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I hereby recommend that the thesis prepared under my supervision by Ian Maclachlan, M. D.

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BERYLLIOSIS

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CHAPTER I

PROPERTIES OF BERYLLIUM

Beryllium (or glucinum) is an element of the magnesium group. It is a hard grayish-black metal, the salts of which have a sweetish taste. This property accounts for the alternate name of glucinum which is still used in the French literature. The oxide of the metal was discovered in 1797 by L. N. Vauquelin (54); it was not until 1828 that the pure metal was isolated by Wöhler (57).

The metal, atomic number 4, has an atomic weight of 9.02. The density of the metal is given as 1.85 at 20°C. and its melting point is listed as 1285°C. (18). Beryllium combines with certain metals to give alloys with desirable properties. Thus, when alloyed with copper, the product has a greater electrical conductivity than copper itself, and is ductile, capable of being cold-formed into various shapes. On cooling, after being treated with heat, the alloy becomes very hard and resistant to fatigue (25).The alloys of beryllium and aluminum are possessed of great strength while being lighter than aluminum by itself. The silicate, sulfide, and tungstate of beryllium fluoresce strongly and the compounds are useful for fluorescent lighting (39).

Chemically, the metal is slightly less basic than magnesium. The reactions of its salts in many respects, however, are similar to those of aluminum. The metal is relatively inert and is little affected by air or by water, but is readily attacked by fluorine, chlorine, and bromine. Beryllium metal is readily soluble in dilute solutions of hydrochloric and sulfuric acids (34).

CHAPTER II

THE USES OF BERYLLIUM

The earliest use of beryllium was in the manufacture of gas mantles, where its addition as the nitrate (0.2 - 0.5 per cent) increased the strength of the mantle. Since 1940, however, the metal has found increasing uses, and today because of its properties, it is used extensively in numerous technical processes and manufactured products.

Alloys of beryllium and copper resist corrosion and can be rolled, drawn, stamped, cupped and spun. After a suitable treatment with heat, the alloys are possessed of great tensile strength, become hard, and are resistant to fatigue. These alloys may also be used for casting (26).

Certain copper-beryllium alloys also have high electrical conductivity, and these find particular application as resistance welding electrodes and for current-carrying springs and switch parts.

Beryllium oxide has been mixed with zinc oxide, silica, and other substances to make phosphors for fluorescent lighting tubes. The phosphor is applied as a coating on the inner surface of the fluorscent lamp tubes. It must have the property of emitting visible light when activated by the ultraviolet rays from mercury vapor. The beryllium content of the phosphors has varied from 16 per cent to 2 per cent. During the second world war, when the health hazards associated

with the use of beryllium compounds came to light all American manufacturers of fluorescent lights joined in the use of formulae in which the concentration of beryllium was maintained in the low range, and more recently, phosphors free of this substance have supplanted those which contained beryllium. Compounds of beryllium are used to make neon sign tubing, refractories (crucibles), luminous indicators, vitreous enamels in ceramics, and certain textile fibers.

The pure metal is remarkably transparent to X-rays, and therefore it is used as windows for X-ray tubes. It is said to be seventeen times as transparent as aluminum (26). A type of beryllium glass is also especially useful in X-ray tubes as a window to filter out stray or reflected electrons in X-ray beams (25).

Very small amounts of beryllium are added to magnesium alloy to prevent drossing and burning during melting, as well as to make the cold metal less susceptible to ignition. It is added also in small amounts to aluminum to enable it to resist tarnishing when employed for a number of purposes such as in the fabrication of cooking utensils (26).

Alloys of beryllium and nickel are strong and hard. A strip of such an alloy, when properly treated with heat, has a tensile strength of 270,000 pounds per square inch (26).

With the development of interest in the physics of atomic nuclei, beryllium has become a highly important substance as a source of neutrons in the manufacture of certain radioactive elements in cyclotrons.

CHAPTER III

INTOXICATION DUE TO BERYLLIUM AND ITS COMPOUNDS

The disease which is caused by beryllium and its compounds is usually the result of occupational exposure. In most cases, the lesions are confined either to the skin or the lungs; occasionally they involve the conjunctiva, upper respiratory tract and internal organs. These lesions are characterized by two types of tissue reaction, and acute inflammation and a fibrotic granulomatous condition; in those cases where the lung is involved, these may be two stages in the same reaction.

History

Industrial intoxication due to beryllium and its compounds was reported in Germany in 1933 (56), in Italy in 1935 (16) and in the U.S.S.R. in 1936 (17). Further reports came from Germany in 1940 and 1942 (2, 35, 58). Fabroni, the Italian author (16), concluded that the type of lung damage produced by the inhalation of beryllium dust was typical of beryllium itself, but the other authors, whose experience was confined to exposure to beryllium compounds containing a fluoride radical, concluded that the latter radical was the etiological agent.

Beryllium has found increasing industrial use in the United States during the past ten years. In 1943, investigations carried out by the U.S. Public Health Service (25), appeared to confirm the opinion of the European authors who had concluded that the fluoride radical was the cause of disease in beryllium plants, and led that agency to issue

a report which stated that beryllium is, of itself, not toxic. It stated further that "whatever toxicity has been found to occur with the beryllium salts is due to the toxicity of the acid radical such as the fluoride or oxyfluoride, or to an objectionable condition brought about by the hydrolysis of certain of its salts, such as the chloride and sulfate." In that same year, and in each subsequent year, reports of industrial intoxication following exposure to beryllium and its compounds have appeared in the American literature, providing an ever increasing body of evidence which seriously compromises the conclusion that the toxicity resides in the acid radical of beryllium compounds.

The clinical manifestations of berylliosis, in the United States, have been observed among workmen in plants in which beryllium compounds are produced from beryl ore, and in others in which men were exposed mainly to metallic beryllium, beryllium oxide and fluorescent powder containing beryllium oxide. Cases of intoxication in plants of the former type, in which the principal exposure arises from the use of beryllium compounds containing fluoride and sulfate, were described by Van Ordstrand et al. in 1943 (51) and 1945 (52) and by De Nardi et al. in 1949 (8, 9). Cases associated with exposure to the metal, its alloys and oxides and to the phosphors were reported in 1944 by Kress and Crespell (27), in 1946 by Hardy and Tabershaw (20), and, in subsequent years, by others. These clinical manifestations appeared at first to be divided into two distinct groups:

those in the industries in which men were exposed to beryllium compounds containing fluoride and sulfate radicals (dermatitis, conjunctivitis, nasopharyngitis, tracheobronchitis and acute pneumonitis), were all acute, while in the industries in which workmen were exposed to beryllium metal, beryllium oxide, or beryllium-containing phosphors, the disease was a chronic granulomatous and fibrosing process in the lungs. Although this distinction is still evident, the occurrence of cases of acute pneumonitis, following exposure to the relatively insoluble metallic beryllium, beryllium oxide and phosphors, has served to form a link between the two groups.

Experimental evidence proving that beryllium is the etiological agent of these diseases is not complete. Although experiments concerned with ascertaining the LD_{50} of soluble compounds of beryllium have shown that they are highly toxic (24, 41), similar experiments carried out with the insoluble compounds have not resulted in acute reactions (24). Acute pneumonitis has been produced in animals following exposure to both soluble (47) and insoluble (13) beryllium compounds, but attempts to reproduce the picture of chronic pulmonary granulomatosis have been only partially successful (13, 44). Recently, granulomas of the subcutaneous tissues have occurred in pigs, following the implantation of fluorescent powders containing beryllium oxide (13).

Studies of the metabolism of beryllium have been handicapped until recently by the difficulty of measuring minute quantities of beryllium in body tissues and fluids.

The development of a sensitive analytical method (5) and the use of a radioactive beryllium isotope have done much to facilitate this type of research, so that understanding of the absorption, distribution and excretion of beryllium is increasing.

Environmental studies in the beryllium-using industries have served to relate beryllium and certain of its compounds to the occurrence of typical clinical manifestations of intoxication (29, 14), but many discrepancies prevent close correlation of disease with severity of exposure; until these discrepancies are resolved only tentative maximal allowable concentrations in the atmosphere of industrial establishments or elsewhere can be recommended.

Epidemiology

Industrial exposure

The clinical manifestations of intoxication due to beryllium are:

1. Acute manifestations (other than acute pneumonitis): contact dermatitis, skin ulcers, conjunctivitis, nasopharyngitis, tracheobronchitis.
2. Acute pneumonitis.
3. Chronic manifestations: pulmonary granuloma, skin granuloma.

Clinical manifestations of the first type have been reported (52) as occurring in plants where beryllium compounds are manufactured from the ore, and have been related

to exposure to dust and mist of beryllium sulfate, dust and fume of beryllium fluoride and fume of ammonium beryllium fluoride (14).

Acute pneumonitis has been reported from the industry in which beryllium compounds are manufactured from the ore (52, 14), where men were exposed to dust and mist of beryllium sulfate, dust and fume of beryllium fluoride, dust and fume of beryllium oxide and dust of beryllium metal; from the fluorescent lamp manufacturing industry where phosphor dust was the source of exposure (32, 27); from the ceramic industry where exposure to beryllium oxide dust occurred (1), and from a shop in which beryllium metal was being machined, cast and welded, thereby giving rise to exposure to fume and dust of beryllium metal and beryllium oxide (1).

Pulmonary granulomatosis has been reported from a variety of industries (see table 1), and has been related to exposure to dust of beryllium metal, beryllium oxide and phosphor. This form of the disease has also occurred among people living in the immediate neighborhood of plants producing beryllium compounds from ore and of plants manufacturing fluorescent lamps. Skin granulomas have occurred in people who had cut themselves with fragments of broken fluorescent lamps, or who had bits of metallic beryllium implanted into the dermis.

None of these evidences of intoxication have been associated with the mining, shipping or handling of beryl ore.

The clinical manifestations of the first two types are characterized by an acutely inflammatory tissue reaction;

the clinical manifestations of the third type are characterized by a chronic granulomatous and fibrotic tissue reaction. The relationship between industry, type of material involved, clinical manifestation and tissue reaction is presented in Table I.

Table I

Industry	Material to Which Men Were Exposed	Clinical Manifestation	Tissue Reaction
Producing compounds from ore	Dust and mist of beryllium sulfate. Dust and fume of beryllium fluoride. Fume of ammonium beryllium fluoride.	Acute (other than acute pneumonitis) Acute pneumonitis	Acute inflammatory
	Dust and fume of beryllium oxide. Dust of beryllium metal.	Acute pneumonitis	Acute inflammatory
Manufacturing fluorescent lamps Preparing phosphors	Dust and fume of phosphor and beryllium oxide	Acute pneumonitis Pulmonary granuloma	Acute inflammatory Granulomatous and fibrotic
Manufacturing ceramics	Dust of beryllium oxide	Acute pneumonitis Pulmonary granuloma	Acute inflammatory Granulomatous and fibrotic
Machining, casting and welding of beryllium metal or beryllium alloys	Fume and dust of beryllium metal and beryllium oxide.	Acute pneumonitis Pulmonary granuloma	Acute inflammatory Granulomatous and fibrotic
Alloying beryllium Crystal manufacture	Dust of beryllium oxide	Pulmonary granuloma	Granulomatous and fibrotic
Neighborhood of plants producing beryllium compounds and of plants manufacturing fluorescent lamps	Exhaust from plants	Pulmonary granuloma	Granulomatous and fibrotic

Etiology

Beryllium compounds containing an acid radical. It may be seen from Table I that the beryllium compounds that contain sulfate or fluoride radicals are associated with clinical manifestations that are characterized by an acute inflammatory reaction. Two possible etiological mechanisms suggest themselves: either the inflammation is caused by the beryllium itself, or it is caused by the acid radical of the compound. It is quite possible that certain of the lesions are due mainly or wholly to this acid radical, and that others are due to the metal. With our present knowledge it is not possible to settle these issues, but the evidence favors the first. It is true that both hydrogen fluoride and sulfuric acid will cause an acute inflammatory reaction in tissues with which they come into contact. On the skin, this takes the form of a burn, the severity ranging from simple erythema to complete charring, depending on the concentration of the acid at the point of contact. On the other hand, there is no salt of hydrogen fluoride, other than beryllium fluoride, that has been associated with a high incidence of contact dermatitis. Nor have the sulfates, other than beryllium sulfate, been so implicated, in spite of the fact that several sulfates are used in therapy; i.e., externally in wet dressings, orally as saline purgatives, and intravenously as diuretics.

When hydrogen fluoride gas or sulfuric acid fume is inhaled in sufficient concentration either will produce

acute chemical pneumonitis. Minimal effects are produced only after the maximal allowable concentration, 3 parts per million in both instances, is exceeded. Two environmental studies, conducted in plants where there was an exposure to beryllium fluoride, have indicated that pneumonitis has occurred after exposure to less than the maximal allowable concentration of fluoride. This would seem to indicate that beryllium was the etiological agent. Eisenbud et al. (14) report the concentration of fluoride that existed during an exposure to beryllium fluoride which resulted in the occurrence of three cases of acute pneumonitis, as less than 3 milligrams per 10 cubic meters of air. The maximal allowable concentration of hydrogen fluoride, expressed in terms of weight of fluoride, would be 23 milligrams per 10 cubic meters of air. Shilen et al. (43) studied the health hazards in a plant producing beryllium oxide at a time when beryllium was considered to be non-toxic. They found that, at various operations where there was an exposure to beryllium fluoride and where cases of dermatitis and pneumonitis had occurred, the concentration of fluoride, expressed as sodium fluoride, ranged from 0.414 to 40.6 milligrams per 10 cubic meters of air. The maximal allowable concentration of hydrogen fluoride, expressed in terms of sodium fluoride, would be 51.53 milligrams per 10 cubic meters.

Animal experiments have also tended to incriminate beryllium rather than the acid radical. Scott (41) has found that the LD_{50} of beryllium sulfate, when administered

intravenously to rats, is only 7.2 milligrams per kilogram, a dose far too small for the lethal action to be ascribed to the sulfate. Hodge et al. (24) have determined the LD_{50} of various beryllium compounds when administered intraperitoneally to rats; the LD_{50} of beryllium oxyfluoride in aqueous solution was 13 mg./kg. for mature animals and 42 mg./kg. for weanling animals; of beryllium sulfate-hydrate in aqueous solution, 50 mg./kg. for mature animals; and of beryllium sulfate-hydrate for mature animals, 110 mg./kg. in aqueous solution and 200 mg./kg. in saline solution. In each instance the dose was too small for the lethal action to be attributed to the acid radical. Stokinger et al. (47) report that grades of acute response to the inhalation of beryllium sulfate mist have ranged from death for the majority of laboratory species at 100 and 50 milligrams of beryllium sulfate hexahydrate per cubic meter of air to just detectable injury in some species at 1 milligram, (40 micrograms of beryllium per cubic meter). The intermediate level of 10 milligrams per cubic meter constitued an LD_{50} for rats only, but produced typical chemical pneumonitis in most species. To demonstrate that this pathological change is due to beryllium itself and not to the sulfate radical, Sprague et al. (46) substituted sodium acid sulfate solution, with a pH of 1.7, equivalent to that of beryllium sulfate solution, for the beryllium salt solution. Twenty guinea pigs and 10 rats were exposed daily for more than two weeks to 75 milligrams per cubic meter of the acid sulfate salt. Seventy-five milligrams per cubic

meter of monosodium acid sulfate is equivalent to 60 milligrams per cubic meter of sulfate ion; 100 milligrams of beryllium sulfate hexahydrate per cubic meter is equivalent to 45 milligrams of sulfate ion per cubic meter. No pathological changes that could be attributed to the exposure were found in any of the animals.

Stokinger et al. (48) have demonstrated that hydrogen fluoride has a potentiating effect on beryllium poisoning by inhalation. They found that hydrogen fluoride vapor inhaled by rats at the concentration of 8 milligrams per cubic meter of air produced a twofold enhancement of the toxicity of a soluble beryllium salt (beryllium sulfate hexahydrate at the concentration of 9 milligrams per cubic meter of air), inhaled by these rats. These authors recognize that the mechanism by which this occurs is obscure. They suggest three possibilities. First, it is possible that fluorine combines with beryllium in vivo, forming beryllium fluoride, a more toxic compound than beryllium sulfate (50). Second, increased ventilation may result from pulmonary injury due to hydrogen fluoride causing an increase in the retention of beryllium during inhalation of beryllium sulfate mist. A third possibility is that hydrogen fluoride and beryllium may behave independently in the body and yet give the appearance of a potentiating action. The concentration of hydrogen fluoride used in this experiment was approximately 3 times the maximal allowable concentration. Exposure to this concentration of hydrogen fluoride has resulted in the death of 4 of 34 rats (37).

Metallic beryllium, beryllium oxide, phosphors. If we turn again to Table I, we see that metallic beryllium, beryllium oxide, and beryllium phosphors are most often associated with clinical manifestations that are characterized by a granulomatous and fibrotic tissue reaction, but that sometimes they are associated with clinical manifestations that are characterized by an acute inflammatory reaction. Let us consider the possibility that these chemicals cause the tissue reaction with which they are associated.

The strongest evidence in support of this possibility has been supplied, fortuitously, by cases of skin granuloma occurring in persons who cut themselves on broken fluorescent lamps. Here the subcutaneous tissue is contaminated by phosphor. The granulomas which result resemble each other and the granulomas that are found in the lungs of fatal cases of chronic berylliosis (10). Experimental evidence that beryllium will cause an inflammatory response accompanied by fibrosis has been presented by surgeons who have studied the use of metals in repairing bone defects (4). They found that an alloy containing nickel, cobalt, chromium, and molybdenum produced no tissue reaction, but that the addition of 1.6 per cent of beryllium to the alloy caused the formation of "chronically inflamed granulation tissue containing many macrophages," and extensive fibrosis with marked lymphocytic infiltration.

The absence of any other possible exposure relates many cases of chronic berylliosis to either beryllium metal, beryllium oxide, or phosphors and forms evidence that they

are the etiological agents of the disease. Experimental attempts have failed thus far to produce in the lungs of animals the granulomas seen in human cases, but pulmonary fibrosis, similar to that seen in human cases, has been produced after several years, by the repeated introduction into the trachea of a phosphor (44) and beryllium oxide (13). Acute pulmonary disease has been produced in rats, with death of all animals in from 100 to 350 days, by intratracheal injection of finely divided, freshly ground beryllium metal (28).

The fact that beryllium metal, beryllium oxide, and phosphors are associated occasionally with acute pulmonary disease rather than the usual chronic form can only be explained on the basis of more effective exposure or by increased individual sensitivity. As will appear later in the discussion, the two forms of the disease are clinically and pathologically related, being different stages of the same general process. Dutra (10), in discussing the pathology, states that he was able to see a progression from the most acute to the most chronic cases; from a stage of acute inflammation through one of the organization of exudate to one of the formation of granulomas. Chronic cases have usually followed long exposure to low concentrations; acute cases have usually followed short exposure to high concentrations.

Levels of exposure

Beryllium fluoride and beryllium sulfate. In the only detailed environmental study of these compounds to be

published to date, Eisenbud et al. (14) state that all their cases of acute pneumonitis were associated with concentrations of beryllium in excess of 0.1 milligram per cubic meter of air, and that exposure to concentrations of 1.0 milligram per cubic meter resulted consistently in the development of cases among exposed personnel. It would appear that if the concentration of these compounds is kept below 0.1 milligram per cubic meter of air, expressed as beryllium, (1.0 milligram per 10 cubic meters), acute pneumonitis would be prevented. Since these compounds have not been freed of responsibility for the production of chronic pneumonitis, it is not possible to say whether this concentration is safe in all respects.

Beryllium oxide, beryllium metal and phosphors. Data on the intensity of the exposure to these chemicals which is likely to be responsible for the production of disease is not yet adequate. Machle (29) states that there is evidence that cases of the disease will occur when exposure to beryllium oxide, (expressed as beryllium), exceeds 100 micrograms per cubic meter of air. The same author has also stated (30) that where the mean concentration was 10 micrograms of beryllium oxide per cubic meter (expressed as beryllium), with a range up to 70 micrograms, there were no cases among persons exposed over periods ranging from three to five years. Eisenbud et al. (14) found that the daily inhalation of 4.0 milligrams of beryllium oxide, (expressed as beryllium), was associated with a high incidence of acute pneumonitis, while in another operation the daily inhalation of 300.0 milligrams

of beryllium oxide, (expressed as beryllium), produced no cases of acute pneumonitis. Eisenbud states that this illustrates the extraordinary variability of the toxicity of the oxide, and suggests that this variability may be a function of its physical properties. Until more is known of the influence of physical properties on the toxicity of beryllium oxide, it would appear to be wise to keep the concentration to 10 micrograms per cubic meter, (0.1 milligram per 10 cubic meters).

The concentration of metallic beryllium that will produce disease is the same as the concentration of beryllium oxide that will produce disease. It is doubtful if beryllium metal, as such, is ever inhaled. Beryllium has a marked tendency to oxidize, both at elevated temperatures associated with machine cutting, welding or casting, or at ordinary temperatures where small particles are exposed to the atmosphere.

The problem of finding a safe level of exposure to beryllium-containing phosphors is now academic, since beryllium is no longer used for this purpose. However Machle (29) states that the disease has failed to put in its appearance among workmen exposed for six years to beryllium phosphors under conditions in which the concentration of beryllium in the atmosphere of the workmen ranged from 2 to 8 micrograms per cubic meter of air.

Physical properties

Solubility. The beryllium compounds that contain acid radicals are relatively soluble, and the oxide and the

phosphors are relatively insoluble. This difference in solubility is thought to be the reason for the difference in the type of tissue reaction typically caused by each of these compounds. If we accept the possibility that the etiological agent in the compounds containing fluorides and sulfates is beryllium rather than the acid radical, we may reason that the greater relative solubility of such compounds, as compared with the metal or its oxides, would enable more ionized beryllium to be brought more quickly into contact with tissue, so that the resulting tissue reaction would be more acute.

A study (40) of the solubility of beryllium oxide and phosphor has shown that the former reaches saturation, (20-30 micrograms per liter), after three days, and the latter, (0.06 microgram per liter), after 19 days. It is likely that these characteristics account for the slow production of disease by these compounds if, as is probable, the beryllium must be ionized before it can produce a typical pathological reaction.

Some light has been thrown on the problem of the extraordinary variability in the toxicity of beryllium oxide, mentioned by Eisenbud et al. (14), by studies now being conducted by Hodge and his associates at the University of Rochester (3). An examination of beryllium oxide particles, by means of the electron microscope, has shown that if the particles have been poorly fired, they present a fluffy, many surfaced appearance, while the well fired particles appear

as smoothly rounded "clinkers". The poorly fired particles have much more surface area per unit weight and presumably would be more soluble than the well fired particles. Eisenbud et al. (14) found that in all their acute cases due to the oxide, freshly heated material was involved. It may have been that this freshly heated material contained a high percentage of poorly fired particles.

Particle size. It is probable that dust and aerosol particles of beryllium compounds behave as do dust and aerosol particles in general, and that particles 10 to 15 microns in diameter are captured in the nose, particles 5 to 10 microns lodge in the bronchial tree, particles less than 5 microns reach the terminal bronchioles, alveolar ducts and alveoli and that particles of the order of 1 micron predominate in this area. However, there have been few investigations of the particle size of beryllium compounds involved in outbreaks of berylliosis. An early report from Russia (59) states that, in a fume of beryllium oxyfluoride which gave rise to cases of acute pneumonitis, 71 per cent of the particles were less than 0.5 micron in diameter and 89 per cent were less than 1.0 micron. Kress and Crispell (27) in reporting two cases of acute pneumonitis due to phosphor containing beryllium state that the onset of the disease occurred three months after the mean particle diameter of the powder was changed from 5 microns to 2 microns. The patients had been exposed for two to three years to particles 5 microns in diameter without contracting berylliosis but

developed it after three months of exposure to particles 2 microns in mean diameter.

Toxicology

There is no evidence that beryllium plays any part in the normal physiology of mammals. Within the limits of available analytical methods, which are capable of detecting 0.1 microgram of beryllium per liter of urine or 0.3 micrograms of beryllium per 100 grams of tissue, the element is not found in the tissues or excretions of persons who have not been exposed to the metal or its compounds (29).

Absorption

There is no indication that beryllium is absorbed through the intact skin, nor is there any clinical evidence that significant quantities are absorbed through the damaged skin of persons suffering from contact dermatitis, skin ulcers or skin granuloma associated with exposure to beryllium compounds. Absorption by way of the gastro-enteric tract is poor. There have been no reports of human morbidity or mortality following accidental ingestion. Animal experimentation indicates that most of any orally administered beryllium compound passes through the alimentary tract unabsorbed and unchanged. When a dog was fed 30 milligrams of beryllium sulfate, 94 per cent of the dose appeared in the feces and only 1.6 per cent in the urine (25). Less than 0.2 per cent or radioberyllium sulfate administered orally was absorbed from the digestive tract (7). The solubility of the beryllium compound has considerable bearing on the degree to which it

can be absorbed. Relatively insoluble metallic beryllium or beryllium oxide can be incorporated to the extent of 5 per cent in the diets of rats without affecting their rate of growth, but the presence of 5 per cent of relatively soluble beryllium carbonate in their diet will completely inhibit their growth (33). Beryllium sulfate and beryllium oxyfluoride, both more soluble than the carbonate, are toxic to guinea pigs when the amounts administered comprise 1.4 per cent and 0.1 per cent of the diet, respectively (25).

Under occupational conditions, the principal absorption of beryllium takes place through the lungs. Some may be taken up directly into the blood stream, as evidenced by its prompt appearance in the urine of apparently healthy exposed persons, but a greater amount probably is absorbed only after it has been first taken up by the phagocytic cells, which transport it via the lymphatics to the blood stream. In fatal cases of acute pneumonitis, there tends to be a relatively high concentration of beryllium in the lungs as contrasted with the small amounts which are found in other organs; in fatal cases of the chronic pulmonary disease, while the concentration in the lung may still be high, larger amounts may be found in other organs, especially in the hilar lymph nodes (see Table II).

Table II

Beryllium in Tissues, Fatal Pulmonary Berylliosis
(Micrograms beryllium per 100 grams tissue)

Tissue	7 Patients with Acute Disease							10 Patients with Chronic Disease								
Lung	9	12	18	20	98	128	220	0*	0.24*	0.33	0.93*	1.6*	1.7	12	16.5	20	78
Hilar node		4							0.67	0.25	6.4					138	
Liver		0.5	0.41	4					0		1.5			8.4	2.0	0	
Spleen		0.4	0.48	0					0	0	0.17			4.3	0.43	0	
Kidney		6	0.74	0					0	0		0.54		27.2	0.18	0	
Rib		0.3		0										13.5	0.44	3.0	
Heart		0.2	0.16													0	
Brain																0	
Thyroid																0	
Blood		0.4															

* Non-occupational disease.

Distribution

Following the intramuscular administration of carrier free* radioberyllium sulfate to rats, the isotope was detected in all the organs and tissues as well as in the blood and excreta (7). The major portion of the absorbed isotope was taken up by the skeleton. Within 24 hours after injection the bone had accumulated 29 per cent of the absorbed radioberyllium sulfate and maintained this approximate level to the 64th day, when the bone contained 27 per cent of the absorbed material. The initial concentration of the liver and kidney was comparable to that of the skeleton but was followed by more than a 10-fold decrease by the 64th day. The radioberyllium sulfate content of the spleen and muscle remained relatively constant throughout the experiment.

Differences in the distribution of radioberyllium were observed after intravenous administration of carrier free radioberyllium sulfate and after administration of beryllium sulfate solution consisting in small part of a radioactive isotope together with a larger amount of stable beryllium sulfate (42). These differences were thought to be due to low solubility of beryllium salts at the pH of body fluids. It is probable that the distribution of active isotope plus carrier in this experiment approximates the distribution of beryllium in the body of a person exposed to beryllium in industry more nearly than does the distribution

* "Carrier free" is a term used (7, 42) to indicate minute amounts of radioactive beryllium sulfate. Radioberyllium sulfate plus carrier designates a mixture of beryllium sulfates made up with minute amounts of Be^7 and considerably larger amounts of the stable isotope Be^9.

of active isotope alone. It was found that the isotope alone was cleared rapidly from the blood, (80 per cent in 7 minutes, reaching a steady level of equilibrium with extra-vascular tissue and fluid after two hours, when 98 per cent of the dose had been cleared from the blood), and it was thought that this was probably the result of a rapid uptake by the skeleton. When the radioactive isotope plus carrier was administered, its clearance from the blood was slower, (80 per cent in 3 hours and 20 minutes; 95 per cent in 6 hours) and it was thought that this indicated that some of the beryllium was insoluble and that its removal from the circulation was brought about in part by the reticulo-endothelial system, since in this experiment the amounts found in the liver, spleen and bone marrow were larger than when the active isotope was given alone.

These experiments, in which it was possible to use less than the toxic dose of beryllium, correlate well with experiments in which toxic doses of beryllium compounds have been administered parenterally and by inhalation, Scott (41) has found, in experiments of this type, in which the compound used was hydrated beryllium sulfate, that the principal lesions which occurred were midzonal necrosis of the liver, necrosis of the distal third of the convoluted tubules of the kidney, and degenerative changes in the spleen and bone marrow.

There is no information available as to the exact toxic effect of beryllium on tissue. It seems that damage

is done to individual cells and that most of the microscopic changes are the expression of repair on the part of the tissue involved.

Excretion

Beryllium that has been absorbed is excreted mainly by the kidneys but also to some extent by the intestine (7, 42). Excretion begins immediately after absorption. When a single dose of carrier free radioberyllium sulfate was given intravenously to rats or rabbits (42), approximately 25 per cent of the dose was excreted in the first 24 hours. On following days there was a gradual decrease in excretion each day from an average of about 1 per cent of the total dose on the 2nd day to 0.4 per cent on the 7th day.

The amounts of beryllium in the urine of apparently healthy persons exposed to beryllium dust and fume approximate the amounts found in the urine of patients suffering from the clinical manifestations of beryllium intoxication (11). Thus the presence of beryllium in the urine is an indication not of berylliosis but of the absorption of beryllium. An additional fact of some clinical importance is that the excretion of beryllium in the urine of persons suffering from either acute or chronic berylliosis varies from day to day, so that one or more negative analytical results cannot be accepted as indicative of freedom from exposure to beryllium.

Clinical manifestations

Dermatitis

The skin lesions which have been noted in those who come in contact with beryllium compounds are:

1. Contact dermatitis
2. Skin ulcer
3. Granulomatous lesions which may be manifestations of systemic berylliosis, occurring in patients with the chronic form of lung disease.
4. Subcutaneous granuloma due to implantation of beryllium or a compound of beryllium.

Contact dermatitis. In 1933, Weber and Engelhardt (56) in Germany reported the occurrence of eczema of the face and hands in men exposed to beryllium fluoride and oxyfluoride. In 1936, Gelman (17), a Russian, reported erythema and papulo-vesicular eruption on the face, neck and hands of men exposed to beryllium fluoride. In 1945 Van Ordstrand et al. (52), in the United States, reported 42 cases of contact dermatitis occurring among workers exposed to beryllium sulfate, beryllium fluoride and beryllium oxyfluoride. This same group subsequently reported (9) additional cases due to the same exposure. All of the persons involved had been exposed to beryllium compounds containing sulfate or fluoride radicals.

Certain contributory factors appeared to operate in the production of any given case. In their report of 195 cases, De Nardi et al. (9) state that occurrence,

severity, and extent of the dermatitis were dependent on relative host hypersensitivity, concentration and duration of contact with the offending fumes and dusts, mechanical injury to the derma, excessive environmental humidity, excessive perspiration, failure of employees to observe safety precautions, and poor personal hygiene. With regard to hypersensitive individuals, the same authors noted that, of their 195 cases, 134 showed definite host hypersensitivity, that a high percentage of patients with severe dermatitis exhibited specific allergy to the compounds by developing an identical dermatitis upon a second exposure in spite of all protective precautions, and, also, that individuals who manifested extreme hypersensitivity by developing a dermatitis on first exposure often went on to develop bronchitis and pneumonitis.

In De Nardi's series (9) the dermatitis appeared in 25 per cent of workmen exposed after 3 to 10 days of exposure. The cutaneous lesions were typical of an eczematoid eruption, which varied in severity and involved the exposed portions of the hands, arms, face and neck, and occasionally, other areas of contact. It is characterized by erythema, which may be edematous, and to which may be added, in more severe cases, papules and vesicles. In the most severe cases, the vesicles rupture and coalesce, producing a weeping, denuded surface.

Treatment consists of termination of the exposure plus the routine therapy applicable to any contact dermatitis. No specific treatment is required.

Ulcers. Ulcers of the skin of workmen exposed to compounds of beryllium were first mentioned by Gelman (17) in 1936 but were not fully described until Van Orstrand et al. (52) did so in 1945. Again the offending agents are identified as compounds of beryllium containing the sulfate or fluoride radical.

In the production of an ulcer, minute crystals of the compound become imbedded in a small break in the skin, usually on the forearm or hand. The tissue surrounding the crystal is destroyed and an ulcer is formed. The surface layer of the skin tends to heal over the crystal inclusion and the ulcer crater, forming an indurated papule which undergoes necrosis and eventually forms a small abscess. Microscopically the affected skin shows a chronic exudative reaction with some attempts at healing. There is no evidence of the formation of a granuloma.

Treatment in both acute and chronic stages, includes incision of the papule, removal of the crystals in the acute ulcers and curettage of the fibrous base. Healing by second intention is complete within seven to fourteen days.

Granulomatous lesions which may be manifestations of systemic berylliosis, occurring in patients with the chronic form of lung disease. Hardy and Tabershaw (20) have described one case, Pyre and Oatway (37) one case, and Grier et al. (19) two cases in which small subcutaneous nodules appeared, apparently spontaneously, in the skin of patients with the chronic type of lung disease. The pulmonary berylliosis in

each instance had developed following exposure to phosphors containing beryllium oxide. The case of Hardy and Tabershaw is described as "a skin lesion on the side of an old burn on the right forearm" first noted two years after the last exposure. A biopsy of the lesion showed the microscopic picture of sarcoid. Pyre and Oatway's case had dusky purplish papules, 1 to 3 millimeters in diameter, on the dorsum of the hands and fingers, which were first observed 5 years after the last exposure. A biopsy of one of these showed "typical granulomata." One of Grier's cases is described as having a few small papules on the right arm and right leg below the knee and one or two on the left leg. These had all appeared over a period of three months, beginning some two years after the last exposure. His other case had many skin nodules on the extensor surface of the arms and on the back. Most of these had appeared over a period of two months, beginning 2-1/2 years after the last exposure. Biopsy of two lesions in each case showed granulomas in the corium of the type characteristic of chronic berylliosis.

It is not by any means established that these lesions are manifestations of systemic berylliosis. It may be that they were caused by implantation of small amounts of phosphor. Grier et al. (19) maintain that the delay in their appearance favors their systemic origin, and it should be added that in clinical appearance and course they differ from lesions definitely known to have followed implantation. However, it is possible that both the delay in onset and the clinical picture are the result of a method of implantation

less traumatic than that associated with being cut by a fragment of a broken fluorescent lamp tube.

No local treatment has been necessary in the cases reported.

Subcutaneous granuloma due to implantation of beryllium or a compound of beryllium. Subcutaneous granulomata occurring in persons who had cut themselves on bits of broken fluorescent lamps, coated on the inside with a phosphor containing beryllium oxide, were first described by Grier et al. (19) in 1948 in an account of 3 cases. Since then Coakley et al.(6) have described one case, Nichol and Dominguez (36) two cases, Dutra (12) four cases and Van Ordstrand (53) one case. There have been several other unreported cases. Dutra (12) has also reported a case in which a granuloma developed on the finger of a woman at the site of a laceration which occurred while she was engaged in machining metallic beryllium.

The clinical history of these reported cases is essentially similar. In all but two the initial injury was a laceration by a piece of broken fluorescent lamp, in one the skin was punctured by a fragment of glass from such a tube, and in one the injury was a laceration that became contaminated by bits of beryllium metal. In a few, gross fragments of the lamp remained in the wound. As a rule the wound healed by first intention, after suturing when this was necessary. After a variable period, ranging from a few weeks to 1-1/2 years, small lumps developed beneath the scars

of the original injuries, becoming larger until they often resembled keloids. Occasionally these lumps were tender and surrounded by an area of erythema. If treatment was delayed, the lumps became fluctuant and opened to discharge thick, greyish white, necrotic material. If treatment was further delayed, the lesions remained in an indolent state, repeatedly healing partially and then re-opening.

Biopsy, in all these cases, showed a granulomatous lesion similar to that seen in the lungs of patients with chronic berylliosis. Beryllium was recovered from the involved tissue in five of the six cases in which analysis was carried out. In two instances (36), these skin lesions occurred in patients suffering from chronic berylliosis following respiratory exposure to phosphors containing beryllium oxide. In none of the others, uncomplicated by respiratory exposure, was there any clinical evidence that beryllium had been absorbed from the skin lesion in quantities sufficient to cause pathological changes in other parts of the body.

Healing followed complete excision of the lesion in all cases.

Conjunctivitis

Conjunctivitis has been described by Van Ordstrand et al. (52) as occurring in men exposed to beryllium compounds containing the sulfate or fluoride radicals. It accompanied contact dermatitis of the upper part of the face or resulted from splashes of the compounds. The signs and symptoms are those of catarrhal conjunctivitis or an acid burn.

Treatment is local and routine, healing is complete, and there are no complications or sequelae.

Inflammation of the Upper Respiratory Tract

Inflammation of the upper respiratory tract associated with exposure to beryllium compounds was mentioned by Gelman (17) and other European authors, but was not fully described until Van Ordstrand et al. (52) did so in 1945. This author and his associates described nasopharyngitis and tracheobronchitis as it had occurred in 90 of their patients.

Nasopharyngitis. Nasopharyngitis occurred principally among tenders at furnaces in which hydrous beryllium sulfate was ignited to yield beryllium oxide, or anhydrous beryllium fluoride and magnesium were used in the production of pure beryllium. The cases reported by Gelman (17) were exposed to vapors of beryllium fluoride.

Patients with nasopharyngitis complained of soreness of nose and throat, mild epistaxis and, occasionally, a metallic taste. On examination, the mucous membrane of the nose and throat was found to be diffusely swollen and hyperemic with occasional hemorrhage due to vascular engorgement of the nasal mucosa. The patients were afebrile, and chest and laboratory findings were normal.

The condition cleared in from 3 to 6 weeks when the patient was removed from exposure and given symptomatic treatment.

Tracheobronchitis. Tracheobronchitis appears to be merely an extension of the nasopharyngitis due to a greater exposure or a greater sensitivity. It occurred among the same group of furnace tenders, and the symptoms of both conditions were usually concurrent. It was characterized by cough which was productive of a small amount of blood streaked mucoid sputum, occasionally by anorexia and weight loss, and in about half the patients by mild dyspnea.

Examination of the chest revealed inspiratory rales over the lower lung fields. These rales were fine early in the disease, later becoming coarse. Vital capacity was often reduced; in some of the patients in whom there was subjective dyspnea, the vital capacity was as little as 30 per cent of normal values. There was occasional low grade fever, although the temperature was never elevated more than 1 degree and chills never developed. Chest roentgenograms, taken each week for three weeks after the onset of the disease, were invariably normal, and on subsequent examinations (9) remained so.

In the treatment of tracheobronchitis, it was found that the patients had to be removed from the hazard and given symptomatic treatment while kept at rest. Except under conditions of complete rest, the recovery of the patient was delayed or he developed pneumonitis. As a rule, recovery occurred seven to twenty-one days after the institution of treatment.

Pneumonitis

Pneumonitis has accounted for a large percentage of the morbidity and for all of the deaths which have resulted from exposure to beryllium and its compounds. It has also been the focal point for most of the controversy concerning the pathogenic properties of these chemicals.

Although acute and chronic types of pneumonitis have been described, Machle et al. (29) maintain that this clinic differentiation is purely arbitrary since all gradations in rate of onset, severity, and resolution on a time basis may be seen between the fatal case associated with symptoms of a violent, acute pneumonitis two weeks after onset, and that in which the patient has roentgenographic evidence of disease, but no clinical disability, six years after the termination of this exposure. Dutra (10) after examining specimens of the lungs of seven persons who died of acute pneumonitis and 13 who died of the chronic form, comes to the same conclusion, stating that, although the pulmonary lesions in the two clinical conditions are different, there is evidence of transition of the pathological lesions of the acute condition to those of the chronic.

However, for convenience in description the pneumonitis is divided into three merging types as follows:

1. Acute fulminating pneumonitis
2. Acute pulmonary berylliosis (acute pneumonitis of beryllium workers)
3. Chronic pulmonary berylliosis (chronic pneumonitis of beryllium workers)

Acute fulminating pneumonitis. It is probable that some of the cases described by Gelman (17) as occurring in workers exposed to vapors in a plant in which beryllium was being prepared from its fluoride, and thought by him to be a type of metal fume fever, would fall into this classification. However this condition has been described completely by only one author, De Nardi (9).

De Nardi states that its occurrence was usually associated with exposure to anhydrous beryllium sulfate fumes formed during a violent chemothermal reaction in the treatment of finely pulverized beryl ore frit with sulfuric acid. Symptoms appeared from 2 to 72 hours after exposure, and usually consisted of spasmodic cough, tightness in the chest with substernal pain, marked exertional dyspnea and, in severe cases, varying degrees of cyanosis. Tracheobronchitis invariably preceded the onset of the pneumonitis. Physical examination revealed acrocynosis, definite and sudden decrease in vital capacity, limited chest expansion, and sibilant rales throughout the chest, simulating an asthmatic attack. The pulse and respiratory rates were elevated, but there was no fever. Roentgenograms showed diffuse infiltration of both lung fields.

Symptomatic treatment and bed rest resulted in recovery in seven to 16 days. Subsequent serial roentgenograms demonstrated complete clearing of the pulmonary infiltration without any tendency toward recurrence.

Acute pulmonary berylliosis (acute pneumonitis of beryllium workers). The earliest cases of the acute pneumonitis to be reported followed exposure to beryllium compounds containing fluoride and sulfate radicals. Beryllium fluoride and beryllium oxyfluoride were implicated as the offending agents in the foreign literature (17, 56, 2), and Van Ordstrand et al. (52) reported cases among workers exposed to the dust and fume of beryllium fluoride, the dust and mist of beryllium sulfate and the fume of ammonium beryllium fluoride. For some years it was thought that these were the only beryllium compounds that would cause acute beryllium pneumonitis (44). However recently cases have been reported following exposure to metallic beryllium, beryllium oxide, and beryllium phosphors. Martland et al. (32) have reported one case, and Kress and Crispell (27) two cases, following exposure to dust and fume of phosphors in the fluorescent lamp manufacturing industry; Aub and Grier (1) have reported cases from among men exposed to the beryllium oxide dust in the ceramic industry, and to metallic beryllium dust and beryllium oxide fume in the machining, welding, and casting of pure beryllium metal.

Clinical manifestations. Clinically and pathologically there is little to distinguish the acute pneumonitis arising after exposure to beryllium compounds containing fluoride and sulfate radicals from that which follows exposure to beryllium metal, beryllium oxide, or phosphors which contain beryllium. The onset takes place during the period of industrial exposure. The incidence

is principally dependent upon the intensity of the exposure, although the occurrence of sporadic cases leads one to believe that individual sensitivity may be a factor.

Symptoms. Symptoms appear gradually over a period of several days to a week beginning usually with increasing dyspnea, followed by cough which may be spasmodic and productive of a small amount of blood streaked mucoid sputum, substernal pain, anorexia, increasing weight loss, and weakness progressing to prostration.

Physical examination. On examination, the patient is found to have little or no fever, increased pulse and respiratory rates, varying degrees of cyanosis, fine to coarse inspiratory rales and sibilant rhonchi heard first at the base of each lung and then in the hilar areas, and reduction in vital capacity.

Laboratory data. Laboratory findings are usually normal; there is no leukocytosis and the sputum is free of pathogenic organisms. Beryllium may be recovered from the urine but its presence only indicates exposure and can in no way be correlated with the disease process.

Roentgenograms. Wilson (55) has described the roentgenographic findings in acute berylliosis as a diffuse haziness or ground glass density similar to that of pulmonary edema, which makes its appearance

in both lungs one to three weeks after the onset of symptoms. Following this initial stage, areas of soft infiltration, similar to those which occur in lobular pneumonia, are seen, accompanied by prominent linear markings and hilar enlargement. These areas appear to undergo absorption, and small nodules make their appearance in both lungs. These clear almost completely after one to four months, and usually before complete subsidence of symptoms.

Course. Typically, the disease becomes progressively worse for two or three weeks, and then gradually improves. Recovery takes from four to twelve weeks and occasionally as long as four to five months. Complete recovery, without residua or sequelae, is the rule. In the approximately 10 per cent of cases which have proved fatal, the usual course is one of steady deterioration until death occurs two weeks to two months after the onset of the disease.

Pathology. Dutra (10) has described the pulmonary lesions in seven fatal cases. Grossly, the lungs were heavy and had lost their elasticity. The cut surfaces were fairly homogeneous and varied in colors from pinkish gray to bluish gray. There was little fluid in the bronchi and bronchioles and no pus was seen. Microscopically, in the earliest cases, there was a diffuse intra-alveolar exudate composed of mononuclear phagocytes and edema fluid. In addition the exudate contained scattered lymphocytes and plasma cells and occasional polymorphonuclear

leukocytes and erythrocytes. In progressively more advanced cases, it was possible to distinguish the vacuolation and eventual degeneration of the phagocytic mononuclear cells, the incorporation of the resulting debris into giant cells formed by the union of other mononuclear cells, and the occasional organization of the periphery of this mass by fibroblasts arising in adjacent alveolar walls, to form a granuloma within the lumen of the alveolus. In all cases there was infiltration of the interstitial tissues of the septal walls by lymphocytes and plasma cells. These were more numerous in the advanced cases and occasionally were grouped with fibroblasts and reticulum into nodules. Dutra expressed the opinion that the pathological picture seen in the acute pneumonitis is closely related to that seen in chronic berylliosis, the latter appearing to be a further development of the former.

Treatment. Treatment consists of bed rest, oxygen as indicated, and the use of antibiotic preparations to control secondary infection and of antispasmodic drugs to control bronchospasm and cough.

Chronic Pulmonary Berylliosis (chronic pneumonitis of beryllium workers).

Type of exposure. This type of pneumonitis was first reported by Hardy and Tabershaw (20) in 1946. The 17 cases so described occurred among workers engaged in the manufacture of fluorescent lamps, and the suspected etiological agent was a phosphor in which beryllium

oxide was incorporated. Since 1946 other cases have been reported from a number of different industries (8, 21, 22, 29, 31, 32, 38, 44, 45). The distribution of these cases is shown in Table III. This table is based on one published by Machle et al. (29) in 1948, having been modified to include more recent information.

Table III

Distribution of Reported Cases of Chronic Berylliosis According to Source and Type of Exposure

Source	Probable Compound	Number of Cases
Processing beryllium from ore	$BeSO_4$, BeF_2, BeO	11
Fluorescent powder manufacture	BeO, Phosphors*	16
Machining beryllium	BeO, BeF_2	4
Fluorescent lamp works	BeO, Phosphors*	51
Alloying beryllium	BeO	7
Laboratory work	BeO, BeF_2	2
Sign tube manufacture	BeO, Phosphors*	3
Ceramics	BeO	2
Crystal manufacture	BeO	2
Non-occupational or "neighborhood" cases	?	9
Fluorescent lamp salvage	BeO, Phosphors*	1

* Powders comprised of calcined mixtures of ZnO, BeO, SiO_2, and in some instances MnO.

The neighborhood cases, occurring in individuals with no history of occupational exposure to beryllium, require special mention. Cases of this type have been reported from the immediate neighborhood of a plant manufacturing fluorescent powders (21) and of plants producing beryllium compounds from beryl ore (15). Eisenbud et al. (15) reported eleven such cases, and conducted an environmental study of the atmosphere in the vicinity of the dwelling places of the victims. Ten of the patients resided within 3/4 mile of the plant. In this area the atmospheric contamination was estimated to have ranged from 0.01 microgram to 0.1 microgram of beryllium oxide (expressed as beryllium), per cubic meter of air during the 7 years the plant had been in operation. The cases were thought to have resulted from exposure to the upper levels of these concentrations, which appear to have existed only during the earlier years of this period. During this same period there was a low incidence of berylliosis within the plant. No satisfactory explanation can be offered at this time for the occurrence of these cases in association with respiratory exposure to such low concentrations. It has been suggested that their occurrence is related to the presence, in the atmosphere of the home, of extremely small particles of beryllium oxide, and also that the patients were unusually sensitive, since the attack rate in the neighborhood was low. Beyond this 3/4 mile zone, in which the concentration of beryllium in the air was lower, only one case is known to have occurred during the seven years of the plant's operation.

This exceptional person lived two miles from the plant and was a member of the household of a beryllium worker from the plant. Apparently the exposure to berylliosis was limited to that associated with handling and laundering the clothing of the workman. Based on the analyses of samples of air taken during the handling and cleaning of similar clothing, it was estimated that 17 micrograms of beryllium might be inhaled by the laundress in the course of any day's handling of the clothing. The correctness of the diagnosis in these cases has not been questioned; in 2 of the cases reported by Hardy et al. (21) and in 2 of the cases reported by Eisenbud et al. (15), the diagnosis was confirmed at autopsy. As a result of the occurrence of these cases, it has been recommended that the prevailing concentration of beryllium in the atmosphere in the vicinity of a plant producing and processing beryllium should be limited to 0.01 microgram per cubic meter of air.

Clinical manifestations. The onset of chronic berylliosis does not necessarily occur during the period of exposure; in various cases it has been delayed from one month to six years from the time of the last contact with the harmful environment. The attack rate of the disease is very low; Hardy (21) found only 36 cases among 1400 workers exposed to similar conditions. There appears to be no predilection due to sex, race, or age. The onset has occurred in a few cases during the course of other acute and chronic diseases and during pregnancy and

the puerperium. In these cases, it is more than likely that chronic berylliosis had reduced the patient's vital capacity insidiously to the point at which the added load of another disease revealed his pulmonary insufficiency subjectively. That the new disease had accelerated the chronic pneumonitis or contributed otherwise to the toxic effects of beryllium, seems dubious.

Symptoms. The symptoms of chronic berylliosis come on very gradually. The first symptoms are usually weight loss and fatigue followed by gradually increasing exertional dyspnea and occasional cough. Anorexia and nervousness may also be present, and the patient may suffer from a "head cold" which fails to clear. This initial stage may persist for weeks or months, to be followed by a stage in which the dyspnea becomes more marked and the cough more persistent. The cough may be non-productive or productive of a small amount of thick mucoid sputum which occasionally is blood streaked. The symptoms of greatest diagnostic value are cough, dyspnea and weight loss. These are frequently present and usually appear early in the course of the disease. In the most severe and prolonged cases, the symptoms of right heart failure appear, with an increase in the dyspnea and orthopnea.

Physical examination. Early in the course of the disease the findings on physical examination are not striking. The patients are afebrile and remain so

unless some intercurrent infection develops. There is usually evidence of weight loss, and tolerance for effort diminishes. The pulse rate is often elevated to the region of 100 per minute. Examination of the chest may show reduction of expansion or a few crepitant rales at the bases, or the findings may be entirely normal. Cyanosis may be present and there may be early clubbing of the fingers. As the disease progresses these findings become more marked. Shortness of breath becomes move obvious and may be present at rest. There may be a considerable loss of weight. The pulse rate may be further increased. Expansion of the chest is further diminished, breath sounds may be distant, crepitant or moist rales may be heard at the bases or throughout the lungs, and sibilant rales at the hilar area. Cyanosis becomes more apparent, and with the development of right heart failure, the liver and spleen may become palpable and the extremities edematous. Occasionally, at this stage, a right-sided enlargement of the heart may be detected and the pulmonary second sound may be accentuated.

Laboratory data. The cellular elements of the blood show no changes peculiar to this disease, although in cases in which heart failure has occurred there may be some degree of secondary polycythemia. The chemical analysis of the blood is usually within normal limits. It has been examined for beryllium in only a few instances and in some of these cases small amounts have been detected. Blood cultures are negative and the sputum is free of pathogenic

organisms. The urine may contain low concentrations of beryllium but otherwise is usually normal. The vital capacity is reduced early in the disease and the reduction becomes more severe as the condition progresses.

Roentgenograms. Wilson (55) has described three stages in the roentgenographic appearance of patients with chronic berylliosis. Any of these may be found in asymptomatic individuals. In the first stage there is a fine, uniform, diffuse, particulate granularity, suggesting a "sand storm", which extends to the periphery. There are no abnormalities of the hilar shadows, no increased linear markings, and no other abnormalities. In the second stage there is a diffuse reticular pattern on the granular background, and the hilar shadows are fuzzy, indistinct, and slightly enlarged.

In the third stage distinct nodules appear uniformly throughout, varying from 1 to 3 millimeters in diameter, and the appearance resembles a "snow storm". The nodules do not coalesce, do not calcify nor cavitate, and there is no definite linear fibrosis. The hilar shadows are fuzzy and indistinct.

In more advanced cases there may be small areas of pneumothorax and basal emphysema may develop. With the development of cor pulmonale, the heart shadow may become slightly larger, and the pulmonary artery may become quite prominent.

Course. This is a severe illness of prolonged duration. The mortality in various series of cases has ranged from 10 to 26 per cent (29, 21), being highest where the exposure was most severe and the attack rates were highest. Machle et al. state that the prognosis in the individual case must be based on the type of onset, course and severity of the case as seen. In their series of cases, patients who suffered from dyspnea at rest or from serious exertional dyspnea,with rapid loss in weight of 10 to 15 pounds shortly after the onset, usually took a generally downward course over a period of years and ended fatally. Occasional patients have shown positive roentgenographic signs of berylliosis for years and yet have remained asymptomatic. Rarely the disease remits clinically, and in some of these patients the roentgenographic findings have disappeared.

Pathology. Dutra (10) has described the pulmonary pathology in 13 fatal cases. He states that from a morphological point of view chronic granulomatosis represents a further development of chronic pneumonitis. Cellular exudate, so prominent in acute pneumonitis, is also a part of the granulomatosis. However, intraseptal lymphocytes and plasma cells are much more numerous than are cells lying free in the alveolar spaces. Large mononuclear cells are present in the alveoli in all cases and polymorphonuclear leukocytes are rare. Extensive regions of emphysema and marked fibrosis are present in all cases.

The fibrosis involves the septa, the granulomata, and the perivascular and peribronchial regions. The granulomata, which are typical of the disease, are formed in part within alveolar spaces by the organization of exudate, and in part within the septal and peritruncal connective tissue. They are comprised of central regions of fibrinoid material or granular debris, and the central regions are surrounded by a peripheral zone of fibrosis in which there is an infiltration of lymphocytes and plasma cells. The centers of the granulomata are occupied occasionally by giant cells of the Langhan's type. There are conchoidal bodies in most cases, sometimes within giant cells, sometimes lying free in debris or in fibrous tissue. The bronchopulmonary and mediastinal lymph nodes show changes which reflect those in the lungs. There are areas of fibrosis, granulomata, and giant cells.

Other organs have not been involved extensively in chronic berylliosis. In all fatal cases there has been cor pulmonale, as indicated by thickening of the myocardium of the right ventricle with hypertrophy of the muscle fibers. The liver and other viscera show evidence of chronic passive hyperemia. In one of the cases discussed by Dutra there were granulomata within the lobules of the liver similar to those found in the lungs.

Treatment. Treatment is largely symptomatic and supportive. Activity may be allowed within the patient's tolerance, alternating with bed rest when

indicated. Further treatment consists of the administration of oxygen as required, antibiotics for intercurrent infection and antispasmodics for bronchospasm. Specific treatment designed to aid in the elimination of beryllium, such as BAL and solubilizing agents, has not been beneficial.

Control Measures

Medical Control. Workers who are known to be exposed to beryllium should be examined at least once a month. At this examination the workers should be weighed and questioned about their health. Loss of weight or the occurrence of unaccountable illness, particularly disease of the respiratory system, must be investigated further by repeated complete medical examinations and roentgenograms of the chest (49).

Roentgenograms of the chest of all exposed workers should be obtained annually.

There are, unfortunately, no laboratory tests that can be used as reliable aids for the detection of cases of berylliosis before the onset of clinical signs and symptoms. The finding of beryllium in samples of urine is an indication of exposure to beryllium, not of berylliosis (11). This test may be used therefore to assist in establishing which members of a plant population should be examined periodically, but is of limited diagnostic value. The cellular and chemical constituents of the blood show no changes peculiar to this disease even in established cases (29). Consequently periodic analysis of the blood for such changes cannot be

depended upon to reveal early cases. The detection of beryllium in samples of the blood of exposed persons has been reported in only a few instances (11). Although the diagnostic value of this procedure has not been fully explored, it is unlikely that it will be found to be more useful than that of analyzing the urine. Periodic estimation of the vital capacity of exposed personnel may be of value in detecting early cases. It is probable that a reduction in vital capacity occurs in some cases before the occurrence of clinical symptoms or other clinical signs, including changes in the roentgenograms. The value of this procedure is limited by the difficulty of carrying it out in a reliable manner.

Hygienic Control. The most important control measures are those designed to keep the concentration of beryllium to which workers are exposed at the lowest possible level. Environmental studies and epidemiological surveys (2) (4) have indicated that clinical cases of berylliosis have not occurred under the conditions of occupational exposure to concentrations of beryllium below 0.1 milligram per 10 cubic meters of air. However, a recent report of the experimental exposure of animals to low concentrations of beryllium sulfate mist (5), and that of the environmental study in connection with non-occupational cases (6), have indicated that the maximal allowable concentration of beryllium may eventually have to be set well below 0.01 milligram per 10 cubic meters of air. Beryllium is apparently one of the most toxic of the elements; apparently, in the present state of our knowledge, it can only be handled with safety when its concentration in the respired air is kept at the

vanishing point. A satisfactory working environment can be attained by the employment of conventional measures of engineering control which prevent the contamination of the air breathed by workmen. For temporary operations, where such engineering control is not feasible, personal protective devices must be employed under conditions of use and supervision which insure their efficiency.

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