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THE BIOLOGICAL EFFECT OF BERYLLIUM AND ITS COMPOUNDS

[Article by V. V. Melnikov and V. F. Kazenashev]

A number of valuable properties such as light weight, resistance to corrosion, refractoriness, low density, high permeability for x-rays etc., have led to the use of beryllium in steel casting plants, non-ferrous casting plants, the chemical, pharmaceutical and petroleum-industries, the ceramics industry, machine tool and nuclear industries, electronics, aviation and rocket construction. In addition, the unusually high toxicity of beryllium and its compounds is known from both experiments and industrial conditions; this places this element in the series of substances with which contact is dangerous to the health of a wide range of people working with it.

The experiments of Gardner and Haslington, who revealed the blastomogenic effect of beryllium, have been corroborated by a number of studies (Barnes; Vorwald; Komitowski and others). These experiments have basically concerned intravenous administration of ZnBe silicate and beryllium oxfde in rabbits for the purpose of obtaining bone neoplasms. The total doses of ZnBe silicate with which a positive effect was produced were 1-2.1 g, and 0.36-1 g for beryllium oxide; the latency period ranged from 7 to 12 months in using ZnBe silicate and from 8 to 11.5 months in using beryllium oxide. No bone tumors appeared in the other experimental animals (guinea pigs, rats). The primary tumors were isolated in some animals and were multiple in others, with localizations in the head of the right femur, in the body of the lumbar vertebrae, in the distal end of the right femur,

in the tibia and humerus, the scapula, hip bones. The tumors often grew into the adjacent muscle and compressed the organs.

In all the works except one, metastases were observed in other organs, most often in the lungs. It is interesting to note that there were no metastases in the animals whose spleen had been previously removed. The metastases in the lungs were small and few in number in some cases, and in others, the tumorous nodes occupied approximately half of the volume of the lung tissue. Focal fibrosis of the bone marrow was observed in the ends of several of the long bones in most of the animals. The red bone marrow contained multiple white macules which were found to be accumulations of dust from the beryllium compounds on microscopic examination.

Several authors have turned their attention to atrophy of the spleen and cirrhosis of the liver. Thus, Janes came to the conclusion that there is a definite correlation between atrophy of the spleen and formation of osteogenic sarcomas. The spleen was normal in five animals in which no tumors were found, although they had received the same amount of beryllium as the rabbits which had developed osteosarcomas.

A positive result was obtained in rabbits after intravenous administration of *40* mg of metallic beryllium powder, beryllium phosphate and lactate and "phosphor" powder which contains beryllium oxide, zinc oxide and silica in the molar ratio of 1:1:1 with a total dose of 0.06–0.09 g. A case of osteosarcoma has been described in rabbits after inhalation of beryllium oxide in the concentration

of 6 mg/m^3 with daily exposure of five hours five times a week for eleven months. A sarcoma in the left pubic bone was found 17.5 months after termination of the experiment.

None of the communications have contained information concerning the formation of malignant tumors in control animals and particularly in rabbits after toxicological experiments, for two decades.

An osteosarcoma which arose after treatment with ZnBe silicate was not shown roentgenologically until 30–52 weeks after terminating the course of injections. The changes indicating the development of an osteogenic sarcoma are usually of a destructive nature; in some cases atypical bone tissue forms. The tumors appear in the area of the epiphyseal-metaphyseal junctions of the long tubular bones, and in flat bones such as the scapulaand hip bones. No osteogenic sarcomas were observed in the diaphyseal sections. Microscopically, the structure of all the tumors was typical of osteosarcomas. Several types of tissue could be distinguished in each tumor - osteo-, chondro- and fibroblastic tissue with alternation of sections of atypical, poorly differentiated fibroblasts, atypical cartilage and bone tissue. "here was a clear difference between the morphological picture of the atypical modular bone and the morphology of the osteogenic sarcoma.

In 1966 and 1969, Tapp reported new methods of obtaining experimental neoplasms with beryllium. Intramedullar injection and subperiosteal administration of the carcinogen were used first. 20 mg of ZnBe silicate powder with 5 µm particle size in the form of a suspension in 0.5 ml of water were administered intramedullarly.

The injection was administered once, with a sterile needle with observation of aseptic measures. The superior end of the right tibia 1 cm below the epiphyseal cartilage was the site of administration. A suspension of Zn oxide was administered to the control animals in the same way. Osteosarcomas developed in 4 of the 12 rabbits between the 12th and 15th month at the side of administration. The author observed multiple metastases in the liver, bones, spleen and adrenals which arose both by hematogenic and lymphogenic pathways. There were no neoplasms in the control animals.

An attempt to provoke an osteogenic sarcoma in the tibia of rabbits by administering beryllium salts under the periosteum was also successful. An incision 20 mm long was made in the skin at the upper end of the tibia under anesthesia in very sterile conditions (Tapp, 1969). The periosteum, which is close to the surface at this point, was slit 5 mm below the epiphyseal cartilage; the incision continued for 15 mm below. After detaching the periosteum from the bone 3-4 mm from each side of the incision, 10 mg of beryllium salt were placed inside the formed cavity,

The author took precautions to prevent the beryllium from coming into contact with other tissues. The periosteum, fascia and skin were sutured with separate layers of catgut. A similar procedure was performed on the opposite bone in the control animals, but they were administered 10 mg of Zn oxide or Zn silicate. All of the animals survived the procedure. Tumors (osteosarcomas) formed between the 10th and 25th month after the operation only in the animals which

had been administered with beryllium salt.

Komitomski obtained osteosarcomas in rabbits by means of intramedullar administration of a beryllium-gelatin capsule containing 25 mg of beryllium.

In one of the experimental works to investigate the toxic properties of beryllium compounds (Vorwald and Reeves), the reaction of the lungs of rats to beryllium sulfate and oxide were investigated. The authors found chat the beryllium compounds caused not only chronic specific pneumonia, burs also progressive epithelial proliferation and metaplasia with ultimate formation of cancer of the lungs.

Insignificant proliferation of the epithelium was usually observed with many chronic inflammatory processes in most types of animals, including rabbits and guinea pigs poisoned with beryllium; this phenomenon was first detected in rats.

A number of authors have experimentally studied the effect of beryllium oxide and sulfate on the respiratory organs (Vorwald and Reeves; Schepers et al.; Wagner, and others). Rats were usually used for the experiments with inhalational or intratracheal administration. Cancer of the lungs was found in the animals 9-13 months after inhalation of beryllium sulfate in concentrations of 2.8-54.7 $\mu g/m^3$ had begun, with a 100% yield of tumors 13-18 months after exposure had begun, and nine months after beginning inhalation of beryllium oxide in the concentration of 48 $\mu g/m^3$. The duration of exposure was from 180 to 540 days for the various authors. Intratracheal injections of beryllium sulfate and oxide in doses of

0.107 and 4.5 mg of beryllium (metal), respectively, with three administrations at a week's interval resulted in formation of tumors eight months after termination of treatment.

Vagner observed cancer of the lungs in rats as the result of inhaling beryllium ore, beryl and bertrandite (minerals which contain beryllium) for 690 days (six hours a day, five days a week) in concentrations of 15 mg/m^2, 620 and 210 $\mu g/m^3$ (metal) respectively.

The fundamental, 8-year investigation of 30 young monkeys (Vorwald) deserves particular attention. An intrabronchial injection of a 5% suspension of pure beryllium oxide in physiological solution or a bronchomural implantation (in the wall of the bronchus) of a suspension or both types used simultaneously were administered to 20 of the 30 animals. The remaining ten monkeys were exposed to the long-term effect of beryllium sulfate in the concentration of 35 $\mu g/m^3$ in a chamber. The first monkey died four years six months after injection of approximately 1 ml of the 5% suspension of beryllium oxide into the wall of the horizontal bronchus of the right lung and intrabronchial administration of 5 ml of the same suspension into the lung. The condition of the animal was extremely serious in the last six months of life. On autopsy, a large tumor was found in the area of the root of the right lung; it obliterated the main right bronchus and occupied a large part of the right lung. A small tumor was found in the area of the diaphragm. Histologically, a clearly anaplastic adenocarcinoma with metastases was found. Four monkeys died shortly thereafter; primary cancer of the lungs was found. Two of the animals

which died received beryllium oxide, and two others underwent periodic inhalation of beryllium sulfate, one monkey for 3241 hours and the other for 3871 hours for more than five years before death. During next 6-8 months, the condition of the remaining animals gradually worsened, and darkened areas were discovered in the lungs roentgenologically.

On autopsy, cancer of the lungs with extensive metastases into the chest cavity was found in all four monkeys.

With respect to malignant tumors including cancer of the lungs with chronic berylliosis in humans, only isolated works touch upon this question; some authors indicate such a possibility (Barnes; P. P. Dvizhkov) and establish a correlation between the above (Hardy; Niemoller; Mancuso). Niemoller describes a case of late cancer of the lungs with metastases in the brain in a patient who had suffered from chronic berylliosis and also a case of the recovery of a patient after diagnosis cf malignant degenerative berylliosis was established on the basis of roentgenological and laboratory findings (cancer cells in the sputum). Van Ordstrand reports that cases of primary lung cancer have been described in patients who had recovered after acute berylliosis. Hall et al., describe primary cancer of the lungs in one patient who had had chronic berylliosis out of 601 cases of acute and chronic berylliosis reported, and Hardy notes three cases of lung cancer out of 650 diseases caused by beryllium. In observing several groups of people who had worked in two beryllium extracting firms from 1937 to 1948; in following up the individual groups until 1967, Mancuso found a definite regularity. Cancer of the lungs most often

occurred in workers with industrial experience of 3–15 months than in those who had worked in the industry for 18 months and longer. The author reports these results of the observations: out of 145 people who had previously suffered from bronchitis or pneumonia of a beryllium origin, 35 died, and six of these had lung cancer and reticulocellular osteosarcoma was found in one.

The material presented indicates that beryllium, which has high general toxicity, can have a blastomogenic effect in some cases.

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