Organic Germanium
A Novel Dramatic Immunostimulant

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The element germanium (Ge) atomic number 32, atomic weight 72.6, tends to pack into a lattice-like structure and displays the electrical conductivity of a semimetal. Since the elements of similar atomic number are biologically-essential trace elements (e.g. selenium), one might anticipate that germanium plays a role in human biochemistry. Germanium occurs in coal deposits, apparently having accumulated to levels as high as 10 ppm from the remains of once-living organisms (1).

In its appearance germanium is like a metal, though technically it is classified as a semimetal. Chemically it resembles silicon at high temperatures and tends to be noncon-ductive at low temperatures. In the 50's and 60's a number of researchers (2-8) investigated the biological activity of germanium and its occurrence in biomaterials; it then became generally accepted that germanium had little biological significance. However, more recent reports by Dr. K. Asai that it occurs in high concentrations in certain medicinal plants, and that a synthetic derivative appears to have significant clinical efficacy, have reopened the question of its biological essentiality (1).

The research and clinical work of Dr. Asai is summarized in his book *Miracle Cure: Organic Germanium* (1). Asai reports that the concentrations of germanium in foods and other biomaterials range from .1 to 1 ppm, corresponding to .1 to 1 microgram of germanium per gram of food material. He also finds that some medicinal plants contain large amounts of germanium, e.g., about 300 ppm for Ginseng radix. Dr. Asai reported that the levels of germanium in medicinal plants range as high as 2000 ppm (roughly 1000 milligrams per pound). These findings by Dr. Asai sparked considerable renewed interest in the nutritional and pharmacological effects of germanium. Asai's determinations of the germanium content of medicinal plants are summarized below:

Shelf fungus (Trametes cinnabarina Fr.) 800-2000 ppm
Note 1 Ginseng (from Shimane Prefecture, Japan) 250ppm
Ginseng (from Shinano district, Japan) 320ppm
Sanzukon (Codonopsis Tangshen) 257ppm
Sushi (Angelicapubescens Maxim.) 262 ppm
Waternut (Trapa japonica Flerov) 239 ppm
Boxthorn seed (Lycium Chinese mill) 124ppm
Wisteria knob (gall) (Wisteria floribunda) 108 ppm
Pearl barley (Coicis Semen) 50 ppm
Gromwell (Lithosemi Radix/ Lithospermum officinale) 88 ppm

Asai concluded that the germanium content of these and other medicinal herbs may be responsible (at least in part) for their therapeutic value (1, 22).

Other plants generally regarded as conducive to good health also contained fairly large quantities of germanium (1):

Garlic 754 ppm
Comfrey 152 ppm
Aloe 77 ppm
Chlorella 76ppm

PHYSIOCHEMICAL PROPERTIES

Ge-132, carboxyethyl sesquioxide of ger-manium is prepared by hydrolysis of a trihalogermanopropionic acid derivative. Its molecular formula is (GeCH2CH2

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COOH) $_2O_3$. X-ray crystallography revealed a three dimensional array composed of three oxygen atoms linked to every germanium atom, thus forming a crystalline structure. The crystal decomposes at approximately 270 degrees C. The infrared absorption spectrum shows a characteristic absorption peak of the Ge-O bond at 800-900 cm. (31)

Ge-132 is insoluble in most organic solvents but soluble in water at 1.19g/100 ml (31 degrees C). In appearance it is a colorless, odorless crystalline powder with a slightly acid, metallic taste. The compound is stable at a pH range between 2 and 12; most stable at pH 7.4; its pk of the carboxyl group is at pH 3.6. It is generally very stable at varying conditions of temperature, humidity and lighting. No decomposed products are detected when Ge-132 is kept at room temperature for 36 months.

Organic Germanium is Essentially Nontoxic

Initial acute and chronic toxicity studies were conducted by Dr. Asai using his "organic germanium compound" ("Ge-132", biscarboxyethylgermanium ses-quioxide), originally synthesized by the Asai Germanium Research Institute in Tokyo, Japan. Germanium was fed to various species of experimental animals, up to very high doses equivalent to several grams per day for a human. The compound was found to be essentially nontoxic even at the highest dosages (1).

Additional toxicological and pharmacokinetic studies have revealed that Ge-132 is indeed of extremely low toxicity, up to an equivalent in humans of many grams per day of "Organic Germanium", the pure sesquioxide material (9, 10).

Ge-132 has almost no effect on normal animals. It may have no action on specific pharmacological receptors. However, it appears to have therapeutic potential on a number of disease models for animals and for humans. Oral administration of Ge-132 were studied. Blood levels reached a peak after 3 hours and almost disappeared 24 hours after oral administration. Most of the compound was found to be extra cellular — in plasma and a small amount in red blood cells. Total excretion (urinary and fecal) amounts to about 100% within 1 to 1.5 days (32). Its distribution in different organs has been studied (32). At 3 hours after oral administration its greatest concentration is in the small intestine from which it is absorbed into the bloodstream. After three hours high concentrations were found in all organs with higher levels in the thyroid gland. High concentrations also in the kidney and bladder. Twelve hours after oral administration only residual amounts were detected in any of these organs. Ge-132 by intravenous administration was found to rapidly pass into tissues and then was rapidly excreted into the urine (32).

Organic Germanium in Treatment of Human Disease

The clinical trials at Dr. Asai's Organic Germanium Clinic in Japan produced results that were impressive, even though they were not controlled studies. Under medical supervision, numerous case histories along with standard blood chemistry parameters were assessed from patients with a broad-ranging spectrum of symptomatologies. These subjects were treated with Dr. Asai's Organic Germanium at dosages ranging from as low as 50 mg to as high as 1000 mg per day. Liver dysfunctions, hepatitis, and various cancers (including leukemias) were just a few of the difficult diseases that responded well to Organic Germanium (1). Diseases of the eye, including cataracts, often responded quickly and dramatically. Organic Germanium produced excellent results when given to hypertensive patients, and proved surprisingly effective at normalizing blood pressure in SHR (spontaneously hypertensive rats) (11). Heart disease, including myocardial infarction and angina pectoris, and Raynaud's Disease responded well to dosages as high as 1400 mg per day (1). Astonishing benefits were reported against mercury, cadmium, and other metal poisons.

Controlled Laboratory Studies Confirm Germanium's Immunostimulant Effects

Organic Germanium has been found also to be a dramatic immunostimulant. In controlled studies it has demonstrated marked anti-tumor effects and interferon-inducing activity, and restored immune function in immune-depressed animals (12-21, 27, 28).

These immunostimulant effects were achieved with oral doses, and no harmful side effects were noted.

Organic Germanium can be assigned to a family of compounds capable of normalizing immune responses in organisms with impaired immune function. In addition, there are reports (14, 15) which describe its ability to enhance NK (natural killer cell) activity in healthy human subjects. Studies on immune-suppressed animals and on patients with malignancies or rheumatoid arthritis suggest that Organic Ge restores the normal function of T lymphocytes, B lymphocytes, antibody-dependent immune cell-killing activity, natural killer cell activity, and numbers of antibody-forming cells, though not enhancing these beyond levels considered normal (13, 21, 23, 24). Antitumor effects of Organic Ge were reported from studies on mice with Lewis lung carcinoma, chemically-induced sarcoma, and leukemias (17, 18, 24).

Ascites heptomas AH44 and AH66, bladder cancer (BC47) and Walker carcinosarcoma 256 are the responding rat tumors; Lewis lung carcinoma (3LL) and 3-methylcholanthrene (MCA) induced fibrosarcoma are representative mouse tumors (17). Prophylaxis of MCA-induced tumorigenesis and spontaneous mammary tumor production in mice were also demonstrated (14). Clinical effects of Ge-132 on the patients with malignant diseases, as well as rheumatoid arthritis, are reported (13). The patients administered Ge-132 include seven cases of malignancy and seventeen cases of rheumatoid arthritis. When Ge-132 was administered orally at 1500 mg per day, and malignant cases were treated with Ge-132 alone or with mild combined chemotherapy, the effects of Ge-132 on the malignancy were primarily detected by tumor size. Seventeen patients with rheumatoid arthritis were also treated with Ge-132 alone or with small doses of prednisolone (under 5 mg per day). These patients were examined with regular testing for circulating lymphocytes, T and B lymphocytes, natural killer cell activity and interferon production.

Three patients with malignancies exhibited decreased tumor size when treated with Ge-132 and immunochemotherapy. One of them was a patient with prostate carcinoma, and metastasis had been observed in the bone and stomach. A patient with cancer of the uterus had a metastasis to the rectum, which was a squamous cell carcinoma. "Her severe constitution improved remarkably after Ge-132 treatment and no relapse was observed at present" (13). Another patient had multiple myeloma. Her huge extramedullar tumor in the abdomen is completely disappeared after sixteen months of Ge-132 and intermittent cyclophosphamide therapy. A patient with postoperative lung cancer (squamous cell carcinoma) was controlled well with Ge-132 alone. T lymphocytes were normalized. The patient with cancer of the pancreas continued with a large abdominal tumor even after two years of Ge-132 and small doses of adriamycin, 5 flurouricyl and mitomycin treatment, but she felt generally well with no pain.

Single oral administration of Ge-132 was performed on two patients with malignancies to evaluate the effect of interferon induction in vivo. Maximum interferon induction occurred after four days.

In rheumatoid arthritis some of the treatment cases with Ge-132 alone were significantly improved and, T and B cell counts, killer cell activity and interferon levels were normalized in some patients.

Germanium Has Analgesic Properties

The analgesic (pain-killing) effect of Asai's Organic Germanium was recognized early during its clinical use. Organic Ge, whether administered orally or by the intravenous route, clearly enhanced morphine-induced analgesia (25). It was suggested that Organic Ge may activate dopaminergic or serotonergic neurons in analgesic pathways, and/or stimulate release of endogenous enkephalins or endorphins (our natural painkillers).

Organic Germanium - A Landmark Development in Nutritional Medicine

The apparent versatility of Organic Germanium in normalizing health and alleviating human diseases suggests that it acts at a fundamental level of life function. The known biological and clinical effects of Organic Germanium are consistent with Dr. Asai's suggestion that it can (at least partially) facilitate oxygenation in our tissues, a factor so critical for maintenance of health and prevention of disease (26). The exact underlying biochemical mechanisms accounting for the

varied effects of Ge-132 are not completely understood. Asai has suggested that the compound either activates, substitutes or facilitates the function of oxygen as the primary electron acceptor. Possibly it facilitates oxygen entry into the red blood cells. In cells which cannot utilize oxygen, for example cancer cells which appear actually to be oxygen-sensitive, we might predict that its presence as an "oxygen-catalyst" could have deleterious effects and likely therapeutic value (30); and it certainly does prove beneficial in selective cancer studies.

The belated discovery of the biologic values of bis-carboxyethyl germanium ses-quioxide, Dr. Asai's "organic germanium compound", is a landmark development in the field of nutritional medicine. The fact that it has profound immunostimulating effects should come as no surprise, given its apparent efficacy as an oxygen substitute and the pivotal role of oxygen in immune function (26). This breakthrough stems from Asai's initial finding that Ge occurs in such high concentrations in medicinal plants. It appears that Asai had identified one of the main active principles responsible for the therapeutic action of many age-old remedies. The late Dr. Asai did not regard germanium as a drug. He stated "I would rather call it a health-giving substance — it restores health to those afflicted with disease, and sustains health in those who are healthy. ...Where body cells lack oxygen, indispensable to life, a gradual decline in function is inevitable and the fire of life will reduce until it is extinguished" (1).

Note 1: Shelf fungus has long been reputed as an effective treatment of cancer, cited by Nobel Prize winner Alexander Solzhenitsyn in his book *Cancer Ward.*

References

1 . Asai K. Miracle Cure: Organic Germanium. New York: Japan Publications/ Kodansha International via Harper and Row, 1980.
2. Whipple GH, Robscheit-Robbins FS. Amer J Physiol 1925;72:419.
3. HueperWC. Amer JMedSci 1931;181:820.
4. Rosenfeld G, Wallace ED. Arch Ind Hyg 1953;8:466.
5. Rosenfeld G. Arch Biochem Biophys 1953;48:84.
6. Schroeder HA, Balassa JJ. J Nutri 1967;92:245.
7. Schroeder HA, Balassa JJ. J Chron Dis 1967;20:211.
8 . Schroeder HA et al. J Nutr 1968;96:37.
9 . Nagata T et al. Chronic intravenous toxicity study with carboxyethylgermanium sesquiox-ide in beagle dogs. Pharmacometrics 1978;16:671.
10. Tomizawa S, Suguro N, Nagashima M. Studies on general pharmacological effects of some germanium compounds. Pharmacometrics 1978;16:682.
11. Sato S, Ishikawa A. The Clin Report 1973;7:719-726.
12. Sato H, Iwaguchi T. Antitumor activity of new novel organogermanium compound, Ge-132. Cancer Chemother 1979;6:79-83.
13. Arimori S et al. In: Immunomodulation by Microbial Products and Related Synthetic Compounds (ed. Yamamura Y et al). Amsterdam: Elsevier Science Publishing; 1981:498-500.
14. Miyao K et al. Current Chemother Inf Dis (Proc 11th ICC and 19th ACAAC Am. Soc Microbiol) 1980;2:1527-1529.
15. Aso H et al. Cancer Chemother 1982;9:1976-1980 (in Japanese with English abstract)
16. Satoh H, Iwaguchi E. Cancer Chemother. 1979;6:79-83. In Japanese with English abstract).
17. Kumano N et al. Antitumor effect of organogermanium compound (Ge-132) in mouse tumors. Current Chemother Inf Dis (proc 11th Int Congress of Chemotherapy and I9th ICAAC Am Soc Microbiol) 1980;2:1525-1527.
18. Kumano N et al. Sci Rep Res Inst Tohoku Univ 1978;25:89-95.
19. Kuga N et al. Acta Path Japonica 1976;26:63-71.
20. Campbell JB et al. Interferon. Can J Microbiol 1975;21:1247-1253.
21. Mizushima Y, Shoji Y. Igaku-no-Ayumi 1980;13:1055-1056 (in Japanese).
22. Asai K. Shoku No Kagaku 1973;12:81 (in Japanese) but see also Mino et al. Determination of Germanium in medicinal plants by atomic absorption spectrometry with electrothermal atomization. Jap Pharm Bull 1980;28:2687-1691.
23. Mizushima Y, Shoji Y, Kaneko K. Restoration of impaired immunoresponse by germanium in mice. Int Arch Allergy Appl Immunol 1980;63:338-339.
24. Yoshidi M, Arimori I. Effects of Ge-132 in vitro on the activity of human natural killer cells. Med Biol 1982;104:87-89 (in Japanese). Arimori S et al. In:Immunomodulation by Microbial Products and Related Synthetic Compounds (ed. Y Yamamura et al) Amsterdam:

Elsevier Science Publishing 1981;pp 498-500.
25. Hachisu M et al. Analgesic effect of novel organogermanium compound Ge-132. J PharmDyn 1983;6:814-820.
26. Levine SA, Kidd PM. Oxygen-immunity, cancer and Candida albicans: the pivotal role of oxygen in immune function. Submitted to Let's Live, April 1986.
27. Aso H et al. Induction of interferon and activation of NK cells and macrophages in mice by oral administration of Ge-132, an organic germanium compound. Microbiol Immunol 1985;29(l):65-74.
28. Suzuki F, Pollard RB. Prevention of suppressed interferon gamma production in thermally injured mice by administration of a novel organogermanium compound, Ge-132. J Interferon Research. 1984;4(2):223-233.
29. Levine SA, Kidd PM. Antioxidant Adaptation: Its Role in Free Radical Pathology. Biocurrents Division, Allergy Research Group, 400 Preda St., San Leandro, CA 94577, 1985.
30. Levine SA, Kidd PM. A free radical-hypoxia-clonal selection theory of carcinogenesis (beyond antioxidant adaptation). J Ortho Psych 1985;14:189-213.
31. Manuscript, Asai Germanium Research Clinic.
32
Manuscript, Asai Germanium Research Clinic.