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THE HISTORY, USES, OCCURRENCES, ANALYTICAL CHEMISTRY, AND BIOCHEMISTRY OF BERYLLIUM–A REVIEW

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THE HISTORY, USES, OCCURRENCES, ANALYTICAL CHEMISTRY, AND BIOCHEMISTRY OF BERYLLIUM–A REVIEW

Jeffrey A. Hurlbut

Abstract. A literature search in Chemical Abstracts dated 1947 through July 1973 and concerning beryllium and beryllium oxide was performed in an attempt to uncover a beryllium exposure bioassay. The history, use, occurrence, analytical chemistry, and biochemistry of beryllium are summarized. The analytical chemistry section discusses ashing, separation, gravimetric, volumetric, spectrophotometric, fluorometric, emission, activation, gas chromatographic, atomic absorption, polarographic, and miscellaneous techniques. The biochemistry portion concentrates on beryllium disease, mechanism of beryllium action, and indices of exposure. There are 318 references.

INTRODUCTION

History

The history of beryllium dates back to about 50 A.D. when Pliny the Elder, a Roman scholar, noticed the similarity between the ore, beryl ($3BeO \cdot Al_2O_3 \cdot 6SiO_2$), and emerald (beryl with a trace of chromium),[1] a prized mineral since 1650 B.C. Beryllium is also present in other gems such as aquamarine, morganite, and heliodor.

The French chemist, L. N. Vauquelin, is credited with the discovery of beryllium.[1-3] The French mineralogist, R. J. Hally, also noticed the similarity between emerald and the more common beryl, and asked Vauquelin to make a chemical comparison. Beryl was previously believed to be a calcium aluminum silicate, but Vauquelin demonstrated that this belief was false and that beryl and emerald contained an oxide of a new alkaline earth metal, which Vauquelin named "earth of beryl." Editors of the journal in which the first report was published suggested the name "glucinium" since beryllium salts had a sweet taste similar to glucose.[1-3] This name and the symbol, Gi, are still used in French literature. The name, beryllium, was given by F. Wohler of Germany in 1828 when he succeeded in isolating relatively pure metal by potassium reduction.[1,3] In 1898, the French chemist, Lebau, prepared greater than 99.5% beryllium by electrolysis.[1]

Beryl is the major source of beryllium, even though at least 30 different beryllium-containing minerals are known. It is commonly recovered with feldspar, spodumene, mica, columbite-tantalite, and cassiterite.[1] The world resources of beryllium are placed at about four million tons and the principal deposits are in Brazil.[3] It is processed primarily in Ohio and Pennsylvania.[4]

Large amounts of beryllium were not introduced into the United States until the 1920's when industry began using it as an additive to copper. Its popularity increased in the 1930's when it was used as an ingredient in fluorescent light tubes, and in the 1940's, beryllium's usefulness increased as outlined in the next section.

In 1886, Siem conducted the first toxicity tests on beryllium compounds.[5] It wasn't until the 1930's and 1940's, however, that its toxic properties were realized, even though industry had used beryllium for several years. European reports describing a disease common to beryllium workers appeared in the 1930's and 1940's.[4,5] In the mid 1940's, corroborative evidence of beryllium's toxicity came from United States sources, but it wasn't until 1949 that government and industry set human exposure limits.[4]

Uses

The principal uses of beryllium stem from the discovery in the 1920's that the addition of small amounts of beryllium to copper forms an alloy six times stronger than copper.[3, 6, 7] In addition to being stronger, beryllium alloys have such favorable characteristics as high tensile strength, good casting and machining characteristics, and high electrical and thermal conductivity. These alloys find many major industrial uses.[4, 6]

The general public first became acquainted with beryllium as an ingredient in the phosphors that gave fluorescent lamp tubes their light. Beryllium phosphors coated nearly all fluorescent tubes until 1949.[3] It was this use of beryllium that first exposed large numbers of industrial workers and the general public to the hazards of beryllium disease.

Beryllium owes its recent prominence and expansion of production to the growth of the aerospace industry and atomic energy program.[8-11] Interest in beryllium for use in components of aerospace vehicles comes from its physical, chemical, and mechanical properties. It has low density, high modulus of elasticity, small thermal coefficient of linear expansion, and high specific heat. It is this last property that is most attractive to spacecraft engineers, and because of it, beryllium was used for the heat shield on Project Mercury capsules. It is also used as a solid rocket fuel because of its low density and high heat of combustion (17 kcal per gram).[9] Unfortunately, though, beryllium has poor ductility and high toxicity.

The usefulness of beryllium in nuclear devices and reactors is based on three properties: its ability to moderate fast neutrons, its ability to reflect thermal neutrons, and its low neutron capture cross section.[10] The first property is important because high-speed neutrons are released in nuclear devices by the fissioning of atoms of nuclear fuel, and these neutrons must be moderated for an efficient fission chain reaction to continue. Beryllium works well in this application because neutrons are highly moderated by collisions with atomic nuclei of small size.[9]

The second property is also useful. Beryllium has the ability to reflect the slowed neutrons and thus conserve fuel.[9] Heavy water and graphite are better neutron reflectors than beryllium, but both present structural problems.[8] The only major problems with beryllium are that it is toxic and therefore difficult to handle, and it must have high purity since trace constituents may absorb neutrons.[10]

TABLE 1. Beryllium Content of Environmental Sample

Sample[a]	Be Content (μg/g or μg/ml)[b]
Urban Air in U. S.[17]	2×10^{-4} to 5×10^{-4}[c]
Urban Air in U. S.[18]	1×10^{-4} to 30×10^{-4}[c]
Earth Crust[18]	3 to 6
Soil[12]	1×10^{-2} to 170×10^{-2}
Soil[18]	0.1 to 1
Lunar Soil[19]	1 to 3
Coal Ash of U. S.[20]	46
Ocean Water[21]	5×10^{-7}
Ocean Water[22]	4×10^{-6} to 40×10^{-6}
Ocean Water, Pacific[12]	2×10^{-6}
Ocean Water, Indian[12]	1×10^{-6}
Tobacco[12]	3×10^{-2}
Tobacco[23]	2×10^{-2} to 8×10^{-2}
Rain[12]	1×10^{-5} to 20×10^{-5}
Foodstuff[12]	$<8 \times 10^{-4}$
Grass[12]	5×10^{-4} to 500×10^{-4}
Coal Ash (2 to 16% Ash)[18]	8000
Coal Ash[24]	300

[a] Superscript numbers are reference numbers.
[b] All concentration units in referenced literature were converted to μg/g or μg/ml.
[c] μg/m³.

Occurrence

The recognition that minute quantities of beryllium and its compounds can cause beryllium disease has led several workers to survey the beryllium content of environmental and human samples.[12] Tables 1, 2, and 3 summarize some of this survey work.

It is apparent from these tables that beryllium content varies from case to case. If the analyses of these samples were accurate, then the single factor of differences in exposure to beryllium is not sufficient to account for this variation. Even lung tissue from one specimen varied markedly in beryllium content from one portion of the lung to another.[13, 14] Likewise, urine varied in beryllium content randomly from sample to sample.[15, 16]

TABLE 2. Beryllium Content of Human Tissues and Fluids Having No Known Beryllium Exposure.

Sample[a]	Be Content (μg/g or μg/ml)[b]
Brain[12]	6×10^{-4} to 10×10^{-4}
Kidney[12]	4×10^{-5}
Spleen[12]	4×10^{-5} to 6×10^{-5}
Liver[12]	3×10^{-4} to 6×10^{-4}
Liver[25]	2×10^{-4}
Muscle[12]	4×10^{-5} to 20×10^{-5}
Vertebrae[12]	9×10^{-4} to 100×10^{-4}
Bone[12]	2×10^{-3}
Hair[12]	2×10^{-2} to 3×10^{-2}
Heart[12]	1×10^{-4} to 8×10^{-4}
Lung, Liver, Kidney[26]	2×10^{-4} to 4×10^{-4}
Lung[27]	3×10^{-4} to 3000×10^{-4}
Lung[25]	2×10^{-4}
Lung[13]	1×10^{-2} to 2×10^{-2}
Lung[12]	3×10^{-4} to 20×10^{-4}
Lung[18]	0.0 to 200×10^{-4}
Lung (avg. of 70 random people)[18]	3×10^{-3}
Blood[18]	$<0.00 \times 10^{-2}$
Blood Ash[28]	6×10^{-2}
Urine[29]	3×10^{-6}

[a] Superscript numbers are reference numbers.

[b] All concentration units in referenced literature were converted to μg/g or μg/ml.

TABLE 3. Beryllium Content of Human Tissues and Fluids Having Known Beryllium Exposure.

Sample[a]	Be Content (μg/g or μg/ml)[b]
Kidney[13]	$<1 \times 10^{-2}$
Kidney[30]	7×10^{-4} to 200×10^{-4}
Liver[13]	3×10^{-4}
Liver[30]	8×10^{-5} to 10000×10^{-5}
Spleen[30]	2×10^{-4} to 300×10^{-4}
Heart[30]	2×10^{-3} to 100×10^{-3}
Lymph Nodes[31]	1
Hair[12]	2×10^{-2} to 4×10^{-2}
Lung[27]	8 to 1900
Lung[13]	1×10^{-3} to 600×10^{-3}
Lung[31]	0.4
Lung[30]	1×10^{-3} to 2000×10^{-3}
Lung[32]	2×10^{-5} to 400000×10^{-5}
Blood[33]	2×10^{-2} to 5×10^{-2}
Urine[34]	1×10^{-4} to 100×10^{-4}
Urine[35]	$<2 \times 10^{-5}$ to 30×10^{-5}
Urine[5]	$<5 \times 10^{-6}$
Urine[16]	$<0 \times 10^{-3}$ to 5×10^{-3}
Urine[30]	$<1 \times 10^{-5}$ to 1100×10^{-5}

[a] Superscript numbers are reference numbers.

[b] All concentration units in referenced literature were converted to μg/g or μg/ml.

ANALYTICAL METHODS

Ashing Techniques

Since ionic beryllium can form stable complexes with many inorganic, organic, and bio-organic materials, it is usually necessary to ash a sample to liberate the beryllium. Any of several techniques can be used. The sample can be dry ashed in a furnace,[36-40] or it can be wet ashed using an oxidizing acid such as HNO_3 or $HClO_4$; combinations of acids are also used.[19, 29, 32, 36-39, 41-48]

In the 1940's and early 1950's, chemists reported erratic results upon dry and wet ashing. Aldridge and Liddell reported possible losses of beryllium resulting from the formation of "volatile" beryllium dichloride during dry ashing.[38] Hubbard and Cholak reported high losses when ashing in a silica or a platinum dish at temperatures as low as 500 °C.[37] Other workers reported losses up to 90% when ashing samples.[49] Such losses, however, were not observed by Underwood and Neuman.[50]

To solve this problem, at least three studies were performed on ashing techniques. Toribara and Chen studied the procedure in 1952[36] and Toribara and Sherman in 1953.[40] Through use of the radioisotope, beryllium-7, these three men found that upon evaporating a sample to dryness, beryllium oxide formed. This beryllium oxide did not extract into organic solvents with the aid of complexing agents and was thus "lost." They recommended heating the beryllium oxide with concentrated sulfuric acid to destroy this insoluble oxide and recover the beryllium.

Sill and Willis, in 1959, also studied this problem.[29] They found that upon evaporating a sample to dryness, insoluble and nonextractable beryllium pyrophosphate might form. Boiling the ashed sample with hydrochloric acid can destroy this pyrophosphate complex[29,45,47] and losses of less than 10^{-4} μg will occur.[29]

Recent work by Black and Sievers indicates that volatile beryllium compounds can be lost during digestion.[53] As much as 90% of the beryllium in orchard leaves is lost during wet or dry ashing at temperatures as low as 200 °C. Apparently the beryllium exists as an organic beryllium complex in the leaves. Black and Sievers also investigated the possibility of volatile beryllium being emitted in beryllium machining operations,[53] and they found that a considerable amount of beryllium passed through the standard filters. The volatile beryllium was collected by the use of cold traps.

Separation Techniques

Since many analytical techniques are not specific for beryllium, the beryllium must first be separated from the sample interferences. A number of methods can accomplish this separation.

Perhaps the oldest and one of the easiest means of separation involves coprecipitation of beryllium hydroxide[40,51] or beryllium phosphate[36,38–40,42,45] with other insoluble hydroxides or phosphates. This method usually separates the beryllium from organic materials and other soluble ions. It also concentrates the beryllium and is apparently quantitative down to submicrogram amounts of beryllium.[36,38,42,45]

The mercury cathode technique is another separation method.[39,40,43,45,46,52] Many transition metals can be reduced and deposited onto a mercury cathode, leaving all of the beryllium in solution. Other means of separations are chelate extraction and various types of chromatography. Ion exchan chromatography is useful since one may employ anionic or cationic resins.[39,40,44,51,54–61] A cationic resin can be used if the beryllium is in the Be^{2+} form, and an anionic resin can be used by forcing the beryllium to the $BeCl_4^=$ or to the $BeF_4^=$ form. Good separations are obtainable, and beryllium concentrations as low as 10^{-4}M can be utilized.[44]

Some of the other types of chromatography used for separation or concentration purposes are thin layer,[62–65] paper,[66,67] electrophoretic,[68,69] silicon oxide column,[70] and vapor phase chromatography. Of the several types of chromatography available, only gas or vapor phase chromatography is capable of separating and detecting picogram quantities accurately (see the "Gas Chromatography" section).

Extraction techniques are probably the most popular separation methods. Beryllium will form stable, organic, soluble complexes with the enol form of beta-diketones. Two such beta-diketones are acetylacetone and trifluoroacetylacetone. They are capable of quantitatively complexing and extracting subpicogram amounts of beryllium into organic solvents. Several workers have investigated and used acetylacetone as an extracting agent.[29,36,39–41,44,46,47,51,71] Trifluoroacetylacetone has also been employed.[17,19,46,51,72–81] Other beryllium complexing agents are diethyldithiocarbamate,[51] 8-hydroxyquinaldine,[51] cyclopentanone-2-carboxyaniline,[82] and thiocyanate-tri-n-octylamine.[83] Ethylenediaminetetracetic acid can successfully be used as a masking agent for these extractions.

Gravimetric and Volumetric Analysis

Gravimetric methods of analysis are used when a sample contains large amounts of beryllium, and when accuracy takes precedence over speed and ease of analysis. Generally, milligram or larger quantities of beryllium can be determined gravimetrically with greater than 1 to 0.1 percent accuracy.[51]

Owing to the lack of many insoluble beryllium compounds of definite composition, the most popular method for determining beryllium gravimetrically involves the precipitation of beryllium hydroxide and subsequent ignition of the oxide,[51, 84, 85] but workers have questioned the accuracy of this method.[86, 87] Recently, analytical chemists have utilized various oxygen-containing, organic-complexing agents such as 1,3-diketones,[82] cyclopentanone-2-carboxyanilide,[82] benzoylacetanilide,[88] benzoyl-*m*-nitroacetanilide,[89] and 2-methyl-8-hydroxyquinoline.[86]

Volumetric procedures can be applied only when beryllium is one of the major constituents. Unfortunately, there are few specific reactions that one can use for this procedure. Perhaps the best known volumetric method involves the titration of hydroxide liberated from the reaction of suspended beryllium hydroxide with an excess of fluoride.[51] Some recent methods involve potentiometric,[90] coulometric,[86] nonaqueous,[91] and amperometric titrations.[92]

Spectrophotometric Analysis

There are numerous spectrophotometric methods for the determination of beryllium. Nearly all involve complex formation between a beryllium cation and an organic chelating reagent. A few of the complexing agents are acetylacetone,[41, 44, 93] trifluoroacetylacetone,[73] cyclopentanone-2-carboxyanilide,[82] 8-hydroxyquinaldine, aluminon, salicylic acid, 5-sulphosalicylic acid, *p*-nitrobenzeneazoorcinol, and beryllon II.[18, 51, 94–97]

There are several drawbacks to these spectrophotometric methods. One is that the practical lower limit is not low enough, even though the detection limit is frequently in the submicrogram range. Another problem is that none of the numerous complexing agents used is specific for beryllium; the investigator must mask or remove the interferences. Finally, most methods are lengthy and tedious.

Fluorometric Analysis

There are basically three different fluorometric techniques, and these are visual or ultra-violet (u.v.), X-ray, and atomic fluorescence. Visual or u.v. fluorescence is by far the most popular of the three and has been the "stand-by" procedure for trace beryllium analysis.

Of the chemical methods discussed so far, the morin- (2′, 4′, 3, 5, 7-pentahydroxyflavone) fluorescence method is the most sensitive. Submicrogram amounts of beryllium can be quantitatively detected in most samples, but there are many variables and interferences.[29] Zermatten first described this method,[98] and since that time numerous workers have published morin-beryllium procedures.[18, 29, 39, 40, 99–103] Even an automatic air-beryllium morin analyzer, capable of detecting 10^{-3} μg Be/m^3 has been developed.[104] Some other u.v. or visual-fluorescence techniques are the 1-amino-4-hydroxyanthroquinone,[18, 43] 1,4-dihydroxyanthroquinone,[18, 43] 2-ethyl-3-methyl-5-hydroxychromone,[105, 106] 6-methyl-1-hydroxyxanthone,[107] and N-salicylidene-*o*-hydroxylbenzylamine[108] techniques.

The other two techniques, X-ray and atomic fluorescence, have been used sparingly. A few workers have employed X-ray fluorescence,[51, 109–111] but the method remains unpopular because the detection limit is not low enough for trace analysis,[51] and the equipment is expensive. At least two groups have tried atomic-fluorescence beryllium analysis using a nitrous oxide-acetylene flame, but the detection limits are not as good as those for atomic absorption.[112, 113]

Emission Methods

Emission methods for beryllium analysis can be broken roughly into two subgroups, flame and spectrographic. Flame emission has not been widely used because of difficulty in controlling the experimental parameters and because the detection limit is no better than other, more-convenient methods. Nevertheless, several groups have recently investigated this method.[114–116] They found that a hot flame, such as a nitrous oxide-acetylene flame, is needed, and that submicrogram quantities of beryllium are not detectable.

Fesefeldt used a spectrographic method for beryllium detection in 1929,[117] and until the 1960's, spectrographic methods were the most satisfactory techniques for detecting and determining traces of beryllium. Submicrogram amounts of beryllium can be readily determined, and there are few interferences. This technique is not ideal, however, because (1) the sample usually has to be ashed to concentrate the beryllium, (2) elaborate standards that closely match the sample matrix need to be prepared, (3) the equipment is expensive and bulky, and (4) poor precision is usually obtained.[51, 103]

The spectrographic methods fall into three related categories: arc (AC, DC, plasma), cathode layer, and porous cup.[18, 51] Numerous workers have described arc techniques in which the sample is placed on an electrode, and light from the electric discharge between the electrodes is admitted to the spectrograph.[18, 37, 40, 42, 51, 118, 119] Another technique is the cathode layer technique.[18, 51, 120, 121] In this method, one coats the graphite cathode with a sample and focuses only on the light originating near the cathode. Beryllium concentrations as low as 5×10^{-4} μg/ml can be detected using this procedure. Finally, some workers have used a porous cup, spark technique.[18, 51, 122, 123] This technique involves the liquid sample being fed into the discarge by percolation through the thin base of a hollow graphite electrode. Some of these techniques have been employed for automatic air beryllium analysis.[51, 103, 124, 125] Additional, miscellaneous techniques are described elsewhere.[51, 126] (See the Miscellaneous portion of this section for other emission techniques.)

Activation Analysis

There are several types of activation-analysis methods available for beryllium, such as alpha, gamma, neutron, and proton activation. Gamma- and alpha-activation techniques are the most popular, but they are not widely used because the equipment is expensive and somewhat foreign to most workers, and because submicrogram quantities of beryllium are not readily detected. These methods are relatively interference free, however, and are quick and require little sample preparation.

The gamma-activation method is based on the interaction of gamma radiation with beryllium, and was first used in the early 1950's.[51, 127–138] The sample is usually irradiated with gamma radiation from an antimony-124 source and the neutrons produced then counted. The neutron counting rate is proportional to the amount of beryllium present.

In the alpha-activation method, a sample is bombarded with alpha particles. The resulting neutrons are again counted and compared to an appropriate standard.[51, 61, 128, 136, 137, 139–142] The alpha particle source is polonium-210. This method lends itself to automation, and automatic beryllium-air analysis instruments incorporating alpha activation techniques have been developed.[140]

Several laboratories have utilized proton-activation analysis[136, 137, 143–145] and neutron-activation analysis[146–148] techniques. In these methods, one determines the beryllium content by measuring the energy of the gamma radiation that is produced upon collision of the sample with the neutrons or protons.

Gas Chromatography Analysis

Although organic chemists have used gas-liquid chromatography with great success since the early 1950's, it was not until 1959 that chemists investigated its potential in the area of trace-metal analysis.[75] This delay was caused by a lack of volatility and thermal stability of metal complexes. The first attempt to analyze metal complexes using gas chromatography involved the volatile metal halides and the volatile acetylacetonates.[75] Additional studies indicated that acetylacetone (AA), trifluoroacetylacetone (TFA), and hexafluoroacetylacetone (HFA) were suited for gas-chromatographic analysis of many metals.

Duswalt in 1959 was one of the first to use acetylacetone as an agent for separating beryllium by gas chromatography.[149] In 1960, Biermann and Gesser[150] again reported the separation of beryllium as the acetylacetonate, but it was not until 1963 that an attempt to quantitatively determine the beryllium content of a mixture was made.[151] Hill and Gesser were able to separate and quantitatively determine 3×10^{-7} g of beryllium as either the acetylacetonate, trifluoroacetylacetonate, or hexafluoroacetylacetonate complex, using a hydrogen flame ionization detector.[151] In 1963, Schwarberg, Moshier, and Walsh investigated the quantitative analysis of beryllium using trifluoroacetylacetone and a thermal-conductivity detector.[75]

Tanikawa and coworkers investigated the beryllium-trifluoroacetylacetone approach in 1966,[152] and Ross, Sievers and coworkers further investigated this approach in 1966,[153] in 1967,[154] and again in 1968.[78] Sievers and his coworkers used an electron-capture detector and were able to quantitatively detect 10^{-13} g of beryllium. They studied the effect of interferences and found that if ethylenediaminetetraacetic acid was used as a masking agent and the excess trifluoroacetylacetone was back-extracted out of the final organic layer, then only fluoride interfered.

Additional studies by Foreman, Gough, and Walker in 1970[79] provided useful data on the column material. The best separations were obtained using a methyl phenyl silicone gum as the liquid phase and Gas-Chrom Z as the support.[79]

This gas-chromatographic method, incorporating trifluoroacetylacetone and an electron-capture detector, has been used for determining trace amounts of beryllium in biological tissues and fluids,[46, 53, 76, 77, 79, 155–157] in air,[17, 46, 53, 158] and in terrestrial, meteoric, and lunar samples.[19, 159] With air samples, the beryllium-containing particles were collected on a filter, wet ashed, and extracted into benzine as the trifluoroacetylacetonate complex. The soil and lunar rock samples were treated in a similar manner except that a sodium carbonate fusion was used in place of the wet ash step. The biological fluid and tissue samples were usually wet ashed, but it was discovered that the ashing procedure was unnecessary;[76, 77, 79] the blood, urine, or tissue sample was simply ground, if necessary, and extracted directly. Radiotracer studies indicated that the extraction was complete in each case.

Two other detectors that workers have used with the gas chromatographic method are plasma excitation with the detection of the emitted light,[160] and mass spectrometry.[53, 80] With the mass-spectrometry approach, Wolf and coworkers fixed the mass-spectrometer detector on an interference-free mass peak of beryllium trifluoroacetylacetone (218 mass/charge), and allowed the column effluent to flow into the mass spectrometer.[80] A peak registered when the beryllium complex eluted, and the peak height was proportional to the amount of beryllium in the sample. The lower limit of detectability was on the order of 10^{-12} g as compared to 10^{-14} g for an electron-capture detector[19] and 10^{-8} g for a flame-ionization detector.[79]

Atomic Absorption Analysis

Beryllium analysis by atomic absorption has been performed using an air-acetylene flame, an oxygen-acetylene flame, a nitrous oxide-acetylene flame, and no flame. Workers used the air-acetylene flame as early as 1961,[161, 162] and Allan obtained a 1% absorption signal for 300 μg/ml using a 120-mm air-acetylene flame.[161] This poor sensitivity for beryllium results from the formation of refractory beryllium oxide that cannot be atomized effectively in the low temperature air-acetylene flame.[71]

The use of an oxygen-acetylene flame solved this refractory-oxide problem but presented additional problems.[71, 163] The oxygen-acetylene flame produced sufficient heat to atomize, but not ionize the beryllium; however, a higher burning velocity proved too rapid for the operation. Also, the danger of flash back was increased. Willis[164] solved these problems when he reported the nitrous oxide-acetylene flame had a temperature almost as high as an oxygen-acetylene flame, but had a lower burning velocity.

The nitrous oxide-acetylene flame has been used extensively for beryllium atomic-absorption analysis.[47, 71, 163–173] The sensitivity for beryllium is 0.03 μg/ml for 1% absorption, the lower detection limit is from 0.01 to 0.002 μg/ml, and the interferences are few.[47, 71, 172, 173]

Bokowski,[47, 71] Nakahara, et al.,[172] Fleet, et al.,[166] and Ramakrishna, et al.[163] studied the effect of various cations and anions on beryllium absorption in a nitrous oxide-acetylene flame. They found that only silicon and aluminum, at concentrations of about 500 μg/ml or greater, interfere with the beryllium-absorption signal. The aluminum interference is reduced with the addition of 2.5 g of 8-hydroxyquinoline to 100 ml of solution.[166] No ions interfered with 1.0 μg/ml of beryllium if they were present at concentrations of less than 100 μg/ml,[163] but numerous ions enhanced and depressed the beryllium absorption signal when they were present at concentrations of 4000 μg/ml or greater.[166] Ramakrishna, et al.,[163] Fleet, et al.,[166] Hicks, et al.,[174] and Nakahara, et al.[172] found that water miscible organic solvents tend to enhance the absorption signal.

The majority of samples were aqueous, but some workers analyzed air and urine samples.[47, 71, 173] Acetylacetone extraction into methyl isobutyl ketone was recommended for urine and air-filter samples yielding less than 0.5 μg/ml of beryllium in the final assay volume.[47, 71, 173]

A new and interesting technique for the determination of trace metals is flameless, atomic-absorption spectroscopy. This technique has been successfully applied to the analysis of beryllium in rock samples.[48] Sighinolfi[48] quantitatively detected beryllium concentrations as low as 1×10^{-3} μg/ml. Potassium, magnesium, sodium, and iron do not cause any appreciable interference to 10×10^{-3} μg/ml of beryllium, when present at 200 μg/ml, but 50 μg/ml of calcium greatly interferes. Five percent (w/v) sulfuric acid eliminates this calcium interference. The sulfuric acid also eliminates the depressant effects of hydrochloric and nitric acids. Aluminum apparently has no strong effects. Sighinolfi obtained excellent results on standard silicate rock samples when using aqueous beryllium standards containing sulfuric acid.

Preliminary results at Rocky Flats, by the author, indicate that beryllium concentrations as low as 5×10^{-4} μg/ml can be detected by the flameless approach. The sensitivity, using a Perkin-Elmer 403 spectrometer equipped with a HGA-2000 atomizer, is about 10×10^{-12} g. Additional results indicate that urine-beryllium concentrations of greater than 5×10^{-4} μg/ml can be directly determined. Spiked urine samples containing 0.25 μg of beryllium per 50 ml of urine were run with and without wet ashing. The beryllium was quantitatively recovered in both cases when compared with acidic, aqueous-beryllium standards.

Miscellaneous Analyses

Researchers have developed numerous, miscellaneous techniques for beryllium analysis. Some of these are polarography, secondary ion-mass spectrometry, laser-microemission spectroscopy, electron-microprobe analysis, phosphorescence, enzyme-inhibition analysis, and ion specific electrode analysis. Of these, polarography has probably been used the most.

Published work on the polarographic determination of beryllium is limited, and early workers experienced difficulty in the determination of beryllium in aqueous solutions.[51, 92] The failure to observe reduction steps, the proximity of the hydrogen steps resulting from the hydrolysis of Be^{2+} ions, and the need for accurate pH control caused many difficulties. The use of dimethylformamide as a solvent alleviated some of these problems and allowed Galova and Pantony[92] to detect 10^{-3} to 10^{-4} M beryllium. Further introduction of organic chelating agents such as *o*-(hydroxy-5-methylphenylazo) benzoic acid allowed workers to detect beryllium concentrations as low as 10^{-6} M.[51, 175–178]

Direct mass spectrometry is not generally applicable to the determination of beryllium since beryllium is insufficiently volatile, but secondary ion-mass spectrometry has proved valuable.[179–181] This approach involves the use of a mass spectrometer modified so that the ion source generates positive ions by ion bombardment.[180] This technique, while appearing to possess high sensitivity (10^{-13} g of beryllium),[181] requires a rather complicated mass spectrometer and can analyze only surface beryllium.

Another useful but restrictive method of analysis is microemission spectroscopy. With this techniqu the sample is excited with a narrow laser beam, nd the emission from the excited beryllium atoms s measured.[13, 182-184] The lower limit of detection is 10^{-12} g, but the sample must contain 50 μg of beryllium per gram of sample,[13] and the recovery of beryllium from the standard is erratic.[183] Small amounts of beryllium can be detected in specific microscopic tissue areas, however.

A technique similar to microemission spectroscopy is electron-microprobe spectroscopy. Three different groups investigated the use of this technique for beryllium analysis,[185-187] but beryllium can not readily be detected by this procedure.[188] Electron-microprobe analysis consists of directing a beam of electrons onto the surface of the sample and measuring the energy of the emitted X rays. Homogeneous standards are required, and sample surface areas as small as one micrometre in diameter can be probed.

Two other analysis techniques are phosphorescence and enzyme-inhibition analysis. The phosphorescence of beryllium complexes has been used to detect submicrogram amounts of beryllium.[189, 190] Also, the degree of inhibition of the enzyme, alkaline phosphatase, has been correlated to the beryllium concentration of the reaction medium.[191, 192] Alkaline phosphatase is a magnesium-dependent enzyme, and beryllium can inhibit this enzyme by tightly binding to the magnesium site on the enzyme.[193] By measuring the rate of the enzyme-catalyzed reaction in the absence of beryllium, in the presence of beryllium standards, and in the presence of the beryllium-containing sample, the concentration of the beryllium in the sample can be determined. This method can detect 0.01 μg of beryllium per ml.[192]

The literature search revealed only three published works on beryllium analysis by ion-specific electrodes.[194-196] The Orion manual[195] suggested taking the calcium ion specific electrode, with its membrane being a solution of calcium dialkylphosphate, and converting it to a beryllium ion specific electrode by soaking it in a beryllium-ion solution. Fleet and Rechnitz[196] used such an electrode to elp measure the rate of complex formation etween beryllium ions and organic-hydroxy acids. They were able to detect 10^{-5} M beryllium.

TOXICOLOGY

Introduction

Siem,[5, 197] conducted animal toxicity studies on beryllium in 1886, but it was not until 1933 that a disease common to the beryllium industry was reported.[198] In the 1930's, German and Russian[198-200] writers reported illnesses among beryllium-using industrial workers and within a decade, additional reports of an illness related to beryllium usage appeared in the European literature.[4, 199, 201-207] In the 1940's, corroborative evidence of a unique disease related to beryllium workers came from the United States,[199, 208-210] but the issue of beryllium toxicity still remained clouded. Some investigators[4, 211] attributed the toxicity to the anion associated with beryllium, and the United States Public Health Service concluded in 1943[212] that "beryllium of itself is not toxic." Subsequent findings in the 1940's established that beryllium was toxic.[4, 209, 210, 213]

In 1946, the hazard that threatened beryllium workers developed a new aspect. The cases reported through 1945 had been acute attacks arising during exposure to beryllium compounds,[3] but in 1946, Hardy and Tabershaw reported a delayed beryllium poisoning.[210] This delayed or chronic beryllium poisoning apparently occurred years after initial beryllium exposure. Of the more than 800 reported cases in the Beryllium Registry,[4, 206, 221] a high percentage are of chronic or delayed beryllium poisoning.[214]

Additional details on the history of beryllium disease can be obtained from a number of sources.[3, 5, 199, 206, 207, 215]

One reason for the 10- to 20-year delay in relating beryllium to the chronic form of the poisoning is that chronic beryllium disease is difficult to diagnose.[3, 4, 199, 206, 214-220] Although many cases of beryllium disease can be recognized by pathologic changes, the observations are not specific for the disease.[4, 220] 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 tissues or in body fluids. The finding of beryllium in tissues does not, in itself, indicate the presence or the possible future occurrence of beryllium disease; it indicates only a past exposure.[14, 15, 30, 34, 199, 215, 220]

Another diagnostic tool is the patch test,[215, 222, 223] which is based on an immunological response to beryllium salts. The test is not always helpful since false interpretations can occur,[215, 223, 317] and it is possible that the test will initiate harmful effects if beryllium is already in the body.[215, 224, 317]

A new, useful diagnostic tool is the blast transformation of lymphocyte test that Deodhar, Barna, and Van Ordstrand are using at the Cleveland Clinic Foundation[316–318] (see the following section, "Exposure Indicators," for details).

Once the chronic disease is diagnosed, there is little that can be done for the person. Steroid treatment has shown some limited success.[3, 206, 215, 220, 225, 226] Workers have also investigated use of the chelating agent, aurintricarboxylic acid,[3, 215, 227–229] but its success has been disappointing.[220, 227, 229] Recent work on chelating agents by Russian workers may show some promise.[230–232] Unpublished work with Vitamin C indicates that this vitamin (in one gram doses) is beneficial in removing beryllium from the body.[233]

A 25-year study of 4,000 beryllium workers revealed no significant mortality-rate departure from the normal expectation.[4]

Acute Beryllium Disease

Beryllium disease can occur in the acute or chronic form. The symptoms of acute beryllium disease have been recently described by several workers.[4, 199, 215, 225] Tepper, Hardy, and Chamberlin[225] defined acute beryllium disease "to include those beryllium-induced disease patterns with less than one year's natural duration and to exclude those syndromes lasting more than a year." Chronic and acute beryllium disease have some similar symptons; the chief difference between the two forms is in the suddenness of onset and in the rate of progression.[218] In the acute form the symptoms usually appear within weeks after the initial inhalation of beryllium by the patient, but rarely last longer than four months.[218]

On the basis of extensive tests, the Atomic Energy Commission concluded in 1950 that all known cases of acute beryllium disease could be attributed to an atmospheric concentration of beryllium compounds in excess of 100 micrograms of beryllium per cubic metre.[3] When the air level exceeds 1000 micrograms of beryllium per cubic metre, nearly everyone affected would develop the acute disease. The crystal structure, particle size, chemical form, the person, and the person's physical condition, however, are all factors in the development of acute beryllium disease.[3, 227, 234, 248]

The acute symptoms usually fall into two classes: respiratory and skin.[4] Beryllium diseases of the skin and conjunctiva occur as contact dermatitus, beryllium ulcers, and ocular effects. Contact dermatitus is characterized by itching and reddened lesions, and may occur on an allergic basis.[4] Beryllium ulcers result from implantation of beryllium-containing materials, and the beryllium must be removed before healing can take place. Ocular effects are similar to acid or alkali eye burns.

The respiratory effects are pronounced and range from a mild inflamation of the nasal and mucous membranes to severe chemical pneumonitis.[4, 218] Acute pneumonitis is rarely encountered because of improved control methods, but it is serious and can result in death. Nonproductive cough, difficult breathing, substernal discomfort, weight loss, appetite loss, and weakness are all symptoms of acute pneumonitis.[4, 218] Present treatment for acute pneumonitis includes the use of oxygen, steroids, and antibiotics.[4]

Chronic Beryllium Disease

Tepper, Hardy, and Chamberlin[220] state 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 that of the acute illness 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 lasting total 'cure'; (3) commonly progressive in severity in spite of the cessation of exposure; and (4) a systemic disease."

The most familiar characteristic of chronic beryllium disease is pneumonitis with accompanying cough, chest pain, and weakness.[4, 5, 206, 220] Death usually results from cardiac failure. There are numerous other disorders, and a number of biochemical abnormalities also occur. Chronic beryllium disease is a general disease, and the patient is more sick than the lung picture would suggest. Beryllium causes massive damage to the cells of practically every organ with which it comes in contact, and lesions are found scattered throughout the organs of the body.[3, 206, 207, 235–238]

As mentioned previously, diagnosis of the chronic form may be difficult. The symptoms are not unique, and there may be a delay of up to 15 years in the onset of chronic beryllium disease from the last beryllium inhalation.[206] Most reported cases have resulted from exposures of two or more years, but there is evidence that one worker acquired the chronic illness after a heavy exposure of less than six hours duration.[214] Again, the crystal structure of the beryllium compound, the particle size, chemical form, the person, and the person's physical shape are all factors in the development of chronic beryllium disease.[3, 227, 234, 248] Finally, the chronic form usually results after the exposed person experiences stress, such as from pregnancy or surgery.[293]

Standard Exposure Limits

In 1949, the United States Atomic Energy Commission established human beryllium exposure limits.[3, 239–241] In no instance has the effectiveness of industrial air standards been so apparent as that established for beryllium. The observance of these imits has produced no new cases of beryllium disease.[239, 240, 243] The limits are as follows:

1. The atmospheric average for an 8-hour period in a plant should not exceed 2 micrograms per cubic metre.

2. No person should be exposed to atmospheric concentrations greater than 25 micrograms per cubic metre at any time.

3. The average monthly neighborhood atmospheric concentration should not exceed 0.01 microgram per cubic metre.

Guidelines set by the American Industrial Hygiene Association are somewhat different.[242, 244] That association indicates a 50-milligram-per-cubic-metre atmospheric concentration for six hours is immediately hazardous to life. Harris[245] feels the present AEC standards are too strict and can safely be raised to 100 micrograms per cubic metre for short exposures and 5 micrograms per cubic metre for long exposures.

There is no specific limit for drinking water even though the United States Public Health Service revised their standards in 1962. The main reason for not setting a limit is that beryllium and beryllium compounds are not readily absorbed from the alimentary tract.[240] Sazhina has, on two occasions, recommended two different standards: 0.001 mg/l (Reference 246), and less than 0.0002 mg/l (Reference 247).

Beryllium Biochemistry

Several groups have recently reviewed the biochemistry of beryllium.[249–252] In the following pages the distribution, excretion and absorption, transport, inhibition of enzymes, and two possible disease mechanisms will be discussed.

Beryllium enters the body mainly by inhalation.[199, 215] Little beryllium is absorbed through the intestinal wall.[199, 227] Beryllium compounds vary in the way they enter the body from the lung, and upon entering the blood stream, they are transported to the liver, spleen, lymph nodes, and bone with varying amounts remaining in the lung.[199, 215, 227] The concentration, particle size, and chemical makeup of beryllium compounds affect the distribution and excretion of the beryllium,[227, 234] but a large percentage of the beryllium is usually quickly excreted in the urine.[199, 215] The beryllium that remains is stored in the major tissue sites[227, 253] and is slowly excreted in the urine. Beryllium received orally is excreted mainly in the feces.[199, 215]

The transport of beryllium from its site of lung deposition has been the subject of many investigations. It is generally agreed that once the beryllium reaches the blood stream, it is in at least two forms.[254–256] Some individuals indicate that a small amount of beryllium is in a chelated, diffusible form,[257] and others indicate a nondiffusible particulate form with the particles being the hydroxides and phosphates.[256, 258] The outstanding question is whether the beryllium is bound to the plasma proteins. Some workers have indicated that it is not,[206, 256, 257, 259] while others have suggested it is.[235, 254, 260] Apparently beryllium can bind to native[235, 261] and denatured serum albumin,[235] and to the α-globulin proteins.[254, 262] The complex may be in the form of a beryllium phosphate-protein complex.[237, 254, 262]

The fact that beryllium inhibits several enzymes indicates that beryllium can bind to proteins.[227, 237, 263–285] Even though several enzymes are inhibited by small amounts of beryllium, workers have concentrated mainly on alkaline phosphatase and phosphoglucomutase.[206] Apparently beryllium can inhibit these enzymes by a number of mechanisms; it might interfere with a phosphoryl-enzyme intermediate, it might compete with magnesium for a magnesium-binding site, it might tie up the normal substrate, and it might act by a combination of these.

Enzyme inhibition may explain some of the toxic effects of beryllium,[227] but there are two other possible chronic disease mechanisms: immunological[235, 286–292, 316–318] and lysosome.[227, 233, 293] The mechanisms for these two approaches are diagrammed in Figure 1.[293]

Both mechanisms are based on beryllium release or redistribution in the body. This has been shown to occur after a stress such as pregnancy or surgery.[293] Once the beryllium is released from storage, an immunological reaction eventually causes cell lysis or a lysosome-membrane disruption occurs, which releases distructive enzymes. Possibly both mechanisms occur, but the evidence supporting the immunological approach is more convincing.[316, 317]

EXPOSURE INDICATORS

Nonindicators

No known case of acute or chronic beryllium disease has occurred from people exposed to beryllium concentrations of less than or equal to the Atomic Energy Commission guideline concentrations.[199, 227, 239, 240, 243] There is still a need, however, for a beryllium-exposure bioassay. A few of the reasons for this need are as follows: (a) the response to beryllium varies from person to person, (b) the cumulative effects of beryllium are not well known, (c) the possibility that an accident might occur in which high concentrations of beryllium are produced is always present, (d) respirators are not always completely efficient, and (e) air-sampling devices may not reflect breathing concentrations of beryllium.

This literature search revealed that there are no published beryllium-exposure bioassays available. The literature search did, however, point out factors that are not indicators of beryllium exposure. The beryllium content of 24-hour urine samples,[4, 5, 15, 16, 30, 34, 220, 229, 294–298] the beryllium content of lung tissue,[3, 5, 13, 14, 220, 229] the beryllium content of the liver, spleen and kidneys,[4, 5, 30, 220, 229] the beryllium content of blood,[5, 220, 229, 295] lung X rays,[199, 227, 296] and the activity of magnesium-dependent enzymes[4] are all nonindicators of total beryllium exposure.

Possible Indicators

Among the body factors that have shown some response to beryllium exposure in animals and/or man are uric acid blood levels,[299] gamma-, alpha- and beta-globulin blood levels, and the blood albumin level.[4, 5, 199, 220, 227, 229, 300–307] The ability of the lung to oxidize various substrates[308] is another

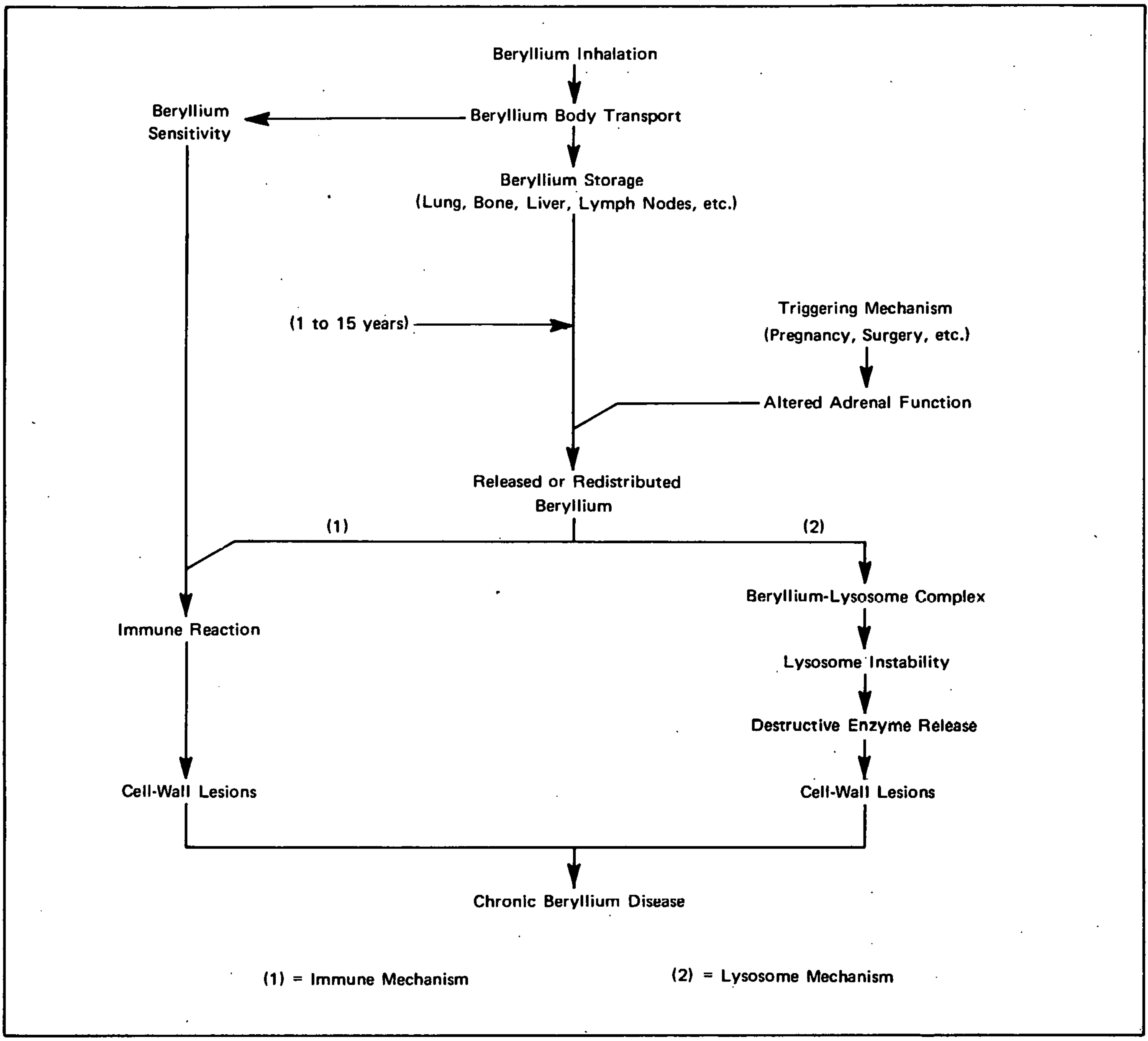

FIGURE 1. Two Possible Chronic Beryllium Disease Mechanisms.

factor as are the relative concentrations of various lactic dehydrogenases,[309, 310] the number of free mercapto groups in blood and urine proteins,[303, 304, 311] the concentrations of various inorganic agents in blood and urine,[33, 199, 227, 293, 312] the adrenal steroid reserve levels,[313, 314] the blood IgG level,[315, 316] and the free amino acid levels of urine.[311]

There are at least two other possible beryllium-exposure bioassays that are promising. Unpublished work with Vitamin C indicates that this vitamin, in one-gram doses, is beneficial in removing beryllium from the body.[233] Following the treatment, relatively high amounts of beryllium are excreted in the urine. The resulting urinary beryllium content may be related to past exposures.

The second promising exposure bioassay is the blast transformation of lymphocyte test also called the lymphocyte transformation test.[316-318] The test consists of incubating the blood of an exposed worker with beryllium compounds and observing the number of blast cells. It is possible that this test will indicate past beryllium exposure for those who are sensitive to beryllium and who are capable of developing chronic beryllium disease.[316, 317] This test will indicate the severity of the chronic disease for those afflicted.[316] The blast transformation of lymphocyte test may prove useful in detecting high-risk workers in the beryllium industry in addition to being a valuable diagnostic tool.[316, 317]

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