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Hydrazine Sulfate vs Cancer

Cons & Pros :

http://www.cancer.gov/cancertopics/pdq/cam/hydrazinesulfate

National Cancer Institute

Hydrazine sulfate is a chemical that has been studied as a treatment for cancer and as a treatment for the body wasting (i.e., cachexia) associated with this disease.
It has been claimed that hydrazine sulfate limits the ability of tumors to obtain glucose, which is a type of sugar used by cells to create energy.
Hydrazine sulfate has been shown to increase the incidence of lung, liver, and breast tumors in laboratory animals, suggesting it causes cancer.
There is only limited evidence from animal studies that hydrazine sulfate has anticancer activity.
Hydrazine sulfate has shown no anticancer activity in randomized clinical trials, and data concerning its effectiveness in treating cancer-related cachexia are inconclusive.
Hydrazine sulfate has been marketed in the United States as a dietary supplement or a nutraceutical by some companies; however, its use as an anticancer drug outside of clinical trials has not been approved by the U.S. Food and Drug Administration.

General Information

Hydrazine sulfate has been investigated as an anticancer treatment for more than 30 years. It has been studied in combination with established treatments as a chemotherapy agent. It has also been studied as a treatment for cancer-related anorexia (loss of appetite) and cachexia (loss of muscle mass and body weight). Similar to other hydrazine compounds, it has a core chemical structure that consists of two nitrogen atoms and four hydrogen atoms.

Hydrazine sulfate is marketed in the United States as a dietary supplement /nutraceutical by some companies. In the United States, dietary supplements are regulated as foods, not drugs. Therefore, premarket evaluation and approval by the U.S. Food and Drug Administration (FDA) are not required unless specific disease prevention or treatment claims are made. The FDA can, however, remove from the market dietary supplements that it deems unsafe. The use of hydrazine sulfate as an anticancer treatment outside of clinical trials has not been approved by the FDA. The FDA has not approved the use of hydrazine sulfate for any medical condition.

To conduct clinical drug research in the United States, researchers must file an Investigational New Drug (IND) application with the FDA. To date, the FDA has granted IND status to at least three groups of researchers to study hydrazine sulfate as a treatment for cancer.[1-3]

In animal studies, hydrazine sulfate has been added to the drinking water or the food supply, or it

has been given by injection. In clinical trials involving cancer patients, hydrazine sulfate has been administered in pills or capsules. Reviewed in [4] In the clinical studies conducted thus far, the dose and the duration of hydrazine sulfate administration have varied.

References

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3. Gold J: Use of hydrazine sulfate in terminal and preterminal cancer patients: results of investigational new drug (IND) study in 84 evaluable patients. Oncology 32 (1): 1-10, 1975.
4. Toth B: A review of the antineoplastic action of certain hydrazines and hydrazine-containing natural products. In Vivo 10 (1): 65-96, 1996 Jan-Feb.

History

During the past 90 years, hydrazine compounds have been studied in animal cells grown in the laboratory, in live animals, and in humans. Reviewed in [1] More than 400 hydrazine analogs (related compounds) have been screened for their ability to kill tumors. In 1996, a retrospective review of scientific studies in which the anticancer activity of hydrazine analogs was investigated found that 65 of 82 evaluated compounds showed some anticancer activity in xenograft models (tumor cells of one species transplanted to another species). Reviewed in [1] Of the 82 tested compounds, seven showed activity against human tumor cells and were, therefore, selected for further testing in pilot studies and phase I clinical trials. Reviewed in [1] Among these seven compounds, only procarbazine (a methylhydrazine derivative, also called ibenzmethyzin or natulan) completed preliminary testing in humans. Procarbazine exhibited anticancer activity in patients with Hodgkin disease, melanoma, and lung carcinoma, and it was ultimately used in several first-line treatment regimens in the 1960s.[2,3] Reviewed in [1] In view of the initial success with procarbazine, hydrazine sulfate, which is similar in chemical composition, was investigated for anticancer activity beginning in the 1970s. During this period, investigation of hydrazine sulfate as a treatment for cancer-related cachexia was also initiated. Research on hydrazine sulfate both as a single agent and in combination with standard chemotherapy regimens continued through the mid-1990s.[4-9]

Although it was proposed in the early 1900s that hydrazine compounds are toxic to animals and to humans, they have been administered as antidepressant (e.g., iproniazid), chemotherapy (e.g., procarbazine), and antituberculosis (e.g., isoniazid) drugs. In addition to medicinal uses, hydrazine compounds have been used in industry and agriculture as components of rocket fuel, as herbicides, and as antioxidants in boiler and cooling-tower water. Reviewed in [10-12] Many scientists consider hydrazine sulfate and other hydrazine analogs to be cancer-causing agents, and they have expressed concern about the safety of these compounds.[1,10,12-21] In the 10th Report on Carcinogens, hydrazine and hydrazine sulfate are listed by the U.S. Department of Health and Human Services' National Toxicology Program as "reasonably anticipated to be human carcinogens."[22] When the antituberculosis drug isoniazid and hydrazine antidepressants are combined with purified DNA in the laboratory, they produce hydrogen peroxide and free radicals that can damage the DNA.[17,23] Reviewed in [14] Hydrazine compounds have been reported to cause mutations and chromosome damage in bacteria and in plant and animal cells. Reviewed in [10]

Two mechanisms of action have been proposed for hydrazine sulfate to explain its potential antitumor and anticachexia properties. Both mechanisms involve the utilization of glucose (sugar), which tumors require as a main source of energy for growth. In one proposed mechanism, hydrazine sulfate blocks gluconeogenesis through inhibition of the enzyme phosphoenolpyruvate carboxykinase.[24] Reviewed in [25-29] Gluconeogenesis is a process by which extra glucose (in addition to that obtained from the diet) can be formed in the liver and the kidneys from the breakdown products of sugars, lipids (fats), and proteins. It has been suggested that cachexia occurs

because the body must use increasing amounts of energy and other resources, including its own protein, to meet the demand for glucose by tumors.[24] Reviewed in [25-30] Blocking gluconeogenesis and interfering with the supply of nutrients to tumors has been proposed as one way to inhibit tumor growth and to prevent cachexia.[24] Reviewed in [25-30]

In the second proposed mechanism, hydrazine sulfate inhibits tumor necrosis factor (TNF)-alpha activity.[31-34] TNF-alpha, which is also known as cachectin, is one of a number of substances normally produced by white blood cells in the body in response to infection by microorganisms and in response to other stimuli such as tissue damage. Reviewed in [31,32,34-36] Higher-than-normal TNF-alpha production has been observed in white blood cells obtained from cancer patients. Reviewed in [35-37] It has been suggested that higher-than-normal levels of TNF-alpha can cause the anorexia, increased energy expenditure, and increased muscle protein breakdown seen in cancer patients. Reviewed in [31,35-37] Some of the muscle protein breakdown products would become available for gluconeogenesis. Inhibition of TNF-alpha activity might, therefore, inhibit tumor growth and prevent cachexia.

References

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In the 1980s, the National Cancer Institute (NCI) conducted preclinical studies of hydrazine sulfate as a single agent, using many of the animal tumor models described above. With the exception of borderline activity against Walker 256 carcinosarcomas in rats, no evidence of antitumor activity was found. Reviewed in [19] In view of these results, NCI recommended against further evaluation of hydrazine sulfate as an anticancer agent. Reviewed in [19] However, clinical investigation of this compound continued, largely because of its potential as a treatment for cancer-related anorexia and cachexia.

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Human/Clinical Studies

Most of the information presented here is summarized in a table located at the end of this section.

Hydrazine sulfate has been studied extensively in patients with advanced cancer. These studies have evaluated the following: a) tumor response and/or survival among patients with various types of cancer,[1-13] b) changes in body weight,[1-6,8,10-12,14] c) carefully measured quality of life, [4-6,15] and d) changes in nutritional or metabolic status.[1,4,12,13,16,17] Clinical studies of hydrazine sulfate have been funded by a pharmaceutical company,[3] the Russian government, [7,9,10,18] and by grants from the National Cancer Institute (NCI).[1,2,4-6,8,11,12,15,16] They have also been sponsored by the North Central Cancer Treatment Group (NCCTG) [5,6] and the Cancer and Leukemia Group B (CALGB).[4,15]

The first clinical tests of hydrazine sulfate as a treatment for cancer were conducted in the mid-1970s by a pharmaceutical company.[3] In an uncontrolled study of 158 patients with advanced disease, it was found that 45 of 84 evaluable patients had subjective improvements (i.e., the patients reported an increase in appetite, a decrease in weight loss, an increase in strength, or a decrease in pain) and that 14 had objective improvements (i.e., there was measurable tumor regression, stable disease, or improvement in a cancer-related disorder) in response to treatment with hydrazine sulfate. Among the patients with objective responses, two had long-term (17 and 18 months) stabilization of their disease and seven had measurable tumor regression, although the extent and duration of these regressions were not specified. Major weaknesses of this study included the absence of a control (i.e., comparison) group and the fact that 74 of the 158 initially recruited patients could not be evaluated because of poor prognosis, missing documentation, insufficient duration of treatment, and/or concurrent therapy (i.e., therapy given at the same time) with other anticancer drugs.[3]

In 1976, Russian investigators reported findings from 95 patients with advanced cancer who had been treated with hydrazine sulfate after all previous therapy (surgery, chemotherapy, and/or radiation therapy) had failed.[9] Three partial responses (i.e., reductions in tumor size of greater than 50% observed for a period of 4 weeks or more) and no complete responses were noted after 1 to 5 months of treatment. Tumor regressions of 50% or less and stable disease (i.e., cessation of tumor growth for a period of 1.5 to 2.0 months or more) were reported for 16 and 20 patients, respectively.

In 1981, the same investigators published findings from 225 patients with advanced disease who had been treated with hydrazine sulfate after all previous therapy had failed.[10] It appears that the 225 patients described in this second report [10] included the 95 patients described in the first report.[9] Partial responses and stable disease were reported for 4 and 95 patients, respectively, after 1 to 6 months of treatment. No patient experienced a complete response. Subjective improvements in appetite, weight stabilization or gain, pain, fever, breathing, and/or mental outlook were reported by 147 patients.

In 1995, the same Russian investigators published findings from 740 patients with advanced cancer. [7] Once again, it appears that 225 of these 740 patients were described in the earlier reports.[9,10] Partial responses and stable disease were reported for 25 and 263 patients, respectively. Complete responses were noted for six patients. Subjective improvements in cancer-related symptoms were reported by 344 patients.

In 1994, the same investigators reported findings from a clinical series involving 46 patients with malignant brain tumors (38 with glioblastomas, four with astrocytomas, and four with meningiomas) and six patients with benign brain tumors.[18] These patients were not described in the other reports.[7,9,10] All patients in this series appear to have been treated with surgery in addition to hydrazine sulfate therapy, and at least some of the patients were also treated with radiation therapy. Complete or partial regression of neurologic symptoms (e.g., seizures, headaches,

sensory and motor disorders, and hallucinations) was reported for 73% of the patients. In addition, longer-than-average survival was reported for most patients. Among the patients with glioblastomas, the increase in average survival time was from 6 months to more than 13 months. [18]

Evaluation of the findings from these Russian clinical series [7,9,10,18] is made difficult by the limited information provided about the patients and their treatment histories. In addition, insufficient information was given about study design and methodology. The absence of control groups; the receipt of prior or concurrent surgery, chemotherapy, and/or radiation therapy by all patients; and the reliance on subjective measures of quality of life are major study weaknesses. Therefore, it is difficult to ascribe any of the positive findings to treatment with hydrazine sulfate. In contrast with the previously described clinical series, three NCI-funded clinical series found no complete responses or partial responses among a total of 79 patients treated with hydrazine sulfate. [2,8,11] In addition, only temporary, minor improvements in appetite, pain, and weight stabilization or gain were reported by the patients in these series. A weakness in these three clinical series was the absence of control groups.

Findings from four placebo-controlled, randomized clinical trials, however, also fail to support the effectiveness of hydrazine sulfate as a cancer treatment in humans.[1,4-6,15] In these trials, survival,[1,4-6,15] objective tumor response,[1,4,15] and carefully measured quality of life [4-6,15] were major endpoints.

One of the trials involved 65 patients with advanced nonsmall cell lung cancer and examined the effects of hydrazine sulfate on survival and nutritional status.[1]. In this trial, patients received either hydrazine sulfate or placebo in addition to a multiple-drug chemotherapy regimen. When all patients were evaluated, no improvement in survival was found with hydrazine sulfate therapy. In addition, no differences were noted in objective tumor response between the hydrazine sulfate group and the placebo group. However, on the basis of caloric intake and the maintenance of serum albumin levels, the nutritional status of the patients in the hydrazine sulfate group was judged better than that of the patients in the placebo group. However, the moderate increases in body weight associated with hydrazine sulfate use did not achieve statistical significance.

A CALGB-sponsored trial also evaluated the use of hydrazine sulfate as a treatment for patients with advanced nonsmall cell lung cancer.[4,15] In this trial, 266 patients received either hydrazine sulfate or placebo in addition to a multiple-drug chemotherapy regimen. No differences in survival, objective tumor response, anorexia, weight gain or loss, or nutritional status were observed between the hydrazine sulfate group and the placebo group. However, the quality of life of the patients who received hydrazine sulfate was found to be statistically significantly worse than that of the patients who received placebo.

The use of hydrazine sulfate as a treatment for patients with nonsmall cell lung cancer was also evaluated in an NCCTG-sponsored trial.[6] In this trial, 243 patients were randomly assigned to receive either hydrazine sulfate or placebo in addition to a multiple-drug chemotherapy regimen. No statistically significant differences were found between the hydrazine sulfate group and the placebo group with respect to either survival or quality of life.

Another NCCTG-sponsored trial tested hydrazine sulfate alone versus placebo in the treatment of 127 patients with metastatic colorectal cancer.[5] In this trial, the patients who received hydrazine sulfate had, on average, shorter survival than the patients who received placebo, a finding that was statistically significant. There were no statistically significant differences between the hydrazine sulfate group and the placebo group with respect to weight gain or loss, anorexia, or quality of life.

Four other clinical trials did find some objective evidence of benefit with hydrazine sulfate therapy. [12,13,16,17] These trials had either nutritional status or metabolic status as the primary endpoint. In a placebo-controlled, randomized trial involving 38 patients with advanced disease, hydrazine sulfate was found to improve the abnormal glucose metabolism seen in cancer patients.[13] In another placebo-controlled, randomized trial that involved 101 patients with advanced cancer and

weight loss, the use of hydrazine sulfate was associated with statistically significant improvements in appetite and either weight increase or weight maintenance.[12] However, the higher average caloric intake observed in this study for patients treated with hydrazine sulfate compared with patients treated with placebo was not statistically significant.[12] Two other clinical studies involving a total of 34 patients with either lung cancer or colon cancer found that hydrazine sulfate was able to reduce the body protein breakdown associated with cancer cachexia.[16,17] In view of the totality of evidence, the overall importance of the findings from these four clinical trials is not clear.

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A search of the PDQ clinical trials database indicates that no clinical trials of hydrazine sulfate as a therapy for cancer are being conducted at this time.

References

[1] Randomized clinical trial Advanced nonsmall cell lung 65; 32; 33, placebo None Yes 1iA
[2] Nonconsecutive case series Various advanced 25; 25; None Slight regression of some metastatic lesions, 1 patient with melanoma No 3iiiDiii
[3] Nonconsecutive case series Various advanced 158; 84; None Measurable tumor regression, 7 patients Yes 3iiiDiii
[4,15] Randomized clinical trial Advanced nonsmall cell lung 291; 135; 131, placebo None Yes 1iA
[5] Randomized clinical trial Advanced colorectal 128; 63; 64, placebo None No 1iA
[6] Randomized clinical trial Advanced nonsmall cell lung 243; 119; 118, placebo None Yes 1iA
[7,9,10] Nonconsecutive case series Various advanced 763; 740; None Complete tumor regression, 6 patients No 3iiiDiii
[8] Nonconsecutive case series Various advanced 25; 25; None None No 3iiiDiii
[11] Nonconsecutive case series Various advanced 32; 29; None None Unknown 3iiiDiii
[12] Nonconsecutive case series Various advanced 101; 71; 30, placebo Improved weight maintenance or gain, 41 hydrazine sulfate treated vs. 17 placebo-treated patients Yes 3iiiDiii
[18] Nonconsecutive case series Glioblastoma, astrocytoma, or meningiomaf 465; 46; None Improved survival, patients with glioblastoma Yes Noneg

No. = number.
a See text for more details.
b Number of patients treated plus number of control patients may not equal number of patients enrolled; number of patients enrolled = number of patients initially recruited/considered by the researchers who conducted a study; number of patients treated = number of enrolled patients who were given the treatment being studied AND for whom results were reported; historical control subjects are not included in number of patients enrolled.
c The strongest evidence reported that the treatment under study has anticancer activity or otherwise improves the well-being of cancer patients. See text and glossary for definition of terms.
d Surgery, chemotherapy, or radiation therapy given/allowed at the same time as hydrazine sulfate treatment.
e For information about levels of evidence analysis and an explanation of the level of evidence scores, see Levels of Evidence for Human Studies of Cancer Complementary and Alternative Medicine.
f This study included six additional patients with benign brain tumors.
g Insufficient information given to permit a level of evidence analysis.

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Adverse Effects

The side effects associated with hydrazine sulfate use have been mainly gastrointestinal and neurologic.[1-12] Nausea and/or vomiting, dizziness, and sensory and motor neuropathies have been reported.[1-12] The sensory and motor neuropathies have included paresthesias (abnormal touch sensations, such as burning or prickling, in the absence of external stimuli) of the upper and lower extremities (i.e., the arms and the legs, including the hands and the feet), polyneuritis (simultaneous inflammation of several peripheral nerves), and impaired fine motor function (e.g., an impaired ability to write).[2,5,7-9] Other side effects have included dry skin and/or itching, insomnia, and hypoglycemia.[1,2,7,9] One case of fatal liver and kidney failure and one case of severe encephalopathy (an injury to the brain) have been associated with the use of hydrazine sulfate.[13,14] The former case involved a man aged 55 years with squamous cell carcinoma of the maximillary sinus who purchased hydrazine sulfate from a source found on the Internet and proceeded to take it without medical advice or supervision. After 4 months he presented with

evidence of renal and liver toxicity, which eventually resulted in death. This case highlights the danger of accessing materials and medical information on the Internet and proceeding with self-medication without seeking proper medical advice and supervision.[15]

The side effects of hydrazine sulfate have been described as mild to moderate in severity, and their incidence appears to have been low. Most side effects are reported to resolve when treatment is stopped. However, limited evidence from animal studies suggests that hydrazine sulfate is highly toxic when combined with either alcohol or barbiturates.[16-18] Reviewed in [19]

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Overall Level of Evidence for Hydrazine Sulfate

Several clinical case series conducted by Russian investigators have indicated that hydrazine sulfate has marginal anticancer activity, but these results are considered inconclusive due to the lack of

control groups and insufficient information provided about study methodology. Well-controlled clinical studies conducted in the United States have shown no evidence of anticancer activity. In addition, evidence concerning the effectiveness of hydrazine sulfate as a treatment for cancer-related cachexia and anorexia is inconclusive. Furthermore, hydrazine sulfate has been shown to increase the incidence of several types of tumors in animals, and it has been classified as a potential carcinogen by the National Toxicology Program of the U.S. Department of Health and Human Services. The use of hydrazine sulfate as an anticancer drug outside the context of clinical trials has not been approved by the U.S. Food and Drug Administration and, thus, cannot be recommended.

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http://www.quackwatch.org/01QuackeryRelatedTopics/Cancer/hydrazine.html

Hydrazine Sulfate: Is It an Anticancer Agent?
Saul Green, Ph.D.

Cachexia is the result of a complex array of metabolic abnormalities which results in loss of appetite, tissue wasting, muscle and visceral organ atrophy, weakness, and loss of fat stores. It may be accompanied by energy, anemia, lowered serum albumin, lowered immune function, lactic acidosis, hyperlipidemia, glucose intolerance and increased gluconeogenesis. These abnormalities alert clinicians to the possibility of an underlying disease.

The relationship between cachexia and cancer has been known for some time. [1] Although cachexia is not a universal feature in cancer, it occurs frequently in lung, pancreatic, and gastric cancer. As a consequence it has been suggested that cachexia may contribute to death. [2,3]

The awareness among oncologists of demonstrable differences between cachexia and starvation prompted many researchers to investigate the mechanisms underlying cachexia in the hope of reversing it. Cachexia is the result of a complex interaction between the growing tumor and the host; when the entire tumor is removed, normal metabolism and weight gain resume.

Gluconeogenesis is the production of glucose from molecules which may not be sugars. This synthesis of new glucose takes place in tissues like liver and kidney when a high-energy compound named phosphoenolpyruvate (PEP) is synthesized by the enzyme PEPCK present in mitochondria.

Enter Hydrazine Sulfate

Hydrazine sulfate (HS) is an inexpensive common chemical which is commercially available for about 11 cents per gram. HS is used in the refining of rare metals, in analytical blood tests, and as an antioxidant in soldering flux. HS is carcinogenic. It induces a range of in vitro genotoxic effects including DNA and gene damage in mammalian cells and bacteria, and chromosomal aberrations in mammalian cells. [4] In 1968, HS was shown to induce lung adenomas, adenocarcinomas and liver cell carcinomas in male rats. [5] HS is either genotoxic or a nongenotoxic carcinogen, i.e., it acts as a tumor promoter for preexisting initiated cells. [6]

HS produces hypoglycemia in dogs and rabbits. [7] In 1966, Brown et al reported that HS caused genetic mutations in normal cells and cautioned that if it was used in animals over the long term, HS should he considered potentially carcinogenic. [8]

Joseph Gold, MD, is a general practitioner and the director of the Syracuse Cancer Research Institute. Gold postulated that a metabolic circuit existed in cancer patients that allows energy needed for tumor growth to be drawn from normal metabolic pathways. According to Gold, lactic acid from tumor glycolysis, amino acids from protein breakdown and glycerol from fat mobilization drive gluconeogenic activity which drains away the energy which normal anabolic processes need to produce and maintain tissue integrity. This alleged "energy short circuit" causes cachexia in cancer. If the circuit could be broken, cachexia would be overcome and the cancer would he deprived of the energy needed to grow. [9]

In 1966 P. D. Ray first published the results of his studies on the effect of L-tryptophane and HS on the formation of phosphoenolpyruvate in the gluconeogenesis in rat liver. [10] Later he reported effects of various hypoglycemia-inducing agents on carbohydrate metabolism in rats. [11] While HS did not react directly with PEP, it did inhibit the conversion of oxaloacetate to PEP, the high-energy compound considered essential for the synthesis of glucose by gluconeogenesis in liver and kidney tissue. He found that the enzyme phosphoenolpyruvate carboxykinase (PEPCK) which controlled new glucose formation in liver and kidney tissues was inhibited by HS.

When Gold learned of these results, he concluded HS was the means to reverse cachexia. He suggested that by feeding HS to cancer patients one could block gluconeogenesis without blocking normal energy metabolism, thus overcoming cachexia and reversing cachexia-dependent tumor progression.

In 1971 Gold reported that HS inhibited the growth of an experimental W-256 tumor in rats. [12] In 1973 he reported HS inhibited PEPCK and growth of the tumors Walker 256, B-16 Melanoma, M-S Lymphosarcoma, and L1210 Leukemia in rats. [13] In 1974 he studied the relationship between PEPCK inhibition and the ability of several known gluconeogenesis inhibitors to affect the growth of tumor cells in tissue culture. He reported that HS was not toxic for these cells. [14] In 1975 Gold reported that HS potentiated standard chemotherapeutic agents like cytoxan, mitomycin, methotrexate, and bleomycin, in rats and mice. [15] In 1975 he published results of an IND clinical trial in which he treated 84 terminal cancer patients with HS. The trial lasted one year and was not randomized, double blinded, or placebo controlled. The results were: subjective improvement, with three-quarters of subjects saying that they had better appetite, weight gain, and a general feeling of "well being." These effects varied widely in terms of their duration, lasting from a few days to several months. The cancer in 14/84 of the patients "stabilized." (There was no mention of the growth of tumors in the rest of the patient group.) There were no significant toxic effects due to HS. No attempt was made to monitor the ability of the HS to influence glucose metabolism of the patients. There were no long-term follow up studies. [16]

More Research

There followed several randomized, double blinded, placebo-controlled clinical trials: Ochoa et al in 1975, [17] H. J. Lerner, [18] S. B. Strum et al., [19] and E. Spremulli et al. [20] All found HS treatment to be of no value in reducing tumor size or in increasing patient survival time. By 1980, Regelson had treated 66 advanced-stage cancer patients and examined them for subjective and objective responses as Gold had done. [21] None of Regelson's patients had objective tumor responses that could he attributed to the HS treatment. There were brief subjective responses but they were no different from what could have been attributed to placebo effect. HS had no effect on survival. In 1982 Gold disputed the conclusions of Regelson and Ochoa, saying their conclusions were based on "politics" and were the result of an Establishment conspiracy to suppress a cheap and effective cure for cancer. [22]

A group in Russia reported results supporting Gold's thesis. [23-25] The effects were the same subjective effects that Gold reported, i.e., a lessening of pain, fever, hemoptysis, and an increased appetite. Filov reported that HS produced a marked psychotropic effect in patients which occurred 23 weeks after the start of the HS administration. Filov described it as a marked "euphoria" and stated that cachectic terminal intestinal cancer patients were unable to recognize the reality of their conditions.

In 1984 and 1987 R. T. Cheblowski [26,27] confirmed that both a decrease in glucose tolerance and an increase in the rate of total glucose production were seen in patients with cachexia. HS treatment for one month resulted in improvement in abnormal glucose metabolism, weight gain, and increased appetite in some patients.

In 1990 Cheblowski examined the influence of HS on the nutritional status and survival in 65 patients with non-small- cell lung cancer. [28] The trials were randomized, double blinded, and placebo controlled. There was no significant difference between HS and placebo groups with

respect to progress of the cancer or survival rate of the patients. The HS treated group did show increased appetite and some weight gain. Again HS seemed to induce a state of euphoria in patients which caused them to believe that they were being cured. Because of modest neurotoxicity of HS, Cheblowski felt that it would not be a good candidate for use in long-term treatment until appropriate trials for safety were run. Cheblowski concluded, "Considering all patients, survival was slightly greater for the HS treated group compared with the placebo group, but the differences did not achieve statistical significance." More studies with better trial design need to be done.

In June 1994, three papers [29-31] described the effects of adding HS to the chemotherapeutic regimens of patients with advanced non-small-cell lung cancer and leukemia, advanced colorectal cancer, and with newly diagnosed non-small-cell lung cancer. All three placebo-controlled double-blinded clinical trials yielded results leading authors to conclude: "This study demonstrates that there is no benefit from the addition of HS to an effective cytotoxic regimen."

A Media Assessment

In July 1994 Penthouse magazine carried a story by Jeff Kamen that proclaimed to its readership, "The Russians are benefiting from Dr. Gold's cancer drug, a drug our own government seems determined to destroy." Kamen, a freelance writer, not a medical research scientist, came to this conclusion after an all-expense paid visit to the N.N. Petrov Research Institute of Oncology in St. Petersburg, Russia, where Gershanovich and Filov, two long-time proponents of HS use in cancer, worked. The Russians told Kamen that they had treated 1000 cancer patients with HS and cured them. Since Kamen believed them, he concluded that the truth about HS had been suppressed in the United States by the NCI and FDA.

In this same article, Kamen cited the testimonial of one Dr. Joanne Daniloff, Department of Veterinary Medicine of the Louisiana State University in Baton Rouge, LA. She is quoted as saying that after the surgical removal of most of her tumor (a glioblastoma multiforme Grade IV), her local physician told her that her cancer was incurable She took HS, and the tumor has not returned. Dr. Daniloff is quoted as saying, "I have read studies that show clear evidence of HS as a chemotherapeutic agent. HS alone has been shown to reduce the size of numerous tumors." Since Daniloff gave no references for these statements, a Medline search was done for the period 1980-1990. No publications were found that offer that evidence. A call was placed to the Department of Veterinary Medicine on January 2, 1997, to personally request those references from Dr. Daniloff. The personnel department and the secretary of the Department of Veterinary Medicine both stated they had no record of such a person on their staff.

Kamen ended his article by announcing that as a result of pressure from Congress, the GAO agreed to investigate the NCI's conduct regarding clinical trials cited above. In September 1995, the GAO concluded that the three large randomized, placebo-controlled clinical trials that were sponsored by NCI were correctly done and that the conclusion that HS was ineffective in extending survival in cancer patients were also valid.

In 1996 British medical scientists published two extensive reviews on the subject of cancer cachexia. [32]

Death Reported

In December 2000, the Annals of Internal Medicine published a case report of a 55-year-old man with cancer of the sinus near his left cheekbone. Instead of undergoing recommended medical treatment, he obtained hydrazine sulfate through a Web site and, for four months, followed the regimen published on the kathykeeton.com Web site. Two weeks later, he was hospitalized with signs of kidney and liver failure. Despite intensive hospital care, he died within a week [33,34].

Summary and Conclusions

My review of all the literature (including Gold's) on the subject of the efficacy of hydrazine

sulphate shows:

HS has never been shown to act as an anticancer agent
Patients do not experience remissions or regressions of their cancer due to HS treatment
Patients treated with HS do not live longer than nontreated patients.
Although HS may correct abnormal carbohydrate metabolism in some cancer patients, the rationale that it acts as an anticancer agent because it deprives cancers of their energy by inhibiting formation of glucose from lactic acid (gluconeogenesis) is erroneous.
HS has not been shown to be an effective anticancer agent.
HS is not risk-free.

For Additional Information

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National Cancer Institute statement on studies of hydrazine sulfate (Aug 17, 1997).

About the Author

Dr. Green (1925-2007) was a biochemist who did cancer research at Memorial Sloan-Kettering Cancer Center for 23 years. He consulted on scientific methodology and had a special interest in unproven methods. The original version of this article was published in the Fall/Winter 1997 issue of the Scientific Review of Alternative Medicine.

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http://www.nomorefakenews.com/archives/archiveview.php?key=1681

Hydrazine Sulfate Alternative Cancer Treatment

These Treatments are Different

You cannot pick an alternative cancer treatment the same way you pick your other medications. Despite the enthusiastic claims of well meaning people:

* Just because an alternative cancer treatment worked for someone else, that does not mean it will work for you.
* Even though there are many viable alternative cancer treatments, there isn't a "best" treatment for a certain type or stage of cancer.
* Most alternative cancer treatments only work on a minority of the people who try it.

A person's unique body chemistry seems to be the most important consideration in selecting an alternative cancer treatment. Only energy medicine offers a selection method that takes body chemisrty into account.

What to Do

Consider taking two treatments, the treatment recommend by someone else or selected by your research and the treatment indicated by energy medicine testing using the Alternative Cancer Treatments Test Kit*.

Introduction

Tumors take their energy from glucose and turn it into lactic acid which must be broken down by the liver. Unfortunately, the liver converts lactic acid to glucose. This cycle is called cachexia and is responsible for the wasting away that is typical of cancer patients. Hydrazine sulfate is designed to stop this wasting away.

Hydrazine sulfate's popularity grew rapidly after the publicity generated at the 1974 NHF(National Health Federation) convention by Dr. Joseph Gold, director of the Syracuse Cancer Research Institute in Syracuse, New York.

Hydrazine sulfate was demonstrating good results, but it was getting too popular. The FDA decided to put on the brakes and withdrew the INDs (Investigational New Drug number). After that, funding dried up, and companies withdrew their interest in researching the drug. All of this despite the fact that the drug was showing good response in a number of studies.

Development

In the 1960s Dr. Joseph Gold, director of the Syracuse Cancer Research Institute in Syracuse, New

York, started looking for a way to stop cachexia (see Introduction). He eventually found that hydrazine sulfate blocked a liver enzyme that supports cachexia.

Pharmacology

Hydrazine sulfate blocks a liver enzyme that is needed for the liver to support cachexia, the wasting away experienced by most advanced cancer patients.

Effectiveness

Hydrazine sulfate has been used for reducing pain and interrupting cachexia. Cachexia stops the wasting away that later stage cancer patients experience. Hydrazine sulfate seems to be effective regardless of the type of cancer. However, hydrazine sulfate does not seem to be effective in removing cancer tumors.

Studies

In 1973 Dr. Joseph Gold, director of the Syracuse Cancer Research Institute performed an animal stuy with hydrazine sulfate. The results showed that it inhibited the growth of several different types of tumors in laboratory animals. It also improved the effectiveness of several chemotherapy drugs.

Dr. Dean Burk, of NCI, called hydrazine sulfate "the most remarkable anticancer agent I have come across in my forty-five years of experience in cancer." He even detailed some case histories of successful treatments with hydrazine sulfate:

Since April 1, 1973, upwards of 30 cachectic or "terminal" cancer patients have been treated with gelatin capsules containing 60 mg of hydrazine sulfate three to four times a day (at intervals of about 6 hours). Usually within 24-48 hours there is a marked return of appetite followed by continued increase in weight, remarkably restored physical activity, and eventually decrease in tumor size, decrease in pain, and related decrease in symptomatology.

One patient, a young man with Hodgkin's disease, was bedridden and severely underweight. After receiving only two doses of hydrazine sulfate he was able to get out of bed and care for himself. After five days of treatment he actually left the hospital for a brief trip. There appeared to be no side effects from the low dosage of the drug employed, and one patient who had a previously inoperable cancer experienced sufficient tumor regression to be operated on.

Another Sloan-Kettering Debacle

It seems that every alternative cancer treatment study that is performed by Sloan-Kettering is run so poorly that no conclusions can be made. Here is just another example:

In September 1973 Dr. Gold joined a research team effort to evaluate hydrazine sulfate's effects. However, it turned out that many of the patients chosen for the study were within days of dying. Also, Sloan-Kettering allegedly did not follow the agreed dosages that were to be administered. In 1974 Sloan-Kettering announced the results of the study, claiming that none of the patients had shown a positive response to hydrazine sulfate and that some of the patients experienced neurotoxic side effects.

Positive Results

In the Journal Oncology, a study was published by Dr. Golden. This study evaluated eighty-four patients with various types of advanced cancer who used hydrazine sulfate. 70 percent of the patients reported improvements, such as increased strength, improved performance, decreased pain, increased appetite, weight gain or cessation of weight loss. Also, 17 percent experienced measurable improvement such as, tumor regression, disappearance of or decrease in cancer-associated disorders, and long-term condition stabilization.

Positive Results from Russia

A study conducted in the Soviet Union confirmed that hydrazine sulfate can retard the growth of several types of cancers in animals. The study also contained results of forty-eight terminal cancer patients who were given hydrazine as a last resort. Out of peas 48 cases, tumor growth altered in 15 percent, and another 20 percent experienced measurable tumor regression; 58 percent of the patients reported subjective improvements, such as reduction of pain, and increased appetite.

A Large Published Study

A large-scale study of hydrazine sulfate was run in 1979 in Russia under the supervision of a Dr. Michael Gershanovich. The study ran for four years and included 225 patients. The results of the study was published. Summarizing the results make it clear that hydrazine sulfate was effective in reversing cachexia and producing disease stabilization in late-stage cancer patients.
A Larger Study

A larger, Soviet study demonstrated the effectiveness of hydrazine sulfate in 740 cancer patients most of whom had used conventional treatments without success. The types of cancer broke down as follows:

200 lung cancer
138 cancer of the stomach
66 breast cancer
63 Hodgkin's disease
31 melanoma

After two to three weeks of therapy, tumor stabilization or regression occurred in 50.8 percent of the patients, 46.6 percent of the patients had improvements, such as decrease in fever, reduced respiratory problems, and disappearance of edema. Other results included, improved appetite and strength, and decrease or elimination of pain.

Fraudulent NCI Testing

Daniel Haley's brilliant book, Politics in Healing, tells how NCI's 1991 clinical trial of the alternative cancer treatment, hydrazine sulfate (HS), was rigged to fail.

A spectacularly promising medicine, HS had shown good results in trials at Harbor/UCLA hospital and in Russia. NCI felt obligated to test the drug. But there was a catch.

The drug's discoverer, Dr. Joseph Gold, had found that HS reacted badly if patients were taking other drugs, especially tranquilizers. Several warnings were given to NCI before it began its test. The warnings were explicit. Patients could DIE if they were taking tranquilizers.

It turned out that none of the NCI patients were warned about this. It turned out that 94% of those patients were in fact on tranquilizers. Barry Tice, an investigator for the US General Accounting Office (GAO), looked into the NCI trial of hydrazine sulfate after it was over. He called Dr. Gold and told him he had found a "smoking gun." There was an internal NCI memo which showed that NCI was well aware of the problems involved in the drug combinations. The GAO did not back up its own investigator. The final GAO report on the NCI clinical trials of hydrazine sulfate simply accused NCI of sloppy bookkeeping.

In the June 1995 issue of the Journal of Clinical Oncology, a letter from the NCI was published. The letter stated that NCI had omitted mentioning, in its own published account of its cancer study, that 94% of the patients had been on tranquilizers. But, because this letter did NOT mention how dangerous that situation was, it looked like NCI was simply admitting to a technical and unimportant mistake. A clerical error.

So what did happen to the patients in the NCI hydrazine sulfate study?

They ALL DIED.

http://alternativecancer.us/hydrazinesulfate.htm

Conclusiveness of Papers

The conclusions of the majority of research papers written about hiders and sulfate shows that it has positive effects for treating cancer and most especially for reducing pain and weight loss. See studies above.
Standalone Ability

Cachexia and is responsible for the wasting away that is typical of cancer patients. Hydrazine sulfate is designed to stop this wasting away it was not intended as a primary tumor biting treatment. However, since there do not seem to be any compatibility issues, hydrazine sulfate seems like a good candidate as an auxiliary treatment especially when the patient is losing weight and in pain.

Ease of Use and Dosage

Hydrazine sulfate only needs to be taken three times a day in a small 60 mg pill. Persons weighing less than 125 lbs. have often been advised to switch to a 30 mg pill.

See the "Hydrazine Sulfate Is an MAOI Avoid These Foods" subsection under Side Effects for a list of foods whose intake you may want to reduce.

People who change their eating habits greatly increase the effectiveness of the supplements they take. Consider reading the "General Diet*" subsection of the Home page.

Side Effects

Although hydrazine sulfate is generally considered nontoxic there are some potential side effects that usually only occur at high doses. These side effects include: dizziness, drowsiness, mild numbness (particularly of the fingers and toes), nausea and mild sensations of itching of the skin. There is actually a positive side effect, hydrazine sulfate often produces a mild euphoria after two to three weeks of use. Polyneuritis (nerve inflammation) sometimes occurs in cases of prolonged and continuous treatment. Dr. Gold stated that vitamin B6 can alleviate this problem. Taking Hydrazine sulfate and tranquilizers during the same time can be fatal.

Hydrazine Sulfate Is a MAOI Avoid These Foods

Hydrazine Sulfate inhibits an enzyme that breaks down monoamines (serotonin, norepinephrine, and dopamine). These are chemicals used by our brain and effect our mood. MAO inhibitors metabolize tyramine, an amino acid. When taking an MAO inhibitor, tyramine is not broken down, and eating foods with tyramine can raise blood pressure and heart beat and cause headaches. Most of the foods containing tayramine are not very healthy so it is good to be avoiding them anyway.

Foods containing tyramine are mostly aged, fermented, or pickled, such as most cheeses (except cottage cheese, cream cheese, and fresh Mozzerlla), lunch meats, hot dogs, yogurt, wines and beers. A more complete list of foods that contain tyramine:

Dry and fermented sausage (bologna, salami, pepperoni, corned beef, and liver), pickled herring and salted dried fish, broad beans and pods (lima, fava beans, lentils, snow peas, and soy beans), meat extracts, yeast extracts/brewer's yeast, beer and ale, red wine (chianti, burgundy, sherry, vermouth), sauerkraut, some fruits (bananas, avacados, canned figs, raisins, red plums, raspberries, pinapples), cultured dairy products (buttermilk, yogurt, and sour cream), chocolate, caffeine (coffee, tea, and cola drinks), white wine, port wines, distilled spirits, soy sauce, miso, peanuts,

almonds, beef or chicken liver, herring, meat tenderizer, MSG (Accent), pickles, and pumpkin seeds.

People avoiding tyramine, reduce their intake of high protein food that have undergone aging and over-the-counter cold or allergy remedy.
Compatibility

There are not any known compatibility issues with hydrazine sulfate and other cancer treatments or supplements. However, taking hydrogen sulfate while taking tranquilizers, can have fatal complications.

Year Available

.Hydrazine sulfate became popular in the 1970s
Relative Cost per Month

One hundred 60 mg pills, enough for one month, costs about $30.

Testimonials and Belief

Testimonials can be a very powerful tool to help in the healing process because they can boost your belief in a treatment. However, reading testimonies is a poor method of making a treatment selection. An alternative cancer treatment with only a 5% success rate can still obtain many genuine and impressive testimonials. A selected group of positive testimonials cannot compare to a published study were all of the qualified case histories are presented, the failures as well as the successes.

For the above reason, it is not a good idea to use testimonials to help you select a cancer treatment. Save testimonials for the role that they perform the best, bolstering belief after treatments have been selected. Using an Alternative Cancer Treatment Test kit is a much better method of making the treatment decision.

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http://www.hydrazinesulfate.org/

THE TRUTH ABOUT HYDRAZINE SULFATE - DR. GOLD SPEAKS

Dr. Joseph Gold, M.D.

For some time now I have refrained from making any comments in regard to information on the Internet concerning hydrazine sulfate. My silence has been occasioned by the hope that our federal and prominent private-sector cancer agencies would endorse the use of hydrazine sulfate, in the wake of clinical trials demonstrating its effectiveness in the treatment of cancer.

But this hasn't happened. Quite the opposite. A casual examination of the Internet shows that information in regard to hydrazine sulfate is composed of a mixture of “endorsements” of hydrazine sulfate from individual patients and their advocates—and the seemingly authoritative disparagement of it by cancer establishment sources. It is this “condemnation” of hydrazine sulfate I wish to address—the scientific gobbledygook of so-called studies, side effects, carcinogenicity, toxicity, cautions, critiques and inferences woven together by our cancer agencies' most talented “spin doctors” into a web of outright misrepresentations, deception and scientific fraud. (As an example of this fraud, NCI has posted an entry on the Internet, “date last modified: 6/18/04,” stating “hydrazine sulfate has shown no anticancer activity in randomized clinical trials,” which as will be seen is patently untrue and does not reflect the ten years of randomized clinical trials performed by Harbor-UCLA Medical Center from 1981-1990 and the many published, peer-reviewed clinical studies based on that body of work.)

The purpose of this statement is to guide you, step by step, through the scientific development of

hydrazine sulfate as an anticancer agent, the clinical trials—and the high-level negative politics which came to surround this drug from the very beginning. It will be plainly seen that the cautions against this drug presented on the Internet by our highest federal health agencies are but an assemblage of misinformation and disinformation which acts to discourage this drug's use both by individual patients as well as by well-meaning physicians.

First and foremost, it is important for you to know that, contrary to implications made on the Internet, clinical trials of hydrazine sulfate have been done and published in peer-reviewed medical journals which circulate worldwide. And the truth is that every single, informed-consent, controlled clinical trial of hydrazine sulfate, performed in accordance with internationally accepted criteria and standards of scientific conduct—without exception—has indicated efficacy and safety of the drug. The only contrary results have been the National Cancer Institute-sponsored trials of hydrazine sulfate in which incompatible agents (medications) were used with the test drug. It must be stressed that no legitimate researcher on this planet would ever knowingly use an incompatible agent—or one even suspected of incompatibility—in the trial of a test drug. Use of an incompatible agent in a drug test, which acts to cause a negative study, can only be the result of incompetence or deliberateness.

Secondly, Internet sources have implicated hydrazine sulfate to be toxic or carcinogenic. Although hydrazine sulfate is carcinogenic—i.e., can cause cancer—in some weanling mice given the drug in their drinking water since birth, there has never been a case of human cancer reported as a result of HS therapy . (In contrast, routinely administered chemotherapy drugs are commonly carcinogenic —and can produce up to 26% of “second cancers.”) Perhaps more importantly, the influential medical journal Annals of Internal Medicine presented a “Brief Communication” (and accompanying editorial) in its December 5, 2000 issue, of a single patient who allegedly died of fatal hepatorenal failure as a result of “HS” therapy. The only trouble was that no firm evidence was presented in this paper that the patient in question ever took hydrazine sulfate. The authors of this article stated: “We could not obtain samples of the product he [the patient] ingested.” This means there was no possibility of a direct examination of what it was the patient was taking. The authors further stated: “His blood was not tested for the presence of hydrazine.” But there are simple spectrofluorometric blood tests that will confirm even the smallest residues of hydrazine sulfate ingested even months earlier. It must be emphasized that no medical journal on earth—of high repute or not—would publish an article and editorial based on one case, calling attention of the medical profession and public to the potential toxicity of a drug gaining in common usage, without incontrovertible, verifiable, air-tight evidence that the patient in question ever took the drug in the first place. No journal would have the ethical recklessness to disseminate an article having far-reaching public health consequences, without absolute proof of its basic assumptions. But the editors and writers of the Annals—with our federal health agencies' knowledge and participation—chose to disseminate their reports to the media of the world, to the medical profession of every country and to the Internet, where the public would be sure to find them. To put this situation in its proper context: While Annals chose to issue a “drug warning” based on one, single presumptive case of fatal toxicity of HS in the 30 years since the drug has been in use, there are tens of thousands of authenticated chemotherapy deaths each year . Has the Annals, or other medical journals, or our federal health agencies, or the prominent private-sector cancer organizations ever let the public know this?

Your life or the life of a loved one or friend may depend on your reading, and understanding, the statement below. References are used in support of the events, happenings and details of this expanded statement.

Scientific Background. Hydrazine sulfate (HS), an inexpensive, mass-produced chemical compound used for many industrial applications, was first proposed as an anticachexia agent based on its inhibition of the gluconeogenic enzyme, phosphoenolpyruvate carboxykinase (PEP CK).1,2 It was further proposed that if tumor energy (ATP) gain and host energy loss (resulting from cancer-induced excessive gluconeogenesis) were functionally interrelated—as seemed probable—HS could also, by indirect and non-toxic means, inhibit tumor growth itself.3 Early in-vivo studies demonstrated that HS could inhibit weight loss (cachexia) and tumor growth in a variety of

transplanted mouse and rat models, without direct cytotoxicity,2-6 could add to the antitumor effects of chemotherapy drugs,7-9 and was free of significant side effects.10 These results strongly suggested HS as a new means of non-toxic cancer chemotherapy.11,12

Adverse Politics Begin. Despite this drug's early promise, from the very beginning of clinical trials, HS was to be met with controversy as a function of government action. On March 8, 1976, veteran congressman James M. Hanley (Chair of the Post Office and Civil Service Committee and a member of many committees and subcommittees) requested a "status report" on HS from the director of the National Cancer Institute, our country's—and the world's—largest and most influential cancer agency. Within two weeks he received a reply which stated: "Hydrazine sulfate has been tested in the Soviet Union at the Petrov Institute in Leningrad [St. Petersburg]. In a clinical study directed by Dr. Michael Gershanovich, no evidence of meaningful anticancer activity was reported. This information was communicated to the NCI under the Joint U.S.-U.S.S.R. Health Agreement of 1972."13,14 Days later, however, reprints of the actual study became available. Its English summary stated: "Clinical observations enabled us to state a definite therapeutic effect of hydrazine sulfate in patients with lymphogranulomatosis [Hodgkin's and non-Hodgkin's lymphomas] and malignant tumors of various localizations, when other measures of specific therapy failed."15

This was exactly opposite of what was communicated to Congressman Hanley. In fact, the text stated that because of the highly positive findings the study was being immediately enlarged. As to whether the NCI response to Congressman Hanley represented an innocent error on the part of the NCI or a deliberate fabrication, a further letter from the NCI, dated June 22, 1976, stated: "An abstract [summary] of the Gershanovich study appeared in Cancer Therapy Abstracts (Vol. 16: No. 4 [19]75-2046), a journal published under contract to the NCI."16 This published abstract antedated the NCI's response to Congressman Hanley by six months. Thus, at the time the NCI was writing to Congressman Hanley that the Soviet data were negative, the NCI already knew these data were positive.

Early Clinical Studies. In 1975 three articles would appear in the medical literature, detailing initial clinical results with hydrazine sulfate. The first, the Soviet study,15 a phase II controlled clinical trial, set forth astonishing results in a class of patients termed "factually terminal [stage 4]," who had become unresponsive, or had failed to respond initially, to conventional therapy: 58 percent demonstrated anticachexia response (weight gain, performance status improvement, normalization of the laboratory indices, etc.), and 35 percent showed antitumor response (tumor regression or stabilization); one year later the initial series of 48 patients was enlarged to 95 patients, with essentially the same results.17 The second, a pharmaceutical-sponsored IND (Investigational New Drug) study of 84 terminal and preterminal patients with different types of cancer demonstrated a 59 percent anticachexia response and a 17 percent antitumor response.18 The third, a small study of 29 patients conducted at Memorial Sloan-Kettering Cancer Center, totally uncontrolled for patient selection, drug dosage and treatment schedule, and prior and concurrent therapy, found no long-term improvements (although transient response was recorded).19 On the basis of this totally uncontrolled MSKCC trial of 29 patients the American Cancer Society, in March 1976, placed HS on its "Unproven Methods" list.20 The ACS stated: "After careful study of the literature and other available information, the American Cancer Society does not have evidence that Hydrazine Sulfate is of any objective benefit in the treatment of cancer in human beings." In its article, the ACS referenced only the uncontrolled MSKCC study, but failed to reference the phase II controlled Soviet trial or the (American) pharmaceutical-sponsored IND study. (In late 1979 the ACS removed HS from its Unproven Methods list, in the wake of increasingly positive data on HS.21)

In March 1979 the Soviet study was enlarged to 225 patients. Published as an abstract in the March 1979 Proceedings of the American Association for Cancer Research, controlled for patient selection and prognosis, performance status, dosage protocol, prior and concurrent therapy, the study reported overall results of 65 percent anticachexia response and 44 percent antitumor response. Anticachexia response was described as "appreciable improvement of appetite and

general status, disappearance or reduction of severe weakness characteristic of the pretreatment period, reduction or complete elimination of pain, tendency toward normalization of the laboratory findings"; antitumor response included tumor regression ("less than 25 to greater than 50% of initial tumor volume") and tumor stabilization (from "3-6 months"); side effects included "minimal nausea, dizziness, anorexia, polyneuritis (1.7%) [tingling of the fingers]"—and the absence of bone marrow depression ("leukopenia and thrombocytopenia were not observed"). In this class of patients no efficacy and safety findings approaching these had ever before been reported. Nevertheless, although arrangements had been made through the Soviet and American governments to have Dr. Gershanovich come to this country to discuss these results, after traveling more than 7,000 miles he was not permitted to present his paper orally at the annual scientific meetings of the American Association for Cancer Research in New Orleans . Asked by the media at this conference whether "consideration should not have been given to the fact that [this] Russian trial was the first large-scale study of [HS], purporting to show significant benefits from its use"—and therefore become subject to open discussion by the world oncology community—the program chairman of the AACR stated: "The Gershanovich paper is not going to be presented, and that's it."22 (In 1981 the Gershanovich data were published as a full-length paper in the American peer-reviewed journal, Nutrition and Cancer.23)

Also in 1979 a negative paper on HS of 25 non-randomized, non-blinded, non-controlled, open-study patients would be published in the journal Cancer Chemotherapy and Pharmacology,24 whose editor-in-chief was an NCI official, authored by Dr. William Regelson (now deceased) and colleagues from the Medical College of Virginia. In this totally unaudited study, 7 of the "negative" patients died (of their disease, not from the drug) within 11 days of starting HS therapy (1 died on the very first day), another was "lost to follow-up" after two weeks, 2 others received prior chemotherapy which had not yet cleared, 1 received concurrent medication shown to be incompatible with HS as long as four years previously,8,15,25 and 16 received HS less than the required four-week minimum (l patient received HS for only 1 day, 9 for 1 week or less, 16 for 2 weeks or less). Of the 25 "negative" patients only five could qualify for evaluation according to established drug-testing protocol. Because only 20 percent of the patients of the study were evaluable, it is unclear how this paper achieved publication, since it was apparent that it could not have been subject to normal, independent peer-review procedures.

The American Medical Association Enters The Fray. In January 1980 the Commentary section of the Journal of the American Medical Association26 would present another negative article on HS, again authored by Dr. Regelson. The JAMA was at the time perhaps the most authoritative medical journal in the world and its prestigious Commentary section, located at the beginning of many issues, was in effect a forum that usually addressed an important social or political medical problem or question—and was thus a reflection of the views of organized medicine at its highest levels. In this Commentary article Dr. Regelson stated that he and "others" had performed randomized, double-blind studies on HS that were negative. ("In both randomized double-blind and nonrandomized studies, our group and others have tested hydrazine sulfate in advanced cancer patients….") But the truth was that Dr. Regelson—or "others"— never performed any double-blind studies and indeed the only study that Dr. Regelson ever performed was the one, previously discussed, in which 80 percent of the patients were unevaluable and which could not have been published on the basis of independent peer-review. In fact Dr. Regelson never once mentioned the Gershanovich results—the only truly controlled (phase II) clinical trial of HS up to that time (1979), which dwarfed all other studies (225/233 evaluable patients) of HS combined. (Gershanovich's name did not appear once in the text.) Of HS Dr. Regelson only stated: "[Hydrazine sulfate] does inhibit the Walker 256 carcinoma [a rat tumor] and has shown synergy with chemotherapy in the L 1210 in mice….Where does that leave us?" Thus extolling the "double-blind" studies he had never published or performed, and omitting any mention of the large-scale, positive, controlled Russian trials that had been published and performed—Dr. Regelson's Commentary article sent an unmistakable message that HS was tantamount to quackery medicine, in effect regarded by the cancer establishment (he referred to himself as "we members of the Establishment") as a pharmaceutica-non-grata . Equally disconcerting was the fact that the editorial staff of the JAMA had apparently not checked to ascertain that Dr. Regelson—or "others"—had

indeed published double-blind studies on HS, in effect that what Dr. Regelson was writing was in fact true. JAMA 's failure to perform this most elementary task served only to reinforce Dr. Regelson's egregiously erroneous “message” to the practitioners of American medicine.

Randomized Clinical Trials. In 1981 the American Cancer Society began sponsorship of prospectively randomized, double-blind, placebo-controlled clinical trials of HS at Harbor-UCLA Medical Center under the distinguished leadership of well known cancer investigators Drs. Jerome B. Block and Rowan T. Chlebowski. (RCTs are considered the “gold standard” of clinical testing, since they tend to minimize bias from all sources.) In February 1984 these investigators reported27 in the respected journal Cancer Research that in a series of 38 patients with widespread lung, colon, breast, throat and other cancers, HS reversed abnormal carbohydrate metabolism associated with cancer cachexia. This represented a watershed work, in that for the first time it was demonstrated (under double-blind, placebo-controlled circumstances) that alteration of abnormal host metabolism could result in measurable clinical benefits, including weight improvement and stabilization, potentially opening the door to a new type of cancer therapy.

Thus by the middle 1980s dual scientific horizons—the Soviets and Harbor-UCLA Medical Center —had emerged, independently corroborating one-another's clinical results on HS, the strong preponderance of data indicating this drug to represent a promising new therapeutic agent.

Politics Deepen . First published in the early 1980s, one of the most influential cancer textbooks in the world was (and still is) CANCER, Principles & Practice of Oncology, whose principal editor was Dr. Vincent T. DeVita, Jr., then director of the NCI. In its first edition in 1983 this textbook carried a chapter, “Unproven Methods of Cancer Treatment,” authored by Dr. Jane E. Henney, deputy director of the NCI (who would become Commissioner of the Food and Drug Administration in 1998). As expected, Dr. Henney's chapter would not include HS, since this drug had been removed from the American Cancer Society's Unproven List three years previously and the Soviet phase II study of 225 patients had already been published in 1981 in the American peer-reviewed journal, Nutrition and Cancer.23 But in this textbook's second edition, published in 1985,28 in the wake of further positive clinical studies, Dr. Henney's chapter, strangely enough, did include HS. By that time the Russian (Soviet) series had been enlarged to 356 patients,29 reporting essentially the same highly positive results as in earlier papers, again in very late stage, refractory patients. In her chapter, Dr. Henney characterized these Soviet results—in this instance 44 percent antitumor response and 50 percent anticachexia response, previously unheard of in this class of patients—as merely showing “hints of subjective activity.” And although the watershed February 1984 Cancer Research Harbor-UCLA article—and its predecessor ASCO abstracts of 198230 and 198331 —were available to her before the chapter went to press (in her chapter Dr. Henney quoted a reference dated April 1984), no mention whatsoever was made of the Harbor-UCLA work.

In subsequent editions of the DeVita textbook Dr. Henney's chapter was entirely removed. Nevertheless, a signal was sent to the oncology world that the two highest officials of the NCI—Drs. DeVita and Henney—had seen fit to characterize HS as an “unproven method” at a time when positive data, including randomized, double-blind, placebo-controlled studies, were emergent from unimpeachable clinical sources.

Harbor-UCLA Grant Application To The NCI . On July 1, 1983 Harbor-UCLA, under the principal investigatorship of Rowan T. Chlebowski, M.D., Ph.D., considered one of this country's leading authorities in intermediary cancer metabolism, submitted a grant application to the NCI to continue its successful, initial studies with HS and extend this salient work with the performance of an all-important clinical outcome study. Over the next few years NCI action would prove disconcerting to the Harbor-UCLA investigators. When Chlebowski and his colleagues made changes in the application recommended by the NCI study section, NCI referred the revised grant application to new and sequentially different study sections, which knew less and less about it and would demand further changes, until action by a third study section—submission to three, successive study sections had never before happened to any NCI grant application—would demand changes that had nothing to do with the original grant application or with changes recommended by the first, and primary, study section. In 1985 Dr. Chlebowski received notice from the NCI that his

grant application had been approved but achieved only a “borderline” funding score, indicating a substantial uncertainty it would be funded. Chlebowski therefore sent an urgent letter to the NCI,32 requesting “special funding consideration.”

In his letter Dr. Chlebowski, stated: “Our cumulative data are largely in agreement with the over 300 patient Russian experience where clinical benefit was observed in approximately half the patients receiving hydrazine sulfate therapy.” Emphasizing the importance of his research, he stated: “If the negative prognostic implications of weight loss in these cancer patient populations could be overcome by hydrazine sulfate—[which he termed “representative of an entirely new class of therapeutic compounds”]—a major therapeutic advance applicable to hundreds of thousands of cancer patients would be achieved.”

Chlebowski received no reply to his letter in over a month. A copy of his letter was then forwarded to the direct attention of Margaret Heckler, Secretary of Health and Human Services, for an “unbiased review of the hydrazine sulfate situation and of Dr.Chlebowski's letter in particular.”33 Two months later Dr. Chlebowski received a “Notice of Grant Award” from the NCI for his three-year project, “Glucose Metabolism and Hydrazine in Cancer Cachexia,” to begin September 1, 1985.

In 1987 three papers were published as a result of this new (and residual ACS) funding. In February34 Chlebowski and colleagues would demonstrate, in a full-length paper, that weight maintenance in HS-treated patients was statistically associated with an increase in the effectiveness of calories ingested, that the mean blood circulatory levels of HS nine hours following a standard oral dose (60 mg) ranged from 0 to 89 ng/ml—average: 45± 16 ng/ml—implying that patients who received no benefit from HS may not be absorbing it from their gastrointestinal tracts (i.e., patients with near-zero blood levels), that side effects were minimal, consisting of low levels of nausea, lightheadedness and “less than 1%” peripheral neuritis. In August35 Harbor-UCLA investigators, again in a full-length paper, demonstrated that HS reduced protein breakdown and preserved peripheral (body) muscle mass in patients with late stage non-small-cell lung cancer (NSCLC); it was also found that HS acted to maintain serum albumin levels , an important prognosticator of survival in these patients.

However, in 1987,36 it would be a third paper published only in abstract form by the Harbor-UCLA investigators which would prove to be most consequential. In this abstract (and in an oral presentation at the annual scientific meetings of the American Society of Clinical Oncology that year) substantive evidence was presented that HS resulted in statistically increased survival in a subset of early patients with NSCLC, which had never before been reported as a result of drug therapy: HS addition to standard chemotherapy resulted in a median survival time of 328 days, vs. placebo addition to standard chemotherapy which resulted in a median survival time of 209 days, the difference being statistically significant to the $p<.05$ level. It was the first time that a treatment directed primarily at abnormal host metabolism was demonstrated to favorably influence survival outcome in patients with malignant disease.

By the beginning of 1988, prospectively randomized, double-blind, placebo-controlled studies had thus indicated that HS: (a) normalized abnormal glucose metabolism, (b) resulted in increased effectiveness of ingested calories, (c) caused weight gain or weight stabilization, (d) reversed protein breakdown and muscle wasting, (e) maintained serum albumin levels, and (f) resulted in statistically significant survival increase in lung cancer patients. However, that same year NCI's Dr. DeVita, representing this country's cancer leadership at its highest levels, would pronounce HS a “ho-hum idea,” referring to this drug as merely “a therapy that gave you plumper people by the time they died”37 (and reaffirming his statement made to the media in 198l: “We throw away drugs that are better than hydrazine sulfate”38).

Multi-Institutional Grant Application to the NCI. Recognizing the large therapeutic potential of HS as a result of their metabolic and clinical outcome studies, Harbor-UCLA investigators undertook to enlarge their work from a single-institutional study to a multicentric study and from examination of a single tumor type, namely lung, to three tumor types: lung, breast and colon. The

institutions involved would be: Harbor-UCLA Medical Center (study headquarters), Emory University Medical Center, University of Toronto Cancer Center, Memorial Sloan-Kettering Cancer Center and M. D. Anderson Hospital and Tumor Institute. Among the co-principal investigators were some of the most distinguished names in cancer medicine and research: Dr. Dan Nixon, Dr. Murray Brennan, Dr. G. G. Boyd, and others. Dr. Chlebowski, a most experienced—and successful—grant writer, undertook to write the initial draft of the multi-institutional grant application, then sent it to his colleagues at the cooperating institutions for their comments, then revised it according to their recommendations. At about the time of publication of the Harbor-UCLA outcome study abstract (1987), Chlebowski sent the completed multicentric grant application to the NCI. Chlebowski, considered a "luminary" in the field of cancer metabolism investigation (he was one of thirteen scientists selected by the U.S. government to help establish a cancer treatment and teaching center in Taipei, Taiwan39), was shocked some months later to receive notification from the NCI that his grant application was not only not approved, but received one of the worst scores possible (at the time a perfect score was '1," the worst "500": the number given to his application was 460). In giving Chlebowski's multicentric application—written in conjunction with some of the country's top research institutes and scientists — such a resoundingly high (poor) score, the NCI in effect gave indication of its apparent displeasure with further, independent trials of HS. Shortly thereafter, NCI — the frequent and assertive adversary of HS since 1976 — assumed sole control of all further clinical testing of this agent.

Hired-Gun Editorial. But the Harbor-UCLA investigators, and HS, would be dealt another surprise at the hands of the cancer establishment. In early 1988, after gathering and collating all the data from its outcome study, Harbor-UCLA sought to publish a full-length paper on this study, detailing all study parameters—including patient selection, concurrent medication, treatment protocols, methods of study conduct, statistical analyses, etc.—in a journal of unquestioned reputation. Anticipating no difficulty in this task, Chlebowski and his co-workers sent this paper off to a mainstream, well regarded, internationally circulated cancer journal, in which they had published many times previously. This journal's editorial board kept his paper for four months—instead of the usual six weeks—and then rejected it. He then submitted the paper to the Journal of Clinical Oncology —a journal of the American Society of Clinical Oncology —considered by many as the emergent, authoritative journal for clinical studies of cancer drugs. In early 1989 the JCO agreed to publish the Harbor-UCLA paper, with "major revisions," most of which related to methodology and details of statistical analyses. However, each time Harbor-UCLA submitted its revisions, the JCO would ask for further changes. Finally, in June 1989 Harbor-UCLA received final acceptance by the JCO, stating its paper would be published in the journal's January 1990 issue.

But it would not be a "normal" publication. Ordinarily a journal submits to the author(s) galley proofs (page proofs) of the paper shortly before publication. These proofs are strictly of the author(s)' article and are for the express purpose of making last minute changes, additions or corrections. No galleys or proofs of any other articles or content appearing in the journal issue are ever sent to the author(s)—which would be considered highly unethical. But when Chlebowski and his group received galleys of their article, included in these galleys were the galleys of yet another paper—an editorial, "Hazards of Small Clinical Trials," taking aim exclusively at the Chlebowski paper and the conclusions reached. Up to this time no journal had ever sought to attack its own lead article. Confronted with the choice of withdrawing their paper with the understanding that the editorial, too, would be withdrawn,40 Chlebowski and his group chose rather to go ahead with publication.

Although in the January 1990 issue of the JCO Chlebowski and his group were able to demonstrate unequivocally that HS addition to chemotherapy significantly extended the lives of NSCLC patients,41 the effect of the editorial (which preceded the Chlebowski paper)42 was devastating. Written by Dr. Steven Piantadosi of the Johns Hopkins Oncology Center (who at the time was also a member of FDA's Oncology Drug Advisory Committee which recommended to the FDA which cancer drugs to approve and which not to approve), the editorial singled out only the HS results, shredding the Harbor-UCLA work on the basis that it was "too small" a clinical study to be valid.

However—and as pointed out in a subsequent issue of the JCO43—the Chlebowski trial was comprised of 65 patients, considered adequate for any phase III single-institution trial, whereas in the same journal issue there were trials of 15, 23, 24, 29, 30, 31, 40, 40, 43, 49, and 51 patients, and the editorial took issue with none of these or the conclusions reached. The effect of this "hired-gun" editorial was to dramatically curtail the use of HS in the U.S., and cast a pall over future, independent clinical research with HS, discouraging individual researchers and their sponsoring institutions from implementing any such undertakings.

(In contrast, in 1990—the same year as the Piantadosi editorial—HS, following approval for use throughout the Soviet Union, was named Sehydrin by the nomenclature commission of the U.S.S.R. Ministry of Health and, one year later, approved by the Pharmacology Committee of the Ministry of Health of Russia [the equivalent of the U.S. Food and Drug Administration] for general oncology use.)

The NCI-Sponsored Studies. In 1988 the NCI announced it would sponsor three large-scale multicentric (multi-institutional) phase III studies of HS, the first (and largest) of which would be conducted under the auspices of the Cancer and Leukemia Group B (CALGB) Cooperative Oncology Group of the NCI, headquartered at the Scripps Clinic in La Jolla . The second and third were conducted by the North Central Cancer Treatment Group (NCCTG) headquartered at the Mayo Clinic. NCI's Cancer Therapy Evaluation Program (CTEP), headed by Dr. Michael Friedman, held the portfolio of the planned HS studies.

HS is an irreversible and potent MAO (monoamine oxidase) inhibitor, a class of compounds that can have potentially deadly interactions with other drugs. For over three decades it has been known that central nervous system depressants—such as barbiturates, tranquilizers and alcohol—are incompatible with MAO inhibitors and use of the two together could result in extremely dangerous effects.44 Because these agents—especially tranquilizers—were commonly used as supportive agents in cancer patients, CTEP and all study chairs of the planned NCI-sponsored studies were alerted that use of HS in conjunction with these agents would constitute a clinical hazard,45-47 were advised that these supportive agents should be excluded in any study of HS (if not, a negative study would result), and were provided published and unpublished data8,15,26,48,49 indicating deleterious interactions between the two. (For example, one of the provided studies indicated that tumor bearing rats given either a benzodiazepine tranquilizer or HS suffered no harmful effects, whereas when the two types of compounds were given together in the same doses, the rats became comatose and a 50% to 60% mortality resulted, depending on which benzodiazepine was given.) CALGB's reply was that after careful review and discussion, "barbiturates, tranquilizers and alcohol will not be specifically excluded."50

In the June 1994 issue of the JCO, the three NCI-sponsored studies were reported as negative.5l-53 Publication of these studies was apparently carefully planned, since they appeared consecutively — even though they were finished at far different intervals (February 1991, October l992, November 1992). The first (CALGB) study was finished a year and a half before the last studies—and held until the last studies were completed, the effect of which was that their simultaneous—and sequential —publication might have greater impact. In the largest of these studies it was emphasized that "no patients received barbiturates and virtually no patients received phenothiazine-type tranquilizers with the exception of prochlorperazine (Compazine), which was used as a short-term anti-emetic [anti-nausea] agent." No mention was made of use of the more powerful benzodiazepine tranquilizers, the implication being that the benzodiazepine tranquilizers were not used. Tranquilizers were thus indicated as used only sparingly and for very short periods of time. Yet another—fourth—article on HS54 appeared in the same journal issue, an editorial identifying HS as a "vampire" and the NCI-sponsored studies as "three stakes in the heart of hydrazine sulfate."

The GAO Investigation. Because of evidence of irregularities presented to Congress, the ranking members of the Subcommittee on Human Resources and Intergovernmental Relations of the House Government Operations Committee ordered a General Accounting Office investigation of the NCI-sponsored HS studies (the GAO is the investigative arm of Congress). This investigation was

commenced in June 1994 under the leadership and direction of 28-year veteran investigator Barry D. Tice, Assistant Director of the GAO, Health Planning Division. The GAO soon learned that far from the exclusion of barbiturates and short-term use of only Compazine as a tranquilizer, the CALGB study included widespread—and in many cases prolonged—use of a spectrum of both phenothiazine tranquilizers as well as the more powerful benzodiazepine tranquilizers, with no exclusion of barbiturates or restriction on use of alcohol. Among the phenothiazine tranquilizers used were: chlorpromazine, perphenazine, prochlorperazine and triethylperazine; among the benzodiazepine tranquilizers were: alprazolam, clorazepate, diazepam, flurazepam, lorazepam, midazolam, oxazepam, temazepam and triazolam; barbiturates included: pentobarbital, phenobarbital, secobarbital and donnatal. These are among the most powerful depressants known, with such trade names as Thorazine, Compazine, Xanax, Valium, Dalmane, Ativan, Restoril, Halcion, Nembutal and Seconal. They are all incompatible—and potentially dangerous—with MAO inhibitors. It was ascertained that many patients in these studies received both phenothiazines and benzodiazepines, and some more than one tranquilizer at a time. As a consequence the CALGB was forced to publish a new paper clarifying the use of these agents. The new paper[55] specified that 94% of all patients received tranquilizers, half receiving the main benzodiazepine tranquilizer used, lorazepam (Ativan), on a long-term (>48 hours) basis, that the data were not computerized and that information regarding the use of concomitant medications "was not complete." At the end of this new paper the authors nevertheless maintained: "The correction and clarifications offered here do not change the conclusions originally reported from our study."

The principal question of this investigation was whether or not HS was an MAO inhibitor. If so, the NCI-sponsored studies would be, by definition, intrinsically flawed (since tranquilizers were known to be incompatible with MAO inhibitors). Despite pharmacology textbooks identifying hydrazine as an irreversible MAO inhibitor over the past 30 years, the NCI vigorously denied to GAO investigators that HS was an MAO inhibitor. On September 14, 1994 Dr. Michael Friedman, associate director of CTEP and in charge of NCI's HS studies, wrote to Dr. Vera A. Gorbunova inquiring whether "Russian oncologists restrict the coadministration of hydrazine with alcohol, antiemetics, tranquilizers and barbiturates."[56] Within three weeks he received a reply from Russian oncologist Dr. M. B. Bychkof: "Hydrazine sulfate is a modulator of biologic reactions…it functions as an inhibitor of monoamine oxidase [MAO] and therefore cannot be used in combination with alcohol, tranquilizers and barbiturates."[57] Nevertheless Dr. Friedman would later write to Barry Tice: "That hydrazine sulfate is an MAO inhibitor seems unsupported by our review of the data."[58]

Repeatedly asserting that HS was not an MAO inhibitor—acknowledgment by NCI of MAO inhibition by HS would be tantamount to an admission that NCI wittingly or unwittingly used known incompatible agents ("negative bias factors") in its HS studies—and leaving GAO investigators confused[59]—NCI submitted to the GAO[60] a series of nine "retrospective analyses" alleging that even if there were an incompatibility between HS and alcohol, tranquilizers and barbiturates, usage of these substances made no difference anyway to the studies' outcome. But these retrospective analyses were filled with statistical irrationalities and subjected to an outside, independent audit by consultant biostatistician Richard D. Wilkins, a former senior biostatistician at a major pharmaceutical company. In his 19-page report, Wilkins summarizes: "The NCI retrospective analyses, as presented, cannot statistically substantiate any claim that the use of adjunctive tranquilizers and/or barbiturates had no (deleterious) effect on hydrazine sulfate drug action or on survival outcome."[61]

On June 5, 1995 the GAO issued its 28-page Final Draft Report[62] of its ten-month investigation which was, in effect, a scathing criticism of the NCI-sponsored studies, which GAO investigators stated actually contributed to, rather than clarified, the controversy surrounding HS. Its title was: "NIH Actions Spur Continued Controversy Over Hydrazine Sulfate Therapy." The report stated: "NCI did not conduct adequate oversight of these trials. It did not take sufficient measures to appropriately address concerns over alleged incompatible agents….The issue of possible incompatibility of hydrazine sulfate with certain other agents is unsettled….The clinical importance of possible interaction between hydrazine sulfate and tranquilizing agents, barbiturates, or alcohol

has not been determined and the issue remains unsettled." This was circulated as a perfunctory courtesy to the Food and Drug Administration, the NCI, the Public Health Service and "interested congressional committees" before publication as an official document. Two days later, as set forth in a published investigative article, NCI representatives met with GAO, expressing "grave concern" lest the Draft Report be made public, and five days later presented GAO with an 8-page memorandum "demand[ing] a major rewrite."63 Shortly thereafter Barry Tice was removed from his position as lead investigator and relieved of all responsibilities in this case. Three months later (September 13, 1995) GAO published its official—new—report of its investigation. The new title read: "Contrary to Allegation, NIH Hydrazine Sulfate Studies Were Not Flawed."64

Tice commented, regarding the changes made in the Draft Report : "There weren't that many words changed from our Final Draft Report, but…the impact of the changes and few key deletions was tremendous. Those changes took NCI almost completely off the hook….In my almost 30 years at GAO I was rarely forced to accept rewrites or deletions that…significantly altered a report's message." 63

Tice retired from his long career at GAO soon after the altered GAO report was published. However, he was still haunted by the lingering doubt as to whether HS was an MAO inhibitor, on which, he knew rested the crux of the entire GAO investigation. As a private citizen, using his own stationery, he wrote to Robert M. Julien, M.D., Ph.D., of St. Vincent Hospital, Portland, Oregon, an acknowledged expert in the field of drug interactions and author of the seventh edition of A Primer of Drug Action65—whose book he had come across after leaving GAO—asking whether HS was an MAO inhibitor.66 Tice received a timely reply indicating HS was "an irreversible MAO inhibitor"67 (Dr. Julien's emphasis).

On October 25, 1999, four years after the NCI had so vigorously denied to GAO investigators that HS could be an MAO inhibitor, lest the NCI-sponsored studies be termed "intrinsically flawed"—four years after the GAO investigation had safely passed—NCI issued a multipage newsletter on complementary and alternative medicine, discussing HS. Its opening line was: "Hydrazine sulfate is an MAO inhibitor…."68

The FDA. On May 7, 199969 FDA's Pharmacy Compounding Advisory Committee (PCAC), convened under the stewardship of Dr. Jane E. Henney, newly appointed Commissioner of the FDA (who as deputy director of the NCI in 1985 included HS in her chapter28 on unproven methods, at a time when positive, placebo-controlled, double-blind data were reporting efficacy and safety of the drug)—met to consider, among other questions, the de-listing of HS from the "bulk compounding list." If HS were de-listed, this drug would become virtually unavailable in this country.

Because of excesses taken by the advisory committees (although these committees were made up of non-FDA scientists and lay people, they were nevertheless sympathetic to FDA concerns and frequently presented only those viewpoints sanctioned by the FDA), Congress passed the Federal Advisory Committee Act of January 26, 1998, which provided that presentations made to the advisory committees be "fairly balanced in terms of points of view presented" and that "the advice and recommendations of the advisory committee will not be inappropriately influenced by the appointing authority. " These two provisions were simply meant to safeguard against one-sided presentations and/or actions.

In flagrant violation of the Federal Advisory Committee Act of January 26, 1998, the "appointing authority" (FDA's Center for Drug Evaluation and Research), however, invited only those who could speak against HS to its PCAC meeting of May 7, 1999. Three outspoken adversaries70,71 of HS gave testimony (in favor of de-listing) to the committee, one of whom (charged with a "conflict of interest" in his role in the NCI-sponsored HS studies72) was not present in person but gave testimony by videotape and live telephone-hookup.

The appointing authority issued no invitations to any qualified proponents of HS to give testimony, either in person or by videotape or by live telephone-hookup, in favor of HS, and thereby balance

the “points of view presented,” as required by the Federal Advisory Committee Act of 1998. As a result the committee—sustaining a virtual blackout of information on the metabolic and clinical efficacy and safety data of the drug as presented in the peer-reviewed journals—voted unanimously, 12-0, to recommend the de-listing of HS from the bulk compounding list.

On February 6, 2001, section 353a of the Food and Drug Modernization Act of 1997, under which authority the PCAC voted its recommendation of May 7, 1999 to de-list HS from the bulk compounding list, was declared unconstitutional by a panel of three judges of the Ninth Circuit Court of Appeals. The FDA thereupon petitioned this court for a rehearing en banc (all 11 justices). The Court unanimously declined to do so. FDA then took this matter to the U.S. Supreme Court, the Justice Department arguing the FDA's case. On April 29, 2002 the Supreme Court upheld the Ninth Circuit Court of Appeals, in effect declaring section 353a—and all action taken under its authority (including the recommended de-listing of HS)—null and void.

Academe Joins In . What could not be done to eliminate HS by official intimidation, by rigged clinical trials, by GAO complicity with the NCI, by one-sided PCAC (FDA) action, our cancer leadership sought to accomplish by enlisting what can only be termed the academic whoredom of one of this nation's premiere medical journals.

As alluded to previously, in its December 5, 2000 issue, the influential medical journal, Annals of Internal Medicine, published a “Brief Communication” and editorial73,74 alleging that HS caused fatal hepatorenal (liver/kidney) toxicity in a single patient. There was one thing “wrong,” however. No proof was presented that the patient ever took HS. The authors stated: “We could not obtain samples of the product he [the patient] ingested.” This meant there was no possibility of a direct examination of what it was the patient was taking. The authors further stated: “His blood was not tested for the presence of hydrazine.” But there are simple blood tests that will detect even the smallest traces of the drug ingested months earlier. It must be emphasized that no medical journal anywhere—of high repute or not—would publish an article and editorial based on one case, calling attention of the medical profession and public to the potential toxicity of a drug gaining in common usage, without incontrovertible, verifiable, air-tight evidence that the patient ever took the drug in the first place. No journal would have the ethical recklessness to disseminate an article having far-reaching public health consequences without absolute proof of its basic assumptions. In this regard the authors wrote: “It is not necessary to be certain that a direct cause-and-effect relationship exist between the product and the adverse clinical event…to file a [toxicity] report [to the FDA].” The authors were in effect stating that it was not necessary to know for sure that HS caused the adverse clinical event before reporting it to the FDA. The authors then stated: “This report [the article and editorial] suggests but does not prove that hydrazine sulfate caused the liver and kidney failure.” Thus, knowing full well that its position was unsubstantiated, the Annals, one of this nation's top medical journals, went ahead anyway, disseminating its “drug alert” to doctors worldwide, across the Internet and onto the front pages of newspapers everywhere—without consideration to the heavy price that large numbers of cancer patients, their families and loves ones would pay if its message were incorrect.

To understand the moral turpitude of the Annals' action, it is necessary to know that—in contrast to the single, reported, presumptive case of fatal HS toxicity (in the drug's 30 years of use)—there are tens of thousands of authenticated chemotherapy fatalities, deaths from chemotherapy drugs, in this country each year . Has the Annals, or other medical journals, or our federal health agencies, or the prominent private-sector cancer agencies ever let the public know this?

AIDS And Hydrazine Sulfate . The two major causes of death (“risk factors”) in AIDS patients are weight loss and viral (HIV) replication. In 1987 Harbor-UCLA Medical Center received a grant from the U.S. National Institute for Arthritis and Infectious Diseases (NIH) to study HS in the treatment of AIDS patients with Kaposi's sarcoma. Prior metabolic studies of AIDS patients by Harbor-UCLA had revealed that weight loss was dependent on serum albumin levels, such that: patients with serum albumin levels equal to or greater than 3.5 g/dL survived more than 730 days from diagnosis; patients with serum albumin levels less than 3.5 g/dL survived 103 days; and patients with serum albumin levels equal to or less than 2.5 g/dL survived only 17 days.75 Since

HS had been demonstrated to result in serum albumin maintenance and weight gain in late stage cancer paitents,41 it was reasoned that this treatment might result in similar metabolic effects in AIDS patients, with the consequence of reversal of disease and/or prognosis.

Although the Harbor-UCLA grant was funded and preparations for the study, including patient accrual, had been in progress, the study was never commenced and study funds were returned to the National Institute for Arthritis and Infectious Diseases.

The reason for this action was attributed to the ongoing HS controversy.

Fueling The Current Controversy. The present controversy surrounding HS is sustained by two "arms." The first is the "difference of opinion" generated by the NCI-sponsored, negative HS studies, in contradistinction to the long-term, positive studies of Harbor-UCLA Medical Center and those headquartered at the Petrov Research Institute of Oncology. But the NCI-sponsored studies of HS—a potent and irreversible MAO inhibitor— were carried out in the presence of incompatible agents. The fact is that "every…informed-consent, controlled clinical trial of hydrazine sulfate—with the exception of the NCI-sponsored studies, confounded by the long-term…use of agents known to be incompatible with MAO inhibitors—has demonstrated efficacy and safety of the drug."76 It must be stressed that use of incompatible agents in a drug trial—or those even suspected of incompatibility—is essentially unknown and violates all accepted international principles of drug testing. Thus, no matter what credentials NCI brings to its sponsored studies—no matter how strenuous its voice to the contrary—the NCI studies are scientifically invalid . Use of an incompatible agent in a drug test in effect violates every precept of study conduct known to science. Nor can the NCI assert that the GAO validated its study conclusions. The Final Draft Report of the ten-month GAO investigation, altered at the last moment, showed the NCI-sponsored studies to be inconclusive, to in fact spur on the HS controversy; its lead—30-year veteran—investigator was relieved of all further responsibility in this investigation; and the GAO report was changed dramatically in support of the NCI-sponsored studies. The changes made "took NCI almost completely off the hook…" according to the lead investigator, Assistant Director of the GAO, Health Planning Division, Barry D. Tice.63

The second "arm" sustaining the HS controversy is comprised of economic factors. Unlike most chemotherapy—and anti-AIDS—drugs which are costly, HS is almost without expense. Fine biochemical companies manufacture HS in essentially two grades: technical—lower purity, and reagent—99+% purity, which is considered drug quality. The listed (catalog) cost for reagent grade —drug quality—HS is only three-quarters of one cent per average human dose (60 mg) administered to a cancer patient. A front-page story from the Sunday, January 26, 2003, New York Times ("Drug Sales Bring Huge Profits, and Scrutiny, to Cancer Doctors") indicates that "cancer doctors are pocketing hundreds of millions of dollars each year by selling drugs to patients….Oncologists can make huge sums—often the majority of their practice revenue—from the difference between what they pay for the drugs [they administer] and what they charge insurers and government programs….oncologists in private practice will typically make two-thirds of their practice revenue from [this] chemotherapy concession."77 Given the extreme inexpense of HS, oncologists are not going to make "the majority of their practice revenue," buying HS at such low prices and reselling it to patients, insurers and government programs, no matter how high the mark-ups. HS thus represents a formidable economic challenge to oncologists, for cancer doctors and those who administrate and direct our cancer programs are well aware that this drug's routine use may significantly reduce not only oncology funding and practice income but may also threaten the fiscal machinery of cancer centers, cancer hospitals, cancer treatment, cancer care, cancer research, cancer administration and cancer pharmaceuticals.

The Toll. More than 1.2 million new cases of cancer are reported in the U.S. each year; more than 600,000 Americans die from this disease annually. The Petrov (Russian) data, corroborated by the Harbor-UCLA data,32,78 indicate that of every million late stage cancer patients treated with HS, more than half a million would receive measurable symptomatic improvement, 400,000 would have their tumors cease growing or regress, and some would go on to long term survival.

If these data are correct—as seems likely—the human toll, in terms of needless suffering and/or premature death, because of a lack of access to HS therapy, has been 5 million persons in the last 10 years in the U.S. alone, many more worldwide.

The National Cancer Institute and the Food and Drug Administration, as well as private-sector cohorts, are principally responsible for this woeful public health calamity. Their sham message to the public—of "validity" of the flawed NCI-sponsored studies, of potentially fatal "toxicity" of HS, of "validation" by the GAO of the NCI study results—has served to deceitfully undermine use of what appropriately controlled clinical trials have demonstrated to be a safe and effective drug and, in so doing, impose a public health menace on significant numbers of cancer patients worldwide.

Concluding Remark . The NCI and FDA have the capacity to reverse the present situation with HS. The new leadership of these agencies can take measures to encourage competitive pharmaceutical sponsorship of this drug—and thus new, independent, large-scale, unbiased clinical trials—to explore fully its therapeutic dimensions in the treatment of cancer and, possibly, AIDS. In so doing, these agencies will move to rectify past ethical and scientific deficits and assume new high ground in the sponsorship of measures beneficial to the public health of peoples everywhere.

Recommendation . For those who may be a candidate for HS therapy, we recommend you take a copy of this entire statement to your physician, together with a copy of the published, controlled clinical trials indicating efficacy and safety of HS, which can be found on our website: scri.ngen.com. Your physician can then help determine a choice of specific therapy for your condition and what role, if any, HS may play in your particular therapy.

Joseph Gold, M.D., is director of the Syracuse Cancer Research Institute and the developer of hydrazine sulfate as an anticancer drug.

ADDENDUM. It has come to the attention of the Syracuse Cancer Research Institute that the National Cancer Institute has placed the following misrepresentations on the Internet on June 18, 2004, repeated verbatim on March 3, 2005 (http://www.nci.nih.gov/cancertopics/pdq/cam/hydrazinesulfate/healthprofessional/allpages/print), in regard to hydrazine sulfate:

(1) "There is only limited evidence from animal studies that hydrazine sulfate has anticancer activity."

(2) "Hydrazine sulfate has shown no anticancer activity in randomized clinical trials."

The first sentence implies there have been no human studies that have demonstrated the anticancer activity of hydrazine sulfate. But, as NCI well knows, there have been many controlled human studies demonstrating the anticancer activity of hydrazine sulfate, dating from as far back as 1975 and published in leading peer-reviewed cancer journals which circulate worldwide (cited in references 15, 17, 23, 27, 29, 34, 35, 41, 78).

The second sentence states categorically there have been no randomized clinical trials demonstrating the anticancer activity of hydrazine sulfate. RCTs represent the "gold standard" of clinical trials, in that they are prospectively randomized, placebo-controlled, double-blind and thus tend to minimize study bias from all sources. But NCI knows there have been four such randomized clinical trials demonstrating the anticancer activity of hydrazine sulfate (references 27, 34, 35, 41), all of which NCI has been aware from the very beginning.

NCI knows that the above statements it has currently placed on the Internet are simply not true.

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United States Patent 4,867,978
Method of prolonging cancerous patient survival in humans with hydrazine sulfate

September 19, 1989

Abstract

Hydrazine sulfate, alone or formulated with liquid or solid carriers, will prolong patient survival when administered to early-stage human cancer patients parenterally or orally.

Inventors: Gold; Joseph (Syracuse, NY)
Current U.S. Class: 424/719 ; 424/709
Current International Class: A61K 33/02 (20060101); A61K 33/04 (20060101); A61K 033/02 ()
Field of Search: 424/166
References Cited [Referenced By]
U.S. Patent Documents

4110437 August 1978 Gold

BACKGROUND OF THE INVENTION

Many different types of chemical compounds have been used in the past to retard or inhibit various tumors in man. More than thirty compounds are approved for use in cancer therapy in various countries, but the achievement of therapeutic benefit has reached a plateau, and the search for antitumor agents continues in various directions.

In 1967, Weitzel and co-workers reported in the Zeitschrift fuer Physiologische Chemie, 348, 433-442 that hydrazine acetate and sulfate inhibit in vivo the growth of ascites carcinoma and sarcoma 180 in the mouse and Walker carcinosarcoma in the rat. It is well known that the results from lower animals cannot be extrapolated in humans. Indeed, the experience at the U.S. National Institutes of Health has been that more than 200 new chemotypes having anticancer activity in animals have failed to show clinically useful anticancer activity in humans, as shown in the following table (Table I was compiled from various reports of the U.S. National Cancer Institute):

In addition, hundreds of analogs of the new and old chemotypes have failed to show anticancer activity in man, in spite of good antitumor activity in animals. In contrast to the above, only about five new chemotype anticancer drugs have reached the market in the last 25 years. Hence, early reports that hydrazine sulfate had antitumor activity in animals did not serve to predict that it might have anticancer activity in humans.

Because of this poor predictability of animal models, the National Cancer Institute of the U.S. National Institutes of Health has now abandoned the mouse model after 25 years of unproductive trial and is instituting a new in vitro program for discovering new antitumor drugs (E. Eckholm, New York Times, Dec. 23, 1986, p. C1).

A total inventory of cancer drugs approved for sale in the United States is set forth in Table II, and it will be seen that most of these are analogs of other drugs. Table III shows that, with one exception, all of the recent New Drug Applications filed for anticancer drugs led to unapprovable ratings by the U.S. Food and Drug Administration. Table IV shows that the last new chemotype which succeeded in the clinic was discovered more than 20 years ago.

A review of the FDA's New Drug Evaluation - Statistical Report (March 1986) shows that no novel anticancer drug is pending approval at the FDA.

Table IV lists the anticancer drugs approved in the United States. The last non-hormonal anticancer agent to be approved in the U.S. was etoposide in 1983.

The following are the years of discovery of the major anticancer drugs on the U.S. market (arbitrarily assumed to be one year before the first publication):

Thus, there have been no new chemotype cytotoxic anticancer drugs discovered in the past twenty years. Consequently, there remains an unfulfilled need for additional cancer drugs for clinical use against tumors in humans.

Up the present time, it has been generally unrecognized that a specific anticachexia agent (by virtue of its ability to interrupt those specific thermodynamic metabolic processes leading to cancer cachexia) possesses antitumor potential, by virtue of a systematic thermodynamic interrelationship between tumor progression (tumor energy gain) and cancer cachexia (host energy loss); this has been taught in the scientific literature since 1974 (J. Gold, Cancer Cachexia and Gluconeogenesis, Ann. N.Y. Acad. Sci., 230, 103-110 (1974)). Thus, while it is true that any antitumor agent may have anticachexia potential, if curative, it is also true that a specific anticachexia agent may have potential for increased patient survival. However, it is not obvious, nor predictable, from the prior art that hydrazine sulfate would possess this potential.

In 1978, the present inventor was issued U.S. Pat. No. 4,110,437 for the treatment of cancer

cachexia with hydrazine sulfate. Investigations were also undertaken to ascertain whether hydrazine sulfate could retard tumor growth in humans. However, these early studies were inadequate and failed to statistically demonstrate antitumor activity.

A group at Sloan-Kettering concluded after a trial that: "The clinical observations recorded in this report fail to support a role for hydrazine sulfate as an anticancer agent. We conclude that its clinical utilization is not warranted at present and do not plan further trials."(Ochoa et al., Cancer Chemotherapy Reports, Part 1, Vo. 59, No. 6, Nov./Dec. 1975; pp. 1151-1154).

In addition, a group at the University of Virginia repoted that: "Hydrazine sulfate as administered in this series failed to demonstrate any objective or subjective antitumor activity and no further trials are currently planned."(Lerner and Regelson, Cancer Treatment Reports, Vol. 60, No. 7, July 1976, pp. 959-966). Another later publication by Regelson et al. stated: "In conclusion, we feel that hydrazine sulfate as given in this study is an inactive compound."(Cancer Chemother. Pharmacol., 3, 121-124, 1979).

Thus, the prior art taught that hydrazine sulfate appeared to be inactive against primary tumor growth in man.

SUMMARY OF THE INVENTION

This invention is based on the discovery that hydrazine sulfate, when administered parenterally or orally in effective, non-toxic amounts to humans with tumors of the lung, prostate, breast, ovaries, thyroid, pancreas, lymph, cervix, gastrointestinal tract and other sites will significantly prolong survival of early-stage human cancer patients, while improving the patient's quality of life.

Description

DETAILED DESCRIPTION OF THE INVENTION

The dosages of hydrazine sulfate employed in the present invention can vary from 1 to 5 mg/kg daily, which is well below the LD50 and has been found to be well tolerated in the majority of early-stage patients so treated for periods of up to four years.

Preferably, the regimen followed is one 60 mg capsule of hydrazine sulfate daily for the first three days, then two such capsules daily for the next three days, and then three 60 mg capsules each day thereafter. In actual practice, patients weighing over 130 pounds do well on three or four 60 mg capsules daily. For patients weighing less than 100 pounds, the regimen followed is preferably one 30 mg capsule of hydrazine sulfate daily for the first three days, then two such capsules daily for the next three days, and then two or three 30 mg capsules each day thereafter. For best results blood levels of hydrazine sulfate should be determined on these patients in order to establish a most effective non-toxic dose.

Hydrazine sulfate therapy can advantageously be combined with other modalities for cancer treatment like chemotherapy, immunotherapy, radiation and surgery.

Hydrazine sulfate is most effective when administered usually by itself one or two hours before meals in the form of a gelatin capsule. If desired, the sulfate can be dissolved or suspended in sterile, aqueous, isotonic saline solution and given orally and parenterally. Likewise, hydrazine sulfate can be formulated with solid carriers such as talc, corn starch or stearic acid and compressed into tablets for oral administration. Such tablets can be enteric coated with shellac or cellulose acetate phthalate in a manner well known to those skilled in the pharmaceutical art.

The efficacy of hydrazine sulfate in prelonging survival in early-stage human cancer patients has now been demonstrated for the first time in a placebo-controlled, double-blind experiment with a statistically significant number of subjects.

Early-stage human cancer patients are distinguished from late-stage human cancer patients on the basis of the nature of their symptoms. These symptoms have been quantitatively correlated by two recognized methods of categorization: the Eastern Cooperative Oncology Group (ECOG) Performance Status Score (also known as Zubrod's) and the Karnofsky Rating Scale. The relationship between these two methods and the resulting division of human cancer patients into early-stage and late-stage, as recognized by ECOG and Karnofsky rating criteria, is set forth as follows:

Stage of ECOG Performance Karnofsky Nature of Cancer Status Score Rating Symptoms _____ Early 0 100 Asymptomatic without physical limitation Early 1 80-90 Symptomatic, but fully ambulatory Late 2 60-70 Symptomatic, but in bed less than 50% of day Late 3 40-50 Symptomatic, in bed more than 50% of day, but not bedridden Late 4 20-30 Bedridden _____

In the placebo-controlled, double-blind experiemnt referred to above, to determine whether hydrazine sulfate treatment is associated with a survival benefit (R.T. Chlebowski et al., "Influence of Hydrazine Sulfate on Survival in Non-Small Cell Lung Cancer: A Randomized Placebo-Controlled Trial", presented at the Annual Meeting of the American Society for Clinical Oncology, May 17-19, 1987, Atlanta, Georgia), sixty-five patients with unresectable, non-small cell lung cancer and no prior chemotherapy were randomized to receive combination chemotherapy with either hydrazine sulfate or placebo addition for a period of up to four years. All received Platinol/Velban/Blenoxane (PVB) chemotherapy every 28 days, consisting of Platinol 100 mg/m.sup.2 ; Velban 4 mg/m.sup.2, days 1 and 2; and Blenoxane 10 units every 8 hours for three doses. After the initial three cycles, the Blenoxane was discontinued and the Platinol dose was reduced to 50 mg/m.sup.2.

Pre-chemotherapy factors including age, sex, performance status (PS), prior weight loss and disease extent were comparable in the two groups, with pre-chemotherapy performance status (0-vs. 2) and prior weight loss (>10%) subsequently influencing overall survival ($p<0.05$). Toxicity was that expected from PVB with three patients not continuing hydrazine sulfate because of additional nausea. Survival by hydrazine sulfate or placebo were:

Median Survival bv Patient Group Treatment Group All Patients PS 0-1 Patients _____ Hydrazine Sulfate 292 days 328 days* Placebo 173 days 209 days _____ Statistical analysis of the data was by the generalized Wilcoxon (Breslau) method. Comparison of the hydrazine sulfate and placebo groups showed statistical significance at the *$P<0.01$ level. All of the survival benefit of hydrazine sulfate was in the performance status 0-1 group. For the performance status (PS) 2 patients, whose condition was poor, survivals were short (median 132 days) and closely comparable whether on placebo or hydrazine sulfate. Thus, hydrazine sulfate addition, as an anti-cachexia agent directed primarily at correcting abnormal host mechanism, significantly increased patient survival in early-stage patients with non-small cell lung cancer.

Specifically, this increased survival time occurred in early-stage human cancer patients with Performance Status 0 or 1 (PS 0-1), whereas late-stage patients (PS 2) did not exhibit prolonged survival.

Several patients with tumors of the prostate, lung, breast, ovary, lymph, cervix, thyroid, pancreas and other tumor sites were treated with hydrazine sulfate according to the preferred regimen previously set forth.

United States Patent 4,110,437
Method of treating cancerous cachexia in humans with hydrazine sulfate

August 29, 1978

Abstract

Hydrazine sulfate alone or formulated with liquid or solid carriers will retard and reduce cancerous cachexia even in the absence of tumor reduction when administered to humans either orally or parenterally.

Inventors: Gold; Joseph (Syracuse, NY)
Appl. No.: 05/765,362
Filed: February 3, 1977
Related U.S. Patent Documents

Application Number	Filing Date	Patent Number	Issue Date
558255	Mar., 1975		
413036	Nov., 1973		
372097	Jun., 1973		
198995	Sep., 1971		
861176	Sep., 1969		

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Field of Search: 424/166
References Cited [Referenced By]

Other References

Weitzel et al., Z. Physiol. Chem., 348, pp. 433-442, (1967)..

Description

BACKGROUND OF THE INVENTION

Many different types of chemical compounds have been used in the past to retard or inhibit various kinds of tumors. Such compounds include insulin, fluorouracil, estrogen, tolbutamide, biguanides and nitrogen mustards. However, the degree of successful therapy to date has been marginal at best so that the search for better and more effective anti-tumor agents especially in humans continues at a feverish pace.

In 1967, Weitzel and co-workers reported in Z. Physiol. Chem. 348, 433-442 that hydrazine acetate and sulfate inhibit in vivo the growth of ascites carcinoma and sarcoma 180 in the mouse and Walker carcinosarcoma in the rat. It is well known that such encouraging results in lower animals cannot be extrapolated to determine what effect the same compounds would have on other tumor types or even on the same tumors in humans. Until now, hydrazine sulfate in particular has never been used to treat cancerous cachexia.

SUMMARY OF THE INVENTION

This invention is predicated upon the discovery that hydrazine sulfate when administered either orally or parenterally in effective, non-toxic amounts to humans afflicted with tumors of the prostate, lung, breast, ovaries, thyroid, pancreas, lymph, cervix or gastrointestinal tract will restore the strength of such patients by reducing the cachexia associated therewith by continuing its use even in the absence of tumor reduction.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The dosages of hydrazine sulfate employed in the present invention can vary from 2 to 5 mg/kg daily which is well below the LD.sub.50 dosage and has been found to be well tolerated in the majority of patients so treated. Preferably, the regimen followed is one 60 milligram capsule of hydrazine sulfate daily for the first three days, then two such capsules daily for the next 3 days and three 60 milligram capsules each day thereafter until the patient shows definite signs of

improvement. If adequate response is observed on two such capsules daily, the patient should be maintained on this dosage and not increased. In actual practice, patients weighing over 130 pounds do well on four 60 milligram capsules daily whereas patients weighing less than 100 pounds generally respond on a dosage of 30 milligrams administered twice a day.

Hydrazine sulfate is most effective when administered by itself one to two hours before meals in the form of a gelatin capsule. If desired, the sulfate can be dissolved or suspended in sterile, aqueous, isotonic, saline solution and given orally or parenterally. Likewise, hydrazine sulfate can be formulated with solid carriers such as talc, corn starch or stearic acid and compressed into tablets for oral administration. Such tablets can be enteric coated with shellac or cellulose acetate phthalate in a manner well known to those skilled in the pharmaceutical art.

Several patients with tumors of the prostate, lung, breast, ovary, lymph, cervix, thyroid and pancreas were treated with hydrazine sulfate according to the preferred regimen previously set forth. Subjective results observed within a week of such therapy included restoration of vigor and a sense of well being. Objective results included cessation of weight loss and ensuing weight gain plus restoration to normal of abnormal blood chemistries. Although the tumors in these patients did not completely regress, there was a definite, noticeable inhibition in the growth of the tumors within 1 to 3 weeks of therapy. In each instance, the hydrazine sulfate was given daily for several weeks just as insulin is given to a diabetic thus making it possible for the patients to endure their affliction and prolong their lives. Less than 3% of the patients displayed minor side effects including transient gastritis which was quickly relieved by reducing the dosage to about one-half for a few days before reinstituting full dosage. Beneficial effects were likewise observed in the retarding and reducing of cancerous cachexia by continuing the use of hydrazine sulfate even in the absence of tumor reduction in said patients.
