneumonitis had died. Persons that survived the acute episode, however, usually recovered completely.

In addition to severe pneumonitis, a much larger number of cases of rhinitis, tracheitis, and bronchitis, as well as contact eczematoid dermatitis and inflammatory lesions of the conjunctiva and cornea, was reported. Acute manifestations of the skin and upper respiratory system (other than pneumonitis) were seen only among employees of the three beryllium extraction plants.

Clinical and epidemiologic evidence seemed to indicate that the acute disease was often caused by massive, though brief, exposure to aerosols of beryllium compounds, sometimes as the result of accidents. The sulfate fluoride and chloride salts were particularly toxic. Also, beryllium oxide was capable of causing the acute disease only when produced at low temperatures. This finding explained the puzzling observation that the oxide produced by Clifton Products Company caused many cases of acute disease, but that no cases were attributable to the oxide produced by the Brush Beryllium Company, despite the fact that the levels of exposure were comparable. The oxides produced by the two companies were chemically identical, but slightly different physical properties caused the Clifton oxide to be more reactive.

By 1948, based on the field studies, a recommendation was made to keep the dust or mist concentrations in workroom air below 25 $\mu g/m^3$, even for brief periods of time, to control the acute disease.[8] The effectiveness of this recommendation was borne out by the fact that 53 cases of acute pneumonitis were reported in 1947; 28 in 1948; and only one in 1949. Fifteen cases were noted between 1950 and 1968, all in beryllium extraction plants.[9] Most cases were associated with accidental massive releases during the start-up of new plants. No instance of the disease has been reported since 1968, and no fatalities have been recorded since 1947.

Here, it should be noted that the recommended standard applied only to *peak* levels of exposure. Establishment of a maximum allowable daily *average* exposure also seemed necessary to control the chronic disease, but the prevalence of cases of acute pneumonitis in the extraction plants, and the observation that many of the acute cases were resulting from sudden exposure to high concentrations of beryllium, led to the determination of an upper limit for even transient levels of exposure. The value of 25 $\mu g/m^3$ was selected because the disease resulted when exposure levels were at 100 $\mu g/m^3$, but not at 15 $\mu g/m^3$.

The chronic disease

Before 1947, no cases of chronic disease were recorded in the beryllium production industry. Nevertheless, cases *were* reported that primarily involved workers from fluorescent lamp manufacturers; a few other cases were connected to the use of beryllium oxide, beryllium metal, and molten beryllium copper. The first known case of berylliosis in Ohio involved a woman who first noticed symptoms in 1944 and died in 1946. The diagnosis, at that time, was Boeck's sarcoid, but her physician reviewed the history of that case in late 1947 and changed the diagnosis to berylliosis in view of what had been learned about the disease in other parts of the country. Strangely, the woman was not a beryllium worker, but lived across the street from the beryllium extraction plant that then existed in Lorain. This was puzzling since no cases were as yet known among the employees who were exposed to much higher concentrations of beryllium during their work. Thus, this case alerted physicians in the Cleveland area and a few other similar cases were recalled that had been misdiagnosed previously. An epidemiologic team from Columbia University, with the knowledge and encouragement of the two Ohio companies, began to survey local physicians and gather information about these cases.[10] No chronic cases were found in Painesville, but nine cases of chronic disease were lo-

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cated among residents in the vicinity of the Lorain plant. Suprisingly, no chronic cases had as yet been reported among the employees of any of the three extraction plants.

Immediately upon learning about the neighborhood cases, the Board Chairman of the Brush Beryllium Company (now Brush Wellman) requested that the Ohio Health Department assist in determining the extent of the problem. At the time, nine neighborhood cases had been discovered. A decision was made to obtain radiographs of Lorain residents; those persons with some evidence of disease would then be studied clinically. A mass program was soon undertaken by the Ohio Health Department; radiographs of more than 6,000 persons were obtained in June 1948. An additional two cases were found and the patients were referred for treatment. The total number of neighborhood cases thus rose to 11 as a result of the mass survey.

Measurements of the beryllium content of dust collected from the atmosphere in the vicinity of the plant demonstrated an association between the concentration of airborne beryllium and the occurrence of chronic beryllium poisoning. On the basis of these studies, a tentative standard of 0.01 $\mu g/m^3$ was recommended for protection of the community around beryllium production facilities.[8] This standard, recommended 36 years ago and now accepted worldwide, was the first ambient air-quality standard for a toxic metal and preceded establishment of standards for other substances, such as lead, sulfur dioxide, and carbon monoxide, by more than 20 years.

The occurrence of cases of chronic disease among residents living near the plant was extraordinary; cases of chronic metal poisoning among people living near industrial plants were unknown in 1948, and are exceedingly rare even today. Yet, the Lorain cases were all the more remarkable because the concentrations of beryllium to which the residents were exposed were orders of magnitude lower than the concentrations of other toxic metals, such as lead, arsenic, or mercury, that were associated with chronic disease. More astonishing was the fact that while studies of berylliosis in the community were underway, no cases were known to have been reported among plant employees who were exposed to concentrations of beryllium in orders of magnitude higher than the concentrations to which the nearby residents were exposed.

The field studies revealed that not all of the cases resulted from exposure to air pollution. Personal hygiene among workers left much to be desired in those days, and the plant employees would return to their homes with beryllium-laden work clothes that would then be laundered by the crude methods used at the time. The clothes would be shaken, boiled, scrubbed, and usually, dried outdoors. Studies were conducted of the housewives' exposure during home washing, and it was found that on average they received as much, or more, exposure from home washing than from air pollution. One of the 11 cases was believed to be due to this source of exposure.

The extraordinary toxicity of beryllium was demonstrated by the fact that the established standard, 0.01 $\mu g/m^3$, was about 1/10,000th of the concentrations established as standards for the toxic heavy metals. The situation in Lorain was not unique since, in 1946, a case of chronic disease had been reported involving a woman who lived across the street from a fluorescent lamp manufacturing plant in Massachusetts. A number of neighborhood cases were subsequently reported among residents in the vicinity of an extraction plant that had operated for many years in Reading, Pennsylvania.

As a result of studies of the neighborhood cases in Lorain, it was advised that the work clothes of the employees be laundered at the plant rather than taken home. No cases of berylliosis from community exposure are known from exposures that began around 1950.

Soon, cases of chronic disease were discovered among employees of the Lorain and Pennsylvania refineries and were being reported from several research laboratories in which beryllium was used either as an oxide or metal. A large number of cases had also been recorded by beryllium copper foundries in which a master alloy of 5% beryllium oxide was poured. Yet, the dose-response relationships, which were quite evident in studies of the acute disease as well as in the investigation of the neighborhood cases, were not discernible among the industrial employees.

In the absence of an epidemiologic basis for a standard, one was proposed using an unusual line of reasoning: Standards set for the highly toxic metals such as lead, mercury, and arsenic had generally been approximately 100 $\mu g/m^3$, and the toxicity of a given dose must be related to the molar concentration. Allowing for the difference in atomic weight, 100 μg of lead or mercury (atomic weight, 207 and 200, respectively) is

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equivalent, on a molar basis, to approximately 4.5 $\mu g/m^3$ of beryllium (atomic weight, 9). If the toxicity of beryllium was comparable to the heavy metals on an atom-for-atom basis, the limit should be approximately 4.5 $\mu g/m^3$. At the time, this seemed to be a conservative approach since the assumption was being made that beryllium was as toxic as lead and mercury—by far the most toxic of all the nonradioactive metals. The standard might have been set at 4 or 5 $\mu g/m^3$, but 2 $\mu g/m^3$ was used to provide additional safety.[8]

Establishment of the Beryllium Case Registry

In 1952, the Atomic Energy Commission financed the establishment of a Beryllium Case Registry (BCR) at the Massachusetts Institute of Technology under the direction of Harriet Hardy.[11,12] The BCR was subsequently transferred to the pulmonary unit of Massachusetts General Hospital and, in late 1977, to the National Institute of Occupational Safety and Health. In a recent review of the epidemiology of beryllium disease, based mainly on data from the BCR, 930 cases are now known to have been reported in the United States (including 561 cases classified as occupational berylliosis, 42 cases of community berylliosis due to air pollution, 23 chronic cases attributable to family contact, and 226 cases of acute pneumonitis).[9]

Unusual epidemiologic features of beryllium disease

Both the acute and chronic manifestations of beryllium disease have been characterized by unusual epidemiologic features. With respect to the acute disease, one report stated that "a high percentage of those who develop dermatitis when first exposed, if they are allowed to continue in the same work invariably develop bronchitis and finally pneumonitis. In new employees, therefore, severe dermatitis or a form suggesting allergy is considered an indication of individual susceptibility to pulmonary or bronchial irritation."[13] Some employees who were exposed to high concentrations of even the most toxic of the beryllium salts did not experience acute respiratory problems, while others would promptly suffer from dermatitis as well as upper and lower respiratory problems. In 1951, George H. Curtis of the Cleveland Clinic used the patch test to examine beryllium workers having eczematous-contact-type dermatitis; all had been sensitized.[14] Dr. Curtis also produced spontaneous flare-ups of eczematous reactions in 8 of 16 persons who had never been exposed to beryllium compounds previously. Consequently, immunologic factors, at least for acute pneumonitis, were indicated.

The epidemiology of berylliosis proved to be far more complicated then expected. The studies in Lorain demonstrated a clear-cut dose-response relationship among residents in the vicinity of the Brush Beryllium Company, but this was not true among those exposed occupationally in spite of the fact that the concentrations of beryllium in the atmosphere they breathed were thousands of times greater than in the atmosphere to which the residents were exposed. Moreover, the amounts of beryllium found in the tissues of persons who died of berylliosis were so small as to be all out of proportion to the severity of the systemic effects produced. In 1951, Sterner and Eisenbud[15] proposed that the chronic effects on the lung were also the result of an immunologic response. This hypothesis has been supported in clinical and laboratory studies conducted in more recent years.[16–18]

An extraordinary feature of berylliosis is the long latency period in some instances. Although a few cases have been reported within a year from the start of exposure, sometimes the condition does not develop for more than 30 years, even though exposure has long since terminated. This suggests that traces of beryllium could reside in the lung in immunologically substantial quantities for long periods of time until sensitization occurs.[15]

Also, berylliosis seemed to develop in only a limited number of persons: approximately 1% of the residents living within 0.25 miles of the Lorain plant and 1.3% of the employees within the plant, despite the fact that the employees were exposed to a much higher concentration of beryllium. A recent review of the epidemiology of berylliosis concluded that an incidence of about 1% seemed to be the limit for a number of cohorts, with one exception: an incidence of 4.9% among employees of a machine shop.[9]

The lack of a dose-response relationship has, in turn, shown that even low levels of exposure can lead to lung disease. For example, 12 cases of berylliosis are known to have occurred among secretaries working in various plants and laboratories where beryllium was used. This is more than 2% of all known cases of occupational berylliosis and is an extraordinary finding since occupational poisoning of secretaries is not ex-

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pected. In one extraction plant which employed approximately 200 people, many acute cases, including a number of fatalities, were recorded during its period of operation, but no cases of berylliosis occurred. Yet, some time after the company went out of business and the plant buildings were being used for another purpose, berylliosis developed in an engineer who had worked in the plant for four years. No beryllium was used in the building during his period of employment, but presumably, he was exposed to residual contamination of surfaces and low levels of beryllium dust.[9]

Although the finding that a sensitizing mechanism is involved was helpful for explaining some of the epidemiologic anomalies, much is still not known about the etiology of berylliosis. Nevertheless, although beryllium production in the United States has greatly increased since the 1940s, new cases have become comparatively rare (*Figure*). Of 347 cases in which the year the person was first exposed is known, 264 were first exposed between 1938 and 1949. The greatest number of cases involved workers first exposed prior to 1943. Considering the long potential latency period for berylliosis, new cases may become evident in the future from exposures in the recent past. Nevertheless, the data of the *Figure* show the enormous improvement that has taken place as a result of the preventative measures adopted.

Question of human carcinogenicity

In 1946, Gardner and Heslington[19] reported that multiple osteosarcomas developed in seven rabbits injected with beryllium containing phosphors. That finding has been followed by other reports of beryllium-induced tumors in rats and monkeys.[20–22] The question of whether beryllium is capable of inducing cancer in humans has been the subject of recent debate. The first epidemiologic studies of beryllium workers failed to show any such relationship, but a slight increase in lung cancer incidence (47 observed as opposed to 34 expected) was subsequently reported.[21] That conclusion has been contested by MacMahon,[23] and an industry-wide study is currently being conducted by the National Institute for Occupational Safety and Health to resolve this question. Because the exposures in the beryllium extraction plants have been reduced one-thousand-fold since the cohorts under study were exposed many years ago, the cancer risk, equivocal as it was from those high exposures, must be much less now given the modern conditions of plant hygiene.

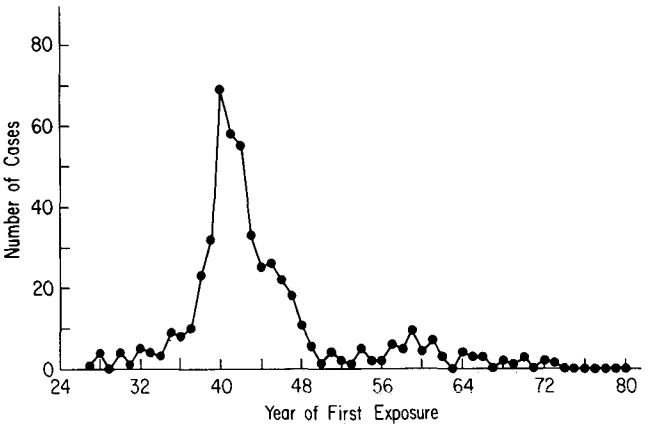

Figure. Number of cases of occupational berylliosis by year of first exposure (1927–1980)

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