



BERYLLIUM POISONING

Beryllium has unique and advantageous properties which make its use imperative in nuclear physics, nuclear reactor technology, metallurgy, and in industry. But there is danger in its use, for beryllium and its compounds have toxic properties and disease-producing potentialities which have not been widely recognized.

Beryllium disease poses many fascinating problems to the physician. Here is a metal closely related chemically to magnesium and aluminum which demonstrate no comparable toxicity. The oxide is characterized by its extreme inertness and insolubility. Why then its extreme toxicity?

This disease was created in 1931 when methods for producing large quantities of beryllium were developed. As early as 1933 Weber and Englehardt, in Germany, recognized an acute pulmonary disease occurring among workers engaged in beryllium extraction. Fabroni observed the disease in Italy in 1935 and a Russian scientist, Gelman, made the interesting and significant observations, in 1936, that the disease appeared in plant watchmen whose posts were as far as one hundred and fifty meters from the factory rooms in which extraction processes were in operation. During 1940 and 1942 further reports appeared in the German literature describing lung disease appearing in persons working with beryllium fluorine vapor.

In 1938, when beryllium began to be used in fluorescent powders, observers in the United States found evidence of beryllium poisoning among two groups of workers: those working with fluorescent powder composed of zinc beryllium manganese silicate (used in making lamps), and those workers engaged in extracting beryllium and its compounds from its ores.

Exposure to the following compounds has produced various forms of beryllium poisoning: beryllium oxide, fluoride, sulfate, chloride, oxyfluoride, carbonate, hydroxide, manganese silicate, zinc manganese silicate, and finely-powdered beryllium metal. The sulfate, fluoride, oxide, metallic dust, and perhaps the hydroxide have been shown to produce the disease in acute form.

The most dramatic form of the disease is the

chronic, which may appear many years after the primary exposure. The chronic form of the disease has a variable course. Very roughly stated, approximately thirty percent of patients with beryllium poisoning of the delayed type die, about thirty percent suffer some degree of chronic invalidism, and the remainder seem to recover completely.

Lest this picture appear too alarming, it is well to discuss the order of magnitude of this problem. Certainly many thousands of individuals have been exposed to beryllium and its compounds. Studies in this country indicate that approximately three hundred and fifty persons have suffered the acute form of the disease. It is difficult to know exactly how many persons died during the acute phase, but the number is probably about thirty. Approximately one hundred and ten cases of the chronic, delayed form have been reported with about thirty-two deaths.

Many scientists are unaware of the toxic potentialities of this metal and its compounds and of the strict protective procedures which must be observed to prevent the development of this insidious and disabling, if not fatal, disease. What then do physicians and biologists know about beryllium poisoning and what information can be given to scientists and technicians who work with it, to protect and preserve their health?

The physicians' interest is heightened by the frustrations engendered at present by the lack of specific therapeutic measures for treating the disease or methods for eliminating stored deposits of beryllium in the exposed person's body. There are many research workers presently engaged in studies of the ultimate biochemical and physicochemical nature of the changes occurring in man and experimental animals after exposure to beryllium and its compounds. Although we do not know why this metal and its compounds are toxic, extensive studies in recent years have begun to round out our knowledge of the clinical manifestations of the disease which point the way to safer methods of handling.

Manifestations

Of special interest to physicians are two features of beryllium poisoning: extremely minute quantities

Twenty-five millionths of a gram of beryllium per cubic meter of breathed air can cause acute lung disease. Industrial users of beryllium have standard practices to protect the workman. It is important that all scientists and technicians learn how to work safely with beryllium and its compounds.

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of the chemical can cause poisoning, and there is often a long, latent period between the last exposure to beryllium compounds and the development—years later—of the form of the disease known as delayed pulmonary granulomatosis.

Advances in metallurgy technology made possible the production of large quantities of pure beryllium and its oxides in the years immediately preceding 1943. The metallurgical processes involved exposure to beryllium oxyfluoride vapors. In factories it was soon observed that there was a high incidence of an acute lung disease resembling acute bronchitis or pneumonia. This acute form of the disease did not differ markedly in its clinical manifestations from other forms of acute chemical pneumonitis which have been observed from the inhalation of the vapors of many other metals or from a type of pneumonia caused by a virus and known as primary atypical pneumonia.

Now in the extraction of beryllium ores workers were exposed to dust and fumes of beryllium sulfate, fluoride, and oxide, as well as to beryllium metal and beryllium copper alloys. Symptoms appeared a few hours to days after exposure and the worker became acutely ill with cough, chest pain, occasionally fever, marked prostration, and on x-ray examination of the chest demonstrated lung findings indicative of acute pneumonia. Most patients recovered completely within a few weeks to months; unfortunately a certain number died. The clinical course of a yet smaller number of patients continued on to a chronic form of the disease. Other manifestations of the acute type, an inflammation of the skin (dermatitis) and conjunctiva of the eye, were also seen.

A group of physicians undertook to study the acute disease occurring in an Ohio factory and in 1943 the first paper appeared in the American literature coming from the Cleveland Clinic and describing these acute cases. With improved house-keeping methods and the introduction of adequate ventilation and filtration, the incidence of the acute lung disease diminished rapidly.

Attention then shifted to the fluorescent lamp industry in the New England area. The year 1938

had seen the introduction of zinc beryllium manganese silicate as the fluorescent constituent of the newly developed lamps. At this period the fluorescent powder contained approximately twelve percent beryllium. Shortly after the introduction of this fluorescent powder, workers became acutely ill in factories manufacturing it and in plants manufacturing the coated lamps. The disease did not differ in its acute form from that seen in the Ohio area.

The Ohio group recorded the history of one person, who, having recovered after a two-month acute illness, developed chronic pneumonitis several years later. It remained for Hardy and Tabershaw in 1946 to draw attention to two of the intriguing features of beryllium poisoning. As Gelman had noted in Russia that certain persons working at a distance from a beryllium plant with no intimate exposure to the substance or its compounds developed lung disease, so Hardy and her associate described the occurrence of the so-named "neighborhood cases." A report in 1947 described illness occurring in three people living in the vicinity of the plants and showing symptoms and findings identical with those suffered by the group working inside the factories. Two of these three persons died. Later eleven neighborhood cases were seen in the vicinity of one of the Ohio plants extracting beryllium.

The other significant and alarming observation of Hardy was that a not inconsiderable number of individuals who had been exposed previously to these toxic beryllium compounds and then were completely absent from any exposure for periods ranging from a few months to as long as five years developed a chronic disease after an intervening period of apparent good health. The manifestations of this illness were primarily those of a severe incapacitating lung disease.

One common denominator was seen in most of these patients, namely: some type of trigger mechanism seemed to set off the onset of this delayed form of beryllium poisoning. This factor in some patients

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was a recent severe respiratory infection, a surgical procedure in others, and in some women the termination of pregnancy precipitated the illness. Fatigue also seemed to play an important part.

It is this form of the illness, called either delayed chemical pneumonitis or chronic pulmonary granulomatosis, which has proven to be the greatest challenge to the medical profession. The intensity of the delayed reaction and the peculiarities of the clinical picture make it unique. It should be understood that this is a disease of the entire body although the most prominent and incapacitating features are centered in the respiratory system.

Development

Autopsies and the extensive experimental projects on beryllium poisoning under way at several of the research institutions in this country are beginning to throw some light on the origin and development of the disease. Tracer studies on animals with beryllium-7 indicate that a large and very significant portion of the injected dose of a soluble salt is rapidly deposited in the bone where it remains almost indefinitely. After a very short period of excretion in the urine, insignificant amounts leave the animal's body. This finding of beryllium deposition in bone may give a possible clue to the mechanism of the delayed appearance of the disease. It is conceivable that the trigger mechanisms, mentioned above, act to release into the general circulation beryllium stored in the bones.

In the human, significant amounts of beryllium are of course found in the lungs (since the portal of entry is through the lungs), in the hilar lymph nodes which drain the lung, and in the liver. Tissue changes are seen in the lungs, liver, and in lymph nodes primarily, and are now well enough recognized to make the diagnosis by microscopic examination of the tissue possible, although the diagnosis cannot be made on the examination of tissues alone. The essential patho-physiologic changes in the lung consist of the rapid proliferation of certain types of cells from the walls of the air sacs in the lungs, eventually filling the sacs. The net effect of this is an interference with the transfer of oxygen from the lung into the blood stream. Many of the phenomena of this disease can be explained on the basis of this chronic oxygen deficit.

There is no need to dwell in detail on the treatment of beryllium poisoning. Suffice it to say that

in the chronic stage therapy is directed toward general supportive measures including supplementation with increased amounts of oxygen until natural reparative and recuperative processes bring about recovery in so far as possible. There is at present no specific therapy.

A Little is Too Much

What facts, then, are of importance to the scientist and technician working with beryllium and its compounds? Studies of autopsy material demonstrate that various tissues contain beryllium in microgram amounts. Therefore it is patent that the quantities of beryllium causing death can be measured in milligrams and micrograms. Observations of air levels have shown that twenty-five millionths of a gram of beryllium per cubic meter of inspired air can cause the acute lung disease.

Not all compounds of beryllium exhibit equal toxicity. The fluoride and oxide appear to be the more toxic of the compounds. Moreover, the toxicity of various samples of the oxide may differ considerably. This factor possibly accounts partially for the phenomenon that some people have been exposed to large quantities of the oxide with no apparent detriment to their health, whereas the exposure to minute quantities of the same compound, but of different lot, has led to the development of the chronic disease and death in others. There are some indications that the low-fired oxides are more toxic than those which have been high-fired. The fluorine in the compound seems to enhance the toxic properties of beryllium.

In the past it has been asked how dangerous is the pure metal. On theoretical grounds it was felt that little danger existed, for instance, from machining it. It is probably true that the surface of the minute chips produced in machining the metal is rapidly oxidized. At least two cases of the acute disease have occurred in workers machining the metal.

Precautions

What, then, can serve as a scheme for the protection of the scientist and technologist who desire to work with beryllium? The problem may be epitomized by stating that contact with beryllium and its compounds should be minimized to prevent the incorporation of *any* amount into the body. This is technically difficult and a realistic attitude must be

adopted. The large plants producing, processing, and utilizing these substances have instituted standard industrial hygiene practices that protect the workman. Greater concern must be expressed for the scientist and technologist in the laboratory who have little understood the hazards and have not had the benefit of instruction in safe methods of procedure. It is to this group, especially, that these suggestions are directed.

In general, the same habits of thought should be encouraged and cultivated by scientists working with beryllium compounds as apply to radioactive substances, for instance. They must think through and plan each operation in advance.

It is not possible at present to set "safe" air levels. It is known that exposure to air concentrations of a beryllium compound containing twenty-five micrograms of beryllium per cubic meter of air has produced the acute form of the disease. This, then, represents a level which never should be permitted. The level to aim at is *nil*. A realistic figure for the prevention of the chronic disease cannot as yet be set. On general principle, it seems wise, at present, to be as conservative as possible and select a figure as low as can be obtained.

Methods of chemical analysis have not been developed for the accurate determination of these minute amounts of beryllium. Spectrographic methods of quantitative analysis must be relied upon and, unfortunately, the availability of spectrographic analysis is not great.

Work with beryllium should never be carried out in an open room. Contamination of air, table tops, and apparatus can serve as a silent and potent source of beryllium—enough to cause disease in the scientist himself and in his fellow worker or laboratory neighbor. All procedure should be carried out in a ventilated "dry-box," shielded and ventilated machining devices, or ventilated hoods. Exhaustion from the hood should not be ignored, as it constitutes a potential hazard on discharge from the ventilating stack. Filtration systems should be present in the exhaust ducts to trap the particles, especially those below one micron in size, before discharge of this air to the outside. This places a heavy financial and technical burden on all contemplating work with beryllium. In the present state of our knowledge it is wise to be overcautious in preventing exposure.

Until it is possible to recognize which oxides are

toxic, and which other compounds and states of the metal can produce disease and under what conditions, we cannot do otherwise. Consultation with qualified physicians and industrial hygienists should be obtained before work upon any beryllium problem is started.

For the protection of health and early recognition of disease, what can be recommended to the physician? There must be continuing dissemination of knowledge concerning beryllium poisoning among all members of the medical profession so that the diagnosis is not confused with other disease—as it quite understandably was in the early days—so that the *early* symptoms of its onset are not missed.

All personnel working with beryllium and its compounds should be under continuing medical surveillance. Stereoscopic chest x-ray films of the highest quality and preferably of the 14" x 17" size should be made at six-month intervals or immediately upon development of unexplained symptoms. Since weight loss is an early finding it is recommended that those exposed be weighed every two to four weeks for the early recognition of significant trends. Measurements of the vital capacity (the lung air capacity between a full inspiration and expiration) should be made at definite intervals. The laboratory should have available a physician, aware of the beryllium problem, to whom the scientist or technologist can turn for consultation upon the development of any deviations from normal good health. Lastly, exposed personnel should give close attention to the ordinary principles of health hygiene: adequate rest and food and vigorous attention to and care of common respiratory infections.

The many valuable and unique properties of beryllium and its compounds make imperative its use and the extension of its use. It is not possible or realistic to say merely that, since beryllium and its compounds are toxic, the use of these substances must be abandoned. Nor is there reason for undue alarm. It is possible and feasible to work safely with beryllium and its compounds, but only if the worker is fully acquainted with the potentialities of danger to himself and his associates. Certain safeguards are necessary and should be observed not once, but in each operation.

