IV. BIOLOGIC EFFECTS OF EXPOSURE

Extent of Exposure

Potential exposures to beryllium-containing fumes and dusts occur both in large scale processing plants and in small plant operations which perform melting, casting, grinding, drilling, machining, etc.[7] In 1971, approximately 8,000 such plants were estimated to be in current operation in the United States. A survey conducted by the U. S. Public Health Service, Bureau of Occupational Safety and Health, in 1970, estimated that 30,000 persons in the work force could have potential exposure to dust or fumes of beryllium. This would include approximately 2,500 persons in the production industry. The total estimate is regarded as being very conservative if the many small plants are included which do not perform dust-generating operations.

Early Historical Reports

European reports describing a disease in beryllium workers appeared in the 1930's and early 1940's.[8-15] A partial list of early literature on beryllium poisoning is listed in Table IV as presented by Hardy[16] and compiled by Williams.[17] Weber and Engelhardt[8] reported in 1933 that in guinea pigs the effect of inhaling water soluble beryllium dust resulted in lung damage. Marradi-Fabroni[9] also described forms of pneumonia in guinea pigs due to beryllium carbonate exposure and suggested the name of "berylliosis" for this pathogenic condition.*

In 1936 Gelman[10] described illnesses among workers in beryllium plants in Moscow. He described two phases of the clinical symptoms caused

*Much confusion has resulted from use of this term[16] because of its similarity in spelling relating to beryl ore (beryllosis) and to use of the term in describing both acute and chronic manifestations of beryllium related disorders. Accordingly, the terms "beryllium disease" and "beryllium poisoning" will be used in this report.

similarity in spelling relating to beryl ore (beryllosis) and to use

by exposure to vapors of beryllium oxyfluoride: the first phase, beryllium fever, was not unlike that caused by exposure to zinc oxide fumes; the second phase was described as an extensive alveobronchiolitis. Two years later he described effects on the skin and X-ray changes in the lungs.[11] In 1940, Berkovitz and Israel[12] noted changes in the lungs from exposures to beryllium fluoride.

These early foreign reports and the beginning American studies which recognized a beryllium hazard found the problems to be basically acute in nature with effects resembling metal fume fever, chemical pneumonia, and related pulmonary irritations associated with well-known gases such as phosgene or chlorine and corrosive acids and alkalies. Some investigators[18] attributed toxicity to the irritant effects of the anions and, the United States Public Health Service Bulletin,[19] in reviewing the effects of beryllium as related to human illness and animal studies in 1943 concluded, "beryllium of itself is not toxic." Subsequent findings of beryllium poisoning in diverse applications[20,21,22] established that beryllium itself was toxic.

The first report of a delayed beryllium poisoning referred to as "delayed chemical pneumonitis" was made by Hardy and Tabershaw in 1946.[22] These investigators reported 17 cases occurring over a three year period in a fluorescent-lamp manufacturing plant. Of particular interest was the fact that a number of the patients did not manifest illness until sometime after leaving their jobs. Beryllium was one of the materials in fluorescent-lamp phosphors. This, along with evidence of exposures reported in the beryllium processing industry[21] and coupled with the report by Gardner in 1946[23] of five foundry worker fatalities where workers had

been exposed in an operation using a 4 percent beryllium master alloy, substantiated the belief that beryllium was the causative agent in the respiratory diseases observed.

Because of increased interest in beryllium in atomic energy development, and based upon studies performed by Eisenbud and co-workers,[24,25] the Atomic Energy Commission in 1949 issued requirements for environmental control for all contractors involved in the handling of beryllium. These requirements were ultimately adopted by professional groups.[26,27]

Effects of Humans

(1) Acute Effects

The classic symptoms of acute beryllium poisoning have been presented by Tepper, Hardy, and Chamberlin;[28] DeNardi, Van Ordstrand, Curtis, and Zielinski;[29] and Hardy and Stoeckle.[30] Condensed descriptions have also been given by the American College of Chest Physicians[31] and the U.S. Public Health Service.[32]

Tepper, Hardy, and Chamberlin[28] stated that: "Acute beryllium disease may be defined arbitrarily to include those beryllium-induced disease patterns with less than one year's natural duration and to exclude those syndromes lasting more than one year."

(a) Acute Effect--Skin and Conjunctiva: Beryllium diseases of the skin and conjunctiva occur as contact dermatitis, beryllium ulcers, and ocular effects.

(i) Contact dermatitis is characterized by itching and reddened, elevated, or fluid-accumulated lesions which appear particularly on the exposed surfaces of the body, especially the face, neck, arms, and hands.[21] Contact dermatitis has not been seen in workers handling beryllium hydroxide, pure beryllium, and present-day vacuum-cast beryllium

metal,[31] but it may occur either on an allergic basis or from primary irritation, following contact with soluble beryllium salts.[33] A latent period is occasionally noted, indicating the development of delayed hypersensitivity.

Secondary exposures in sensitized individuals result in more rapid development of the dermatitis, often after exposure to lesser amounts of material. Van Ordstrand and his co-workers[21] found that persons with contact dermatitis, if allowed to continue work, might develop bronchitis and pneumonitis from additional exposure. Moisture conditions also influence the severity of beryllium-induced dermatitis. Following cessation of exposure and with simple local treatment, the skin eruptions usually disappear within one to two weeks.

(ii) Beryllium ulcers result from crystal implantation of soluble or insoluble beryllium materials in cutaneous areas previously injured as a result of abrasions, cuts, etc. Abscess and ulceration frequently result. Lesions often last for several months and physical removal of the crystals is necessary before healing can take place. After removal of the foreign material, recovery is rapid and complete, usually within two weeks.

(iii) Ocular effects may occur as inflammation of the conjunctiva in "splash burn" or in association with contact dermatitis.[21] Splashes may also cause corneal burns closely resembling those produced by acids and alkalies. Fluid accumulation and reddening around the eye socket are frequently noted.

(b) Acute Effects--Respiratory: Beryllium-induced acute respiratory effects range from a mild inflammation of the nasal mucous membranes and pharynx, to tracheobronchial involvement, and finally to a severe chemical pneumonitis. Recovery generally ranges from one to six weeks in mild cases; however, recovery from acute pneumonitis may be prolonged to six months following exposure. Severe cases may become fatal. Eighteen acute pneumonitis fatalities were reported[28] following development of pulmonary edema.

(i) Beryllium rhinitis and pharyngitis involve inflammation of the nasal mucosa and pharynx, frequently accompanied by mild nosebleeds. Fluid and blood accumulate in the mucous membranes, and ulcerations may occur. Gelman[11] in reports of cases in Russia described perforation of the nasal septum, but this has not been reported in the United States. Fever and positive chest manifestations are absent. Patients occasionally describe sensations of a peculiar metallic taste. This condition is difficult to diagnose since it closely resembles that seen with the common cold.

(ii) Acute tracheobronchitis is non-specific and not beryllium-related as far as its clinical picture is concerned. The diagnosis can only be made on the basis of beryllium exposure. The effects are characterized by non-productive spasmodic cough, substernal discomfort and burning, tightness of the chest, and moderate difficulty with breathing upon exertion. Other findings include normal body temperature, decreased vital capacity with varying degrees of breathing difficulty, limitations of chest expansion, and sibilant rales in the hilar and basal lung areas. Clinical laboratory findings are within normal limits provided secondary infections are not present. Chest X-ray examinations may show an increase in bronchio-vascular

markings[29] and recovery is usually complete within one to four weeks.

(iii) Acute pneumonitis, while potentially the most serious of the acute syndromes, is encountered only rarely due to improved control methods and prompt medical treatment of beryllium exposures. Both rapid and delayed onsets of this disease have been reported[21,29,34,35] depending upon the magnitude and duration of the exposure. Symptoms of rapidly developing pneumonitis usually occur within 3 days, and possibly up to 8 days, after brief but massive exposures; whereas, the delayed form causes symptoms some weeks after prolonged exposure to lesser concentrations of beryllium compounds. Workers should be observed by a physician to decide whether or not symptoms are due to beryllium overexposure. The following symptoms, although varying in sequence of onset, are representative of acute pneumonitis. Workers complain of progressive cough (generally nonproductive), difficult breathing with tightness of the chest, substernal discomfort or pain, appetite and weight loss, and general weakness and tiredness.[35] The pain usually subsides during the early stages, but the cough may increase in severity so as to become extremely exhausting. Other observations show varying degrees of decreased vital capacity with breathing difficulties, rapid pulse, and cyanosis. Signs of diffuse lung involvement may be noted with fine-to-medium sibilant rales noticeable in the lower thorax. Temperature generally remains normal with the exceptions of secondary infections or during the terminal stages of pneumonitis. Clinical laboratory tests are generally within normal limits. Reported X-ray changes[21] consist of (1) diffused haziness of both lungs, (2) development of soft irregular infiltration areas with prominent peribronchial markings, and (3) appearance of discrete large or small nodules similar to those frequently observed in chronic beryllium disease or sarcoidosis. Importance was placed on the fact that clearing of the lungs preceded

peribronchial markings, and (3) appearance of

complete remission of other symptoms or absence of physical signs.[21] Aub and Grier[35] and Hardy and Stoeckle,[30] however, observed greater persistence of the X-ray findings. Hardy and Stoeckle[30] emphasized the similarity of the observed nodular densities with those frequently seem with bacterial and viral bronchopneumonias or with pulmonary edema. Pathological tissue studies from six patients revealed a nongranulomatous acute or subacute pulmonary edema.[36] Treatment for acute beryllium pneumonitis should include the use of oxygen, steroids, and antibiotics.

(2) Chronic Effects

Tepper, Hardy, and Chamberlin[28] stated that ". . . the term chronic is arbitrarily applied to beryllium disease of more than one year's duration. The clinical character of the chronic illness differs from the acute in that the former is: (1) frequently separated by a period of years from the time of the etiologic beryllium exposure; (2) prolonged in duration with at present (1960) little, if any, evidence for a lasting total 'cure'; (3) commonly progressive in severity in spite of the cessation of exposure; and (4) a systemic disease." These authors also believe that the term "berylliosis" was a poor choice to describe the disease caused by exposure to beryllium and its compounds because considerable confusion was created by its use.

Pneumonitis with accompanying cough, chest pain, and general weakness is the most familiar and striking characteristic of chronic beryllium disease.[30] In addition, pulmonary dysfunction and systemic manifestations may be present. The systemic effects include right heart enlargement with accompanying cardiac (congestive) failure, enlargement of the liver and spleen, cyanosis, digital "clubbing", and the appearance of kidney stones.[37] A number of biochemical abnormalities also may be manifested through changes in serum proteins, liver function, and uric acid and urinary calcium levels.

The delayed onset of pneumonitis is often precipitated by some acute stress; for example, pregnancy, viral respiratory infections, surgery, etc.[30] Hardy and Stoeckle[30] noted that 40% of the women with chronic disease who had become pregnant after beryllium exposure experienced pneumonitic symptoms in conjunction with their pregnancy. The factors responsible for the delay in onset are not known. Sterner and Eisenbud[38] postulated a time lag for development of immunologic processes in susceptible exposed persons.

(a) Chronic Effects - Complications: The development of congestive heart disease (cor pulmonale) has frequently been of greater clinical significance than primary beryllium disease itself.[28] Tepper, Hardy, and Chamberlin[28] pointed out that the incidence of tuberculosis has been conspicuously rare considering the fact that a number of patients have been placed in tuberculosis sanatoriums for treatment due to misdiagnosis of beryllium disease. Further complications due to drug treatment, particularly steroid therapy, and problems of anxiety associated with the disease-producing effects attributed to beryllium have persisted in spite of improved control measures and the decreasing incidence of reported disease cases.

Tepper, Hardy, and Chamberlin[28] pointed out also that the pulmonary neoplasia observed in beryllium-treated animals (see section on animal toxicity) has not been observed in humans. Hardy[39] stated in 1965 that from the 734 entries in the Beryllium Case Registry, although 20 malignant tumors had been recorded, it was "impossible to incriminate beryllium as a carcinogen in human beings on this evidence."

The Committee on Toxicology of the National Academy of Sciences - National Research Council reported,[40] "While certain beryllium salts and

oxides have been productive of osteogenic sarcomas in rabbits following intravenous administration and primary lung tumors in rats and monkeys following inhalation, there is no evidence that community or industrial exposure to beryllium compounds is associated with an increase in the incidence of cancer in humans."

In 1970 Mancuso,[41] in an epidemiological study based upon mortality of beryllium workers, found an equal or higher rate of cancer of the lung in employees employed for a short duration (3 to 15 months) as contrasted to those employed for a longer period (18 months or longer). A higher mortality rate was also suggested among the short duration employees of one plant, but this was not supported by results from a second plant. There was an indication that prior chemical respiratory illness influenced the subsequent development of lung cancer. It was stated that beryllium was acting with other factors, rather than as a single etiology related to the duration of employment (see Correlation of Exposure and Effects).

(b) Chronic Effects - Pathological Changes: Studies of pathological changes due to chronic beryllium disease in over 100 cases have been reported by Williams[42] and Dudley.[43] More recently, Freiman and Hardy[44] discussed pulmonary pathology in 130 cases from the U.S. Beryllium Case Registry. Based on the degree of interstitial cellular infiltration they found that 80 percent of the cases studied showed moderate to marked infiltration whereas in the remainder, cellular infiltration was only slight or absent. Clearly defined granulomatous lesions were not always present. The group with prominent interstitial cellular infiltration could be subgrouped into two groups in which granuloma formation was either

well formed or else poorly-formed-to-absent. Where cellular infiltration was slight or absent, granuloma formation was numerous and well formed. Dudley[43] in 1959 reported that the occurence of granulomatous lesions often tended to draw attention away from the more fundamental diffuse interstitial infiltration of which the granulomas were only a part. This same reaction was also seen in skin, liver, kidney, lymph nodes, and skeletal muscle. Cardiac muscle, spleen, and pleura also could be involved. Freiman and Hardy[44] suggest a distinct relation between the intensity of interstitial cellular infiltration and the forecast of disease severity, with the possibility that the degree of granuloma formation may play a significant secondary role. Calcific inclusions were also commonly present, being observed in about two-thirds of the lungs from patients with chronic disease. In addition, increased tissue levels of beryllium were noted in most cases.

Although most cases of beryllium disease can be recognized by pathologic changes,[44,45,46,47] the observations are not specific for the disease. Pulmonary sarcoidosis, "farmers lung",[48] fungus diseases, and various pneumoconioses are but a few disorders which also produce a similar pathologic picture. Differentiation between sarcoidosis and chronic beryllium disease is the most difficult. Similarities and differences between the two disorders have been presented for diagnostic purposes.[44,49]

(c) Chronic Effects - Treatment: Early treatment of chronic beryllium disease was purely symptomatic with oxygen providing great relief in cases where impaired ventilation was noted. Antibiotics were only of value to treat secondary infections. Long periods of bedrest were employed.

Patients were occasionally transferred to warm or dry climates to provide temporary relief, but no detectable change in the course of the disease was noted.[30] Steroid therapy, initiated in the early 1950's[50,51,52] has proven to be extremely beneficial. Continued therapy with steroid congeners has markedly improved the clinical course of the disease, but because of the prolonged course of the disease, investigators are hesitant to claim "total cures." The incidence of relapse and disability has been reduced. With an adequate steroid regimen,[53] the clinical status of many patients has improved, allowing them to return to useful jobs.[54]

(d) Chronic Effects - Diagnosis: As stated by Van Ordstrand[55] in 1959, "twelve to fifteen years ago it appeared that the diagnosis of beryllium poisoning was not a difficult problem. Today it is not so certain." The diagnosis of chronic beryllium disease requires supportive evidence of X-ray findings, immunological tests, pulmonary function tests, and the establishment of beryllium exposure by finding beryllium in urine or tissue or by strong epidemiological evidence of exposure. The final diagnosis rests upon an evaluation of the entire clinical picture.[56] Sarcoidosis presents the most troublesome problem in differential diagnosis of chronic beryllium disease. Hardy and Freiman,[44,45] in presenting beryllium disease as a continuing diagnostic problem, listed specific differences between beryllium disease and sarcoidosis. These differences include weight loss and severe loss of appetite, rarely seen in sarcoidosis, the presence in histopathologic sections of intense cellular infiltration with nodular lesions and abundant calcific inclusions, the absence of many characteristic localization patterns frequently seen in sarcoidosis,

and the occurrence of significant amounts of beryllium in the tissues of many patients.

(i) X-ray changes were reviewed by Gary and Schatzki[57] in a study of all available X-rays in the Beryllium Registry, and they concluded that there was not an orderly sequence of lung involvement as had been previously postulated,[22,58] but rather, definite reaction types which persisted unchanged for many years. Disease which began with nodular manifestations stayed nodular. Further, they stressed that because of the several types of response seen on films, it appeared impossible to make a differential diagnosis by radiological means alone.

In 1970, Weber, Stoeckle, and Hardy,[59] in a study of 8 cases observed for up to 18 years, reported that X-ray changes, most frequently involving the upper lobes, consisted of granular, nodular, and linear densities occurring singly and in combined forms. Mixed patterns of granular and nodular densities were most commonly seen. Persistence of granular densities alone was rarely observed. Small and scattered linear densities often developed, and in advanced cases, were very marked and associated with emphysema. Fibrotic changes confined to the lower lobes were rarely seen. With fibrotic and emphysematous changes, granular and nodular densities diminished to a point where X-ray diagnosis was not indicated.

Chamberlin[60] stated that clinical and X-ray findings alone established only presumptive diagnosis of beryllium disease. Although X-ray findings are not specific, the appearance of a known pattern of beryllium disease on a chest film should immediately alert the physician to the possibility of this diagnosis.

(ii) Tissue sensitization has been reported. Sterner and Eisenbud in 1951[38] proposed that beryllium acts to produce allergic sensitization in tissues. In 1959, the patch test developed by Curtis was claimed to give favorable differentiation between chronic beryllium disease and other pulmonary diseases.[61] The positive patch test did not serve as an absolute diagnostic sign for chronic beryllium disease; in fact, in cases where differential diagnosis has been difficult, the patch test has not been very helpful.[28] Jett[61] has shown an immunologic basis to chronic beryllium disease, and a hypersensitivity phenomenon has been demonstrated.[63] Since the skin patch test can develop a hypersensitive state in persons who have never been exposed to beryllium, its use in differential diagnosis is generally discouraged and the test is best avoided in screening persons who are to be exposed to beryllium.[28]

(iii) Tissue and fluid analysis for beryllium is used to establish previous exposure to beryllium. The detection of beryllium in tissue or urine is evidence of exposure to beryllium only, not necessarily to the presence of beryllium disease.[64] Lung biopsy has been recommended as a means for positive beryllium identification.[65] Frequently, negative findings of beryllium in the lungs of persons having known exposure to the material are due to inadequate sample quantities. At least a 5 gm specimen is recommended for lung tissue.[28] The chances of positive analysis are accordingly reduced for other organs since they contain much less material than the lung. Beryllium is not generally considered to be a natural environmental contaminant; however, Cholak[66] tabulated the presence of extremely small quantities in soil, coal, and air.

(iv) A variety of ventilatory function and gas studies have been utilized in the diagnosis of chronic beryllium disease. Wright[67] indicated a difficulty of oxygen transfer across the pulmonary membranes as the basic defect in chronic beryllium disease. An increase in the alveolar-arterial oxygen tension difference is often noted, and studies have confirmed the problem of oxygen diffusion.[68,69,70]

In contrast, Andrews, Kazemi, and Hardy,[71] in 1967 found that in addition to a restrictive pattern of dysfunction, 39 percent of their 41 patients studied showed changes of obstructive lung disease developement. Patients with an obstructive defect fared worse clinically, with cor pulmonale developing in many. The factors which determined whether airway obstruction or restrictive defects occurred in beryllium workers were largely unknown, but pointed up the value of multiple lung function criteria, particularly forced expiratory volume at 1-second ($FEV_{1.0}$), peak flow (PF), and maximal breathing capacity (MBC).

Animal Toxicity

(1) Toxicity and Potential Health Hazards

A sufficient number of animal toxicity studies have been reported[64] to permit the following generalizations. Soluble beryllium salts (as represented by the sulfate and fluoride), low-fired high surface-area oxide, the hydrated oxide, beryllium hydroxide, and the metal powder in adequate concentration are rapidly (acutely) toxic by all routes of administration.[72,73] when the inhaled concentrations are high, acute and chronic pneumonitis are produced, often following a single exposure. In general, the more soluble, the more rapid and severe is the acute response.

The correlation of biologic activity with chemical and physical properties is demonstrated by the lesser toxicity of beryllium oxide

prepared at 1600°C as compared with beryllium oxide calcined at 1100° and 500°C. The high-fired beryllium oxide induced a minimal cellular reaction and fewer adenocarcinomas as compared with that produced when the low-fired (500°C) compound was injected in rats intratracheally.[74]

Although there are varying quantities of beryllium in the different alloys and beryllides, the intermetallic forms of beryllium and certain alloys of low beryllium content produce little or no activity in rats intratracheally injected with these substances. The fact that no frank beryllium lung disease occurred in experimental animals from these alloys is in conflict with the report of beryllium disease in workers exposed to beryllium-copper alloys,[75] possible a reflection of species or habit differences.

Bertrandite and beryl ores containing 4 percent beryllium have been reported to have tumorigenic capability whereas, in comparison, bertrandite ore containing less than 1.5 percent beryllium lacks this capability.[76] The lack of tumor induction by phenacite ore (1.5 percent beryllium content) parallels the finding with bertrandite of similar beryllium content.[76]

In general, soluble beryllium salts and some of the more insoluble beryllium compounds produce acute inflammatory reactions in animals. Major factors which influence toxicity include solubility, particle size, and percentage of beryllium in the compound. The rate of biological response seems to be related to the rate of solubility. About half of the industrially important forms of beryllium readily induce pulmonary tumors, particularly in the rat, a response that has not yet appeared in beryllium workers. The more rarely produced osteogenic sarcoma and rickets are peculiar to experimental animals, although the granuloma of the skin with ulcer occurs in man as well.

experimental animals

(2) Absorption, Fate, and Excretion

Beryllium is demonstrably toxic by most routes of administration; the routes most commonly employed in animal experiments being intravenous, intraperitoneal, inhalation, intratracheal instillation, subcutaneous, and oral.[77] Noticeable, however, is the difference in oral toxicity to that by other routes. The sulfate, highly toxic by all other routes at a single dose level, is practically nontoxic by mouth at a level several thousand-fold greater by multiple dose (3750 mg/kg/day).[78,79] Beryllium does not localize in the lung, but is transported to all tissues of the body.

(3) Beryllium Effects Peculiar to Animals

Beryllium is capable of inducing primary pulmonary cancer in animals. Evidence has accumulated incriminating a number of beryllium compounds; particularly beryllium oxide, hydroxide, sulfate, and fluoride; as carcinogens for experimental animals.[80]

Osteosarcoma, reported by many investigators using beryllium oxide and zinc beryllium silicate by different routes of administration,[81,82,83] appears to be a beryllium disease that has been demonstrated only in animals, possibly the result of massive exposures not encountered by beryllium workers.

Beryllium "rickets" is likewise a condition not seen in man, probably because the rickets were produced in young animals on diets with substantial amounts of $BeCO_3$ (0.5 and 2%),[84] conditions not met in the human situation.

A toxic macrocytic anemia that has been reported to result in animals exposed by inhalation to beryllium compounds and substantiated by demonstrated interference in both heme and globin synthesis[85] seems not to have been noted in individuals with beryllium disease.

Finally, the morphologic changes in the lungs of animals with alveolar metaplasia, do not resemble in all respects those seen in man.

(4) Biochemistry

Although a considerable number of biochemical investigations have been made during the past two decades,[64] both in the living animal and in tissues excised from animals exposed to beryllium, little of practical clinical value has resulted. The one promising early indicator of response, the interference in the activity of a generally distributed metal-activated enzyme of beryllium,[86] was abandoned when later investigations[87] failed to show a consistent depression in enzyme activity in animals exposed to beryllium throughout a 15-month period.

Beryllium has been found to have especial affinity for intracellular inclusion bodies.[88,89] Further, in guinea pig studies, beryllium has also been found to localize in the granular layer of the skin.[90] As alkaline phosphatase comprises about 50 percent of this layer, it has been surmised that beryllium is bound to the phosphatase.

General adrenal imbalance is proposed as a governing mechanism for the sudden onset of "latent" beryllium disease months and years after exposure to beryllium has ceased by causing tissue redistribution of beryllium into sensitive body sites, resulting in a more severe systemic reaction.[91]

Attempts to find, by animal experimentation, effective therapeutic agents that would rid the body of deposited beryllium[92,93] have met with no human success of clinical importance, at least where long-deposited beryllium is concerned.

beryllium is concerned.

(5) Limitations of Experimental Toxicology

An exact parallelism in the response of animals and man does not always exist. Animals respond toxicologically to beryllium with changes that are morphologically different from those observed in man. In the rat, epithelialization has ultimately resulted in development of an adenomatous tumor. The epithelial proliferation and primary pulmonary cancer was induced in rats after long-term, daily repeated exposures to beryllium sulfate at an average concentration of 643 $\mu g/m^3$ (55 $\mu g/m^3$ of beryllium) and has not been reproduced in man even after long periods of time and high exposure levels. In man, the granulomatous disease seems only to be progressive in this respect. Hence, the carcinogenic exposure-effect relationship observed in animals does not correlate to man. The human organism has not been observed to respond in the same manner as rats to beryllium exposure; therefore, animal studies contribute only indirectly and provide no correlation of human exposure-effect relationships as they pertain to development of a recommended environmental standard.

Beryllium Case Registry

The Beryllium Case Registry was instituted in 1951[54] at the Massachusetts General Hospital to provide a central source for cases of diagnosed beryllium poisoning. Prior to beginning the Registry, a report[94] in 1948 had compiled 108 chronic cases and analyzed them by industrial process. By 1958, the Beryllium Case Registry had recorded 393 chronic cases out of a total of 606;[95] twenty-seven originally acute cases had become chronic. As of 1963, 675 cases were on record,[96] 760 as of 1966,[54] and 822 as of this writing (May, 1972). Annually reported Registry cases decreased considerably following institution of industrial control measures in 1949; nevertheless,

approximately 15 cases per year have consistently have been added to the Registry since 1962.

Chronic beryllium disease has occurred subsequent to the institution of control measures in 1949. Peyton and Worcester[95] reported 10 cases in the Registry (4 acute and 6 chronic) whose first exposures occurred after 1949. In addition, follow-up and new cases of chronic beryllium disease reported by Lieben and Williams[97] imply, from the relatively young ages of some patients, that chronic beryllium disease has been contracted from initial exposures subsequent to 1949.

A 1972 inquiry to the Registry[98] for cases of chronic beryllium disease contracted from initial exposure subsequent to 1949 produced at least 20 case histories; ten representative examples are shown in Table V. The majority of these cases have been diagnosed subsequent to 1965 and have involved direct handling and the resulting inhalation of beryllium. Of interest is that recent cases are occurring not only in smelting and extraction operations, but also in alloy and ceramics operations where contaminant control reportedly has been quite successful. Although environmental exposure levels are generally difficult to relate to individual patients, two items are presented in Table V. For the alloy worker, operations were performed without proper ventilation and exhaust installations. This case occurred from machining and polishing an alloy containing approximately 0.6 percent beryllium. The second example involved a machine-shop operator having maximum daily-weighted average exposures of 5.9 μg Be/m^3 according to the employer.[98] However, the worker was involved in maintenance activities and, from his own report, hood doors were frequently

left open during machining operations. It is apparent that exposure levels were probably much higher than reported.

It is interesting to note that the estimated duration of exposure ranged from 6 weeks to 9-1/2 years for the cases listed in Table V. This would seem to indicate that for development of chronic beryllium disease, comparatively short time intervals are all that are necessary at the relatively low levels believed to be found in industry since 1949.

The Director of the Registry also indicates that the incidence of confirmed chronic beryllium disease is continuing and at least three new cases will be admitted to the Beryllium Case Registry in 1972.[98]

Information from the Beryllium Registry has been valuable in (1) criteria selection for diagnosis of beryllium poisoning, (2) judgment of effectiveness of controls, and (3) evaluation of the clinical course of beryllium disease and response to therapy. Hardy[54] points out, however, that there are three important deficiencies in the Registry: (1) lack of knowledge of the size of population at risk; (2) incomplete data describing the amount of beryllium exposure; and (3) failure to learn of all cases of the disease in a beryllium-using industry.

Neighborhood Cases

The term "neighborhood case" has been applied to a patient in which beryllium disease has developed as a result of what is believed to be indirect exposure outside a plant. Neighborhood cases of beryllium exposure were first recognized by Gelman in 1938.[11] Additional reports of non-occupational cases were reported[25,99,100,101] in individuals either living in close proximity to beryllium handling plants (generally within one mile) or having some direct contact, sometimes unknowingly, with beryllium. An example is given[28,99] of a woman whose daughter, a worker

in a fluorescent lamp plant, came home from work daily with a fine powder on her shoes and in her clothes. The daughter herself developed chronic beryllium disease. During the two-year course of the steadily progressive and finally fatal disease, she was cared-for by the mother, who subsequently also developed the disease and died. By 1966 a total of 60 neighborhood cases had been reported.[54]

In 1949, an extensive community program was conducted in the locality of a beryllium processing plant.[25] From a review of the program's approximately 10,000 X-ray films and multiple air analyses, there emerged recommendations for in-plant and community atmospheric limits for beryllium (see section on Development of Standard).

In nearly every instance of a reported neighborhood case, close examination of the circumstances indicates exposure to be caused, or contributed to, by means other than ambient air pollution. Factors involving laundering of work clothes, having relatives who were beryllium refinery employees, having a milk route within a plant neighborhood, house-cleaning requirements, etc., have all been reported.[97] In one instance, individuals affected lived several miles away from the industrial site but were found to have visited a graveyard and to have tended graves regularly across the street from the beryllium refinery.

It has yet to be definitely established whether ambient air contamination alone, at a distance from a plant, can cause chronic beryllium disease.

Correlation of Exposure and Effects

Clinical findings in some current chronic beryllium disease cases indicate recent initial exposures, and there are new cases of the disease still being reported.[98] Nevertheless, extreme difficulties are presented when attempting to correlate workroom exposure levels of beryllium with

cases of either acute or chronic beryllium disease. The absence of quantitative data on exposures to beryllium in reports prior to 1947 is understandable since (1) airborne beryllium had not at that time been conclusively identified as a cause of disease and (2) no reliable analytical methods had been developed.[102] Undoubtedly, extremely high concentrations were encountered (see Environmental Data).

From 1949 to 1961, controls were imposed by the AEC on industrial beryllium producers through specific contract requirements to meet occupational standards. In some cases industry did not meet the AEC standards that were developed. Little is known of the environmental conditions since 1961.

A survey was performed in 1968 by the U.S. Public Health Service in which 1600 employees were studied from four beryllium production plants. Chest X-rays were taken and gaseous diffusion tests with spirometry measurements were performed in conjunction with a selected questionnaire. Results obtained from the study indicated the possibility of beryllium related pulmonary impairment in isolated cases; however, the data were inconclusive.[103]

A retrospective cohort study of cause-specific mortality among 3,921 males employed in two beryllium plants during January, 1942 through December 1967, was conducted.[104] Comparison was made between the risk of death among beryllium workers with that expected on the basis of age-sex-calendar time of specific mortality rates for the general population. of the United States (Tables VI to X).

Mortality patterns, including mortality from respiratory tract cancer, revealed no significant departure from expectation in this population. Even when consideration was given to a lapsed time of ten years and of fifteen

years after onset of employment, no evidence was demonstrated for an association between beryllium exposure and lung cancer induction in man. Likewise, no association was detected for intensity, duration, or calendar period of exposure to beryllium.

Certainly, exposure levels today are well below those encountered in the early 1940's. Whether a large safety factor is present in the current occupational environment exposure standard for beryllium is unknown. There has been no comprehensive, long-term control study relating environmental beryllium concentrations with a cause-and-effect relationship to beryllium disease; therefore, the level to which a revised standard could be recommended is largely one of conjecture.