Commentary and update: Beryllium granulomas of the skin: a small window to understanding

William L. Epstein, M.D.[1]

Serious consequences can result from injuries to the skin by a foreign substance, depending on its noxiousness and the individual response. Local granulomas are a chronic unwanted outcome. The "prosector's wart," primary inoculation tuberculosis, among the earliest known, is comparable to deep fungal granulomas that occur in laboratory workers who misinoculate themselves. Why, then, should a single case report of cutaneous granulomas following laceration with a broken fluorescent light tube be included in this volume venerating the many diverse and significant contributions of dermatologists at the Cleveland Clinic? The primary author was not even a dermatologist; the paper itself was not well written; and, by the authors' own admission,[1] theirs was not even the premier description; they counted three prior papers (a slight miscalculation). But that is a narrow, officious view. This case report exemplifies the teamwork of the Departments of Dermatology and Cardiopulmonary Disease in investigating an important "new" occupational disease, berylliosis, and, incidentally, in establishing occupational dermatology at the Cleveland Clinic.

Discovered before 1800, beryllium remained unrecognized industrially for its ability to form strong, light-weight alloys for almost a century and a half. It was developed throughout Europe during the 1930s, and some of its toxic properties were discovered. In about 1938 American manufacturers imported the methods, and beryllium processing plants sprang up in Ohio, Pennsylvania, and Massachusetts. Early on it was used as a phosphor [$ZnBeMg(SiO_4)Mn$] in fluorescent light bulbs. In 1943 in the *Cleveland Clinic Quarterly*, Van Ordstrand[2] reported the first three cases of acute beryllium pneumonitis as a new occupational disease in the United States. Thus began his commitment to this intriguing and multifaceted disease that spanned the next 20 years. At the time, Van Ordstrand was a staff physician in the Department of Cardiopulmonary Diseases at the Cleveland Clinic. He worked with a team including Joseph DeNardi and John Zielinski, both of whom were consultants or industrial physicians for the Brush Berryllium Company in Lorain, Ohio. In time they were joined by George Curtis, a dermatologist at the Cleveland Clinic.

Following up pulmonary illness reports at the fluorescent lamp plant in Salem, Massachusetts, Hardy and Tabershaw, two occupational medicine physicians, proved that "Salem sarcoid" was a new disease, chronic pulmonary berylliosis. Their work is chronicled in a recent article by Hardy.[4] Additionally, she was the driving force behind development of the United States Beryllium Case Registry[5] and is regarded historically as the leading figure in the evolving saga of berylliosis.

In 1945 Van Ordstrand's group recounted their vast experience with "beryllium poisoning" dating back to 1940.[6] They had examined 170 workers with acute skin and pulmonary disease; 5 had died. Contact dermatitis and beryllium ulcers were recognized, but at the time Van Ordstrand's group was working without the aid of a dermatologist. Chronic pulmonary disease with skin granulomas also had been recorded,[3,7] but it was not until 1948 that pure cutaneous granulomas inflicted by broken fluorescent lights

[1] Professor and Chairman, Department of Dermatology, University of California, San Francisco, CA 94143.

were described first by Grier et al[8] in Boston and then in quick succession by clinicians and pathologists in the United States and Canada.[9–16] At this time a medical student, Robert Funkhauser at Harvard, suggested the skin granulomas of the first case might be connected with beryllium phosphor exposure.[8]

By 1953 the Cleveland Clinic dermatology team described in their best paper[17] three of the main types of skin lesions, namely, (1) acute dermatitis, i.e., contact dermatitis, which also involved the mucous membranes and nasopharynx; (2) beryllium ulcers; and (3) cutaneous granulomas. Earl Netherton, the doyen of dermatology at the Cleveland Clinic, was included as dermatologist in the 1950 case report by Van Ordstrand,[1] and undoubtedly saw the patient clinically.

George Curtis then became the dermatologist on the Van Ordstrand team. He was a staff dermatologist at the Cleveland Clinic who had just returned from Army duty during World War II with a penchant for patch testing. Between 1947 and 1951 he examined several beryllium plant workers with occupational rashes. His patch-test findings, published in the *Archives of Dermatology*, indicated positive contact-type delayed hypersensitivity responses in all 13 patients.[18]

His patch-test methods, with 1% and 2% BeF_2, sensitized 8 of 16 controls. He believed this was because of repeated testing, but I and others who have studied beryllium know that BeF_2 is a potent contact sensitizer, and no more than 0.1% as an open patch should be used. The difficulties notwithstanding, Curtis's findings set in motion a controversy concerning the pros and cons of patch testing as an aid to diagnose pulmonary berylliosis that persisted until a thorough analysis appeared in the February 1959 issue of the *Archives of Industrial Health* solely devoted to the problem of berylliosis.[19] In this volume Curtis[20] and Byron Waxman,[21] then an Assistant Professor of Microbiology at Harvard, came to the same basic conclusion, namely, that a positive contact patch to beryllium simply indicated prior exposure to beryllium and not necessarily presence of the disease, much as the tuberculin skin test signifies prior exposure to the tubercle bacillus but not necessarily active tuberculosis. Thus, Curtis's work stimulated immunologic thinking, but did not breach conventional dogma; neither did it provide the vital clue to pathogenesis.

On June 30, 1949, the electric light industry voluntarily removed beryllium from phosphors in fluorescent bulbs; however, case reports and studies continued unabated for the next decade.[19] The Case Registry remained highly active well into the 1960s when a dramatic decrease was seen in registered cases as industrial hygiene controls were instituted.[5] Nevertheless, the problem continued since beryllium was too useful, and its applications too profitable. By the mid 1970s the Case Registry at Harvard still reported a small but continuing number of new patients.[22] New sources of exposure, such as camp lanterns and dental devices, continued to appear. Modern in vitro tests were developed to aid diagnosis,[23,24] and as late as 1982, fatal cases were still being recorded from broken fluorescent light exposure.[25]

What was the real significance of beryllium granulomas of the skin? What did investigation add to understanding of pathomechanisms? In 1950 medical science was not very sophisticated about immunology. It was generally accepted that only plasma cells made antibody, and the lymphocyte's role was unclear, although it was thought to be active in delayed hypersensitivity reactions such as the tuberculin skin test, and possibly in contact-type delayed hypersensitivity. The cause of berylliosis was mysterious and as controversial as that of sarcoidosis. The debate included irritant, toxic, and hypersensitivity reactions. Unfortunately, the numerous experimental studies of the time produced a myriad of conflicting results. Sterner and Eisenbud,[26] in a classic analytical dissertation, commented that chronic beryllium granulomas "present an incidence, time-of-onset, dose-response and histopathologic pattern which does not conform to the usual concept of a chronic chemical intoxication." They favored an immunologic etiology with two specific target organs, the lung and the skin. Compounding the consternation was uncertainty about the actual offending agent. Beryllium oxide, beryllium silicate (causing a type of silicosis), or a combination of beryllium and an unusual diptheroid, as advanced by Leroy Gordon, the highly respected director of Saranac Laboratories, were possible causes. An important discovery, which helped to solve this problem, was made by Ian Sneddon, who reported one of the few cases of cutaneous granuloma in England.[27] In studying this case, he performed patch tests with beryllium sulfate and nitrate as outlined by Curtis and obtained strongly positive delayed patch test results in 48 hours. However, the skin

lesions did not heal, and three weeks later when he biopsied the active sites, he found organized epithelioid cell granulomas. This simple observation cleared the air and pointed to beryllium ions as solely responsible for inducing granulomatous inflammation. Shortly thereafter, Shelley and Hurley[28,29] discovered that zirconium in deodorants produced a similar type of granulomatous reaction, and that it was an inducible or allergic phenomenon.[28,29]

In the next few years we and others refined the information and clearly established the concept of granulomatous hypersensitivity as an immunologic response to metals such as beryllium and zirconium.[30,31] We suggested that this was a different type of delayed hypersensitivity distinct from conventional cell-mediated immunity and that it probably accounted for the organized epithelioid cell granulomas seen in tuberculosis, tuberculoid leprosy, and sarcoidosis. By 1970 it appeared that a new type of immunologic reaction had, in fact, been identified. During the following decade, the marvellous intricacies of the immune system were revealed, and the generation of clinical immunologists and pathologists reexamined the situation in complex granulomatous disease models with better techniques. Their findings and pronouncements relegated the "new phenomenon" to just another form of conventional cell-mediated immunity,[32,33] and there it will remain until someone else realizes that *delayed* and *granulomatous* hypersensitivity are not identical. The challenge is to demonstrate that organized epithelioid cell granulomas are primarily derived by a disorder of macrophage differentiation and function, independent of, but modified by, T cell activity.

References

1. Van Ordstrand HS, Netherton EW, De Nardi JM, Carmody MG. Beryllium skin granulomas from a broken fluorescent tube; report of a case. Cleve Clin Q 1950; **17:**34–37.
2. Van Ordstrand HS, Hughes R, Carmody MG. Chemical pneumonia in workers extracting beryllium oxide; report of three cases. Cleve Clin Q 1943; **10:**10–18.
3. Hardy HL, Tabershaw IR. Delayed chemical pneumonitis occurring in workers exposed to beryllium compounds. J Indust Hyg Toxicol 1946; **28:**197–211.
4. Hardy HL. Beryllium disease; a clinical perspective. Environ Res 1980; **21:**1–9.
5. Hardy HL, Rabe EW, Lorch S. United States beryllium case registry (1952–1966); review of its methods and utility. J Occup Med 1967; **9:**271–276.
6. Van Ordstrand HS, Hughes R, De Nardi JM, Carmody MG. Beryllium poisoning. JAMA 1945; **129:**1084–1090.
7. Pyre J, Oatway WH Jr. Beryllium granulomatosis alias miliary sarcoid, Salem sarcoid, miliary sarcoidosis, chronic beryllium poisoning or delayed chemical pneumonitis; description and report. Ariz Med 1947, **4:**21–29.
8. Grier RS, Nash P, Freiman DG. Skin lesions in persons exposed to beryllium compounds. J Indust Hyg Toxicol 1948; **30:**228–237.
9. Shook CF, Powell JP. A beryllium case. Indust Med 1948; **17:**403–404.
10. Doane GP. Wounds contaminated by beryllium phosphor. JAMA 1949; **139:**1047.
11. Coakley WA, Shapiro RN, Robertson GW. Granuloma of the skin at site of injury by a fluorescent bulb. JAMA 1949; **139:**1147–1148.
12. Nichol AD, Dominguez R. Cutaneous granuloma from accidental contamination with beryllium phosphors. JAMA 1949; **140:**855–860.
13. Dutra FR. Beryllium granulomas of the skin. Arch Dermatol Syph 1949; **60:**1140–1147.
14. Neave HJ, Frank SB, Tolmach JA. Cutaneous granuloma following laceration by fluorescent light bulbs. Arch Dermatol Syph 1950; **61:**401–406.
15. Shorten EA, Giffen HK. Delayed subcutaneous beryllium granuloma. Arch Surg 1950; **60:**783–786.
16. Gerrie J, Kennedy F, Richardson SL. Beryllium granulomatosis. Can Med Assoc J 1950; **62:**544–547.
17. De Nardi JM, Van Ordstrand HS, Curtis GH, Zielinski J. Berylliosis; summary and survey of all clinical types observed in a twelve-year period. Arch Indust Hyg 1953; **8:**1–24.
18. Curtis GH. Cutaneous hypersensitivity to beryllium; study of 13 cases. Arch Dermatol Syph 1951; **54:**470–482.
19. Kaufman AR. Uses of beryllium and its compounds. Arch Environ Health 1959; **19:**91–93.
20. Curtis GH. The diagnosis of beryllium disease, with special reference to the patch test. Arch Environ Health 1959; **19:**150–153.
21. Waksman BH. The diagnosis of beryllium disease, with special reference to the patch test. Discussion of paper by Dr. Curtis. Arch Environ Health 1959; **19:**154–156.
22. Hasan FM, Kazemi H. Chronic beryllium disease; a continuing epidemiologic hazard. Chest 1974; **65:**289–293.
23. Hanifin JM, Epstein WL, Cline MJ. *In vitro* studies of granulomatous hypersensitivity to beryllium. J Invest Dermatol 1970; **55:**284–288.
24. Williams WR, Jones Williams W. Development of beryllium lymphocyte transformation tests in chronic beryllium disease. Int Arch Allergy Appl Immunol 1982; **67:**175–180.
25. Karkinen-Jääskeläinen M, Määttä K, Pasila M, Saxen L. Pulmonary berylliosis; report on a fatal case. Br J Dis Chest 1982; **76:**290–297.
26. Sterner JH, Eisenbud M. Epidemiology of beryllium intoxication. Arch Indust Hyg 1951; **4:**123–151.
27. Sneddon IB. Berylliosis; a case report. Br Med J 1955; **1:**1448.
28. Shelley WB, Hurley HJ. Experimental evidence for an allergic basis for granuloma formation in man. Nature 1957; **180:**1060–1061.
29. Shelley WB, Hurley HJ. The allergic origin of zirconium deodorant granulomas. Br J Dermatol 1958; **70:**75–101.
30. Epstein WL. Granulomatous hypersensitivity. Prog Allergy 1967; **11:**36–88.
31. Epstein WL. Metal-induced granulomatous hypersensitivity in man. Adv Biol Skin 1969; **11:**313.
32. Adams DO. The granulomatous inflammatory response; a review. Am J Pathol 1976; **84:**164–191.
33. Boros DL. Granulomatous inflammations. Prog Allergy 1978; **24:**183–267.