# Unconventional therapies for cancer: 4. Hydrazine sulfate

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*Education*

*Éducation*

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*This article, on hydrazine sulfate, is fourth in the series that reviews the safety and effectiveness of 6 unconventional therapies commonly used by Canadian cancer patients. The purpose and methodology of the review appear in part 1 (*CMAJ *1998;158[7]:897-902). Annotated bibliographies providing more detailed references are available in print from the Canadian Breast Cancer Research Initiative (CBCRI; address appears at end of article). The reference lists and the lay summaries of the findings (published in 1997) can be found on the CBCRI's Web site (**www.breast.cancer.ca**). The following article adapts the lay summary on hydrazine sulfate for clinicians and provides references for the key findings. [Copies of this and other articles in the series can be found on* CMAJ*'s Web site (**www.cma.ca/cmaj/series/therapy.htm**).]*

*The Canadian Breast Cancer Research Initiative does not endorse the use of any particular unconventional therapy. It urges patients to evaluate all evidence carefully and to consult their caregiver in order to make thoughtful and fully informed personal decisions.*

*This article has been peer reviewed.*

*CMAJ* 1998;158:1327-30

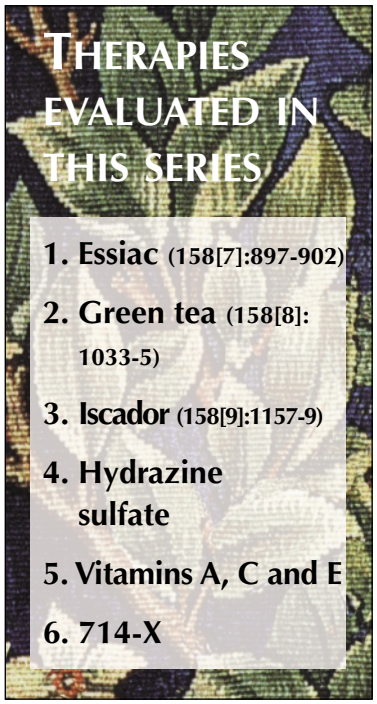
Unlike most unconventional therapies, hydrazine sulfate was developed in a way that more closely parallels the development of conventional therapies: a probable mechanism of action was identified and some research using animal models was conducted before the product was made available to patients.

The principal proponent and developer of hydrazine sulfate is Dr. Joseph Gold, an American research oncologist now at the Syracuse Cancer Research Institute, a private, nonprofit institute that performs cancer research, including studies of hydrazine sulfate alone or in combination with other chemotherapeutic agents. In developing hydrazine sulfate, Gold was influenced by the research of Dr. Otto Warburg, a 1931 Nobel prize winner who had proposed that an important distinguishing feature of cancer cells is their propensity to obtain energy through the anaerobic, rather than the aerobic, metabolism of glucose.[1] This difference between cancer cells and normal cells was confirmed by Gold and other investigators.[2,3] Gold, noting that gluconeogenesis (the process whereby the products of anaerobic metabolism are reconstituted into glucose) required a great deal of energy, postulated that excessive gluconeogenesis was a major determinant of cancer-related cachexia. As a result of further experimentation, Gold concluded that the enzyme phosphoenol pyruvate carboxykinase (PEP-CK) played an important role in gluconeogenesis and proposed that inhibition of this enzyme would impede gluconeogenesis and reduce the severity of cachexia.[4]

Gold tested a number of substances thought to interfere with gluconeogenesis, including L-tryptophan[5–7] and hydrazine sulfate,[8–10] in an effort to identify an agent that would inhibit PEP-CK. He found that hydrazine sulfate was the most effective for this purpose.[8,10] He reported that, in clinical studies, the use of hydrazine sulfate resulted in improved appetite and reduced weight loss,[11,12] and he proposed that it be used as an adjuvant therapy to prevent cachexia.

In addition to its effects on gluconeogenesis, Gold also reported that hydrazine sulfate administered to rats with transplanted tumours inhibited tumour growth and increased survival.[8] In the past, Gold has advised the use of hydrazine sulfate in patients with breast cancer, sarcomas, Hodgkin's disease and other lymphomas, and neuroblastomas. He now recommends its use for all forms of cancer.[13]

Gold recommends that hydrazine sulfate be used in conjunction with conventional therapeutic agents. He believes that combining these agents may re-



sult in an enhanced effect, a position for which there is some support.[14,15]

Hydrazine sulfate is usually administered orally, with food or immediately before eating. It may also be given by injection. The usual cycle of treatment is 60 mg 3 times daily for 30–45 days followed by a rest period of 2–6 weeks. The cycle can be repeated as many times as desired. Each 60-mg dose is available in capsule form or in 15-mL vials for injection.

The product is available legally in Canada, and physicians can obtain information about its availability by contacting the Health Protection Branch of Health Canada. The Health Protection Branch does not object to the use of hydrazine sulfate as long as the patient is under medical supervision. Although the product is not expensive, its costs are not covered by public or private health insurance plans. In the US, hydrazine sulfate is available to physicians through the Investigational New Drug (IND) program of the Food and Drug Administration. Hydrazine sulfate is more widely used in Europe, especially Russia, where it is known as Sehydrin. Further information about the availability of hydrazine sulfate can be obtained by contacting Dr. Gold directly (Syracuse Center Research Institute, 600 E Genesse St., Syracuse NY 13202 [**www.ngen.com/hs-cancer**]).

Hydrazine sulfate and its parent chemical hydrazine are well known industrial chemicals used in refining certain metals and in the production of some rocket fuels, insecticides and rust-prevention agents. Industrial-quality hydrazine sulfate can be obtained from industrial sources for laboratory research.

## Safety

The side effects have been reported as mild and transient when hydrazine sulfate is taken as recommended by Gold.[11,16] However, nausea, pruritis, dizziness, drowsiness, excitation and peripheral neuropathies (motor and sensory) may develop in 5% to 10% of patients.[16,17] Hydrazine, a metabolite of hydrazine sulfate, has been reported to have cytotoxic effects on hepatocyte cell cultures.[18]

Although the scientific literature reporting serious adverse interactions between hydrazine sulfate and alcohol, barbiturates and tranquillizers (particularly benzodiazepines) is limited,[19,20] Gold insists that these combinations are contraindicated. Gold believes that these combinations may lead to increased toxicity and decreased effectiveness. He also cautions that because hydrazine and hydrazine sulfate are monoamine oxidase inhibitors, people using hydrazine sulfate should avoid foods that are rich in tyramine (e.g., certain cheeses).[21,22]

In animal studies, hydrazine sulfate and other related compounds have been shown to be carcinogens or co-carcinogens in some species.[23–26] No human studies indicating such findings were found. Although no evidence was found that hydrazine sulfate produces any teratogenic effects, other hydrazine derivatives have been shown to be teratogens in several animal species.[24,27] Therefore, pregnant women and women of child-bearing age who are having unprotected sex should avoid using hydrazine sulfate.

## Laboratory and clinical evidence

Several researchers have noted that hydrazine sulfate inhibits the enzyme PEP-CK[7,28,29] and that it may interfere with gluconeogenesis.[7,30,31] Some animal studies have reported that these effects are potentiated when hydrazine sulfate is used in conjunction with other agents known to affect carbohydrate, lipid or protein metabolism positively.[32–34]

Hydrazine sulfate has been reported to have a cytotoxic effect on human glioblastoma cell lines.[35] This finding has led some to suggest that the agent may be of value in the management of glioblastomas.[36] A few animal studies have shown that hydrazine sulfate can stabilize or inhibit tumour growth. Most of these studies were by Gold,[8,9] but some other researchers have reported similar results.[33]

Gold's findings from animal studies suggesting that hydrazine sulfate enhances the effects of conventional chemotherapeutic agents[15,37] serve as the basis for his recommendation that it be used in conjunction with any appropriate conventional therapy for cancer.

With respect to clinical evidence, the scientific literature has fairly consistently reported that hydrazine sulfate is metabolically active and that it may normalize the carbohydrate metabolism of cancer patients with cachexia.[14,16,38,39] However, the mechanisms of cachexia are now considered to be complex and to involve much more than anaerobic glucose metabolism. The prevailing theory is that cachexia results from a combination of metabolic abnormalities, including abnormal lipolysis caused by a combination of reduced energy intake and the effects of substances released by tumour tissue.[40–42]

In terms of a direct effect of hydrazine sulfate on tumour growth, the clinical evidence has been much less consistent. A noticeable discrepancy was found between the results of clinical studies performed in the US and those conducted in Russia. Most of the US studies showed minimal, if any, beneficial effects,[38,43–47] whereas those conducted in Russia typically reported significant improvements in well-being, tumour stabilization and survival.[16,36,48,49] The exceptions to this generalization are the studies carried out by Gold[11,12,50] and by Chlebowski and colleagues[14,16,39] in the US that showed positive results.

The Russian studies were mostly case series, and some included patients with many different types of cancer.[49,51] Although reports of case series are of more value than anecdotal reports, it is difficult to evaluate the effects of hydrazine sulfate reliably in the absence of a control group and in a study population whose conditions and prognoses differ widely. Also, because most of the outcomes are subjective, the possibility of placebo effects must be considered.

The most recent US studies were randomized controlled trials that showed no benefit from the use of hydrazine sulfate in patients with advanced lung and colorectal cancer.[45–47] However, Gold and other supporters of hydrazine sulfate were unconvinced by these findings. They argued that the treatment protocol used in these studies did not comply fully with the recommendation that patients receiving hydrazine sulfate strictly avoid the use of agents such as barbiturates, alcohol and benzodiazepines. (Gold believes that these substances interfere with hydrazine sulfate's effectiveness.[52–56]) The expressed concerns of both Gold and the public[57] subsequently led to a review of the study by the US Government Accounting Office in 1997. This review found that the protocol used by the investigators was appropriate given the information available to them, but it did not formulate or express an opinion on the effectiveness or otherwise of hydrazine sulfate.[58] The potential benefits of hydrazine sulfate as an adjunctive therapy in the management of cancer remain controversial.

## Conclusion

There is good evidence that hydrazine sulfate inhibits gluconeogenesis. Therefore, it *may* play a role in reducing the severity of cachexia and in improving the quality of life of cancer patients. The value of hydrazine sulfate as an antitumour agent — specifically its capacity to stabilize tumour size, cause tumour regression and improve survival — remains uncertain.

Further clinical research is needed to confirm and quantify the benefits of hydrazine sulfate in reducing the severity of cachexia and in improving quality of life, alone or in combination with conventional chemotherapeutic agents. In addition, further animal and clinical studies to assess the antitumour effects of hydrazine sulfate, either alone or in combination with conventional chemotherapeutic agents, should be considered. The design of these studies is challenging, and in order to ensure that their results are of the greatest possible value in confirming or refuting claims of hydrazine sulfate's effectiveness, the studies should ideally be done in collaboration with Gold, the main proponent of hydrazine sulfate in Canada and the US.

This article reports some of the work carried out by the Task Force on Alternative Therapies of the Canadian Breast Cancer Research Initiative (CBCRI). The CBCRI is the main funder of breast cancer research in Canada and was established in 1993 as a consortium of the Canadian Cancer Society (CCS), the National Cancer Institute of Canada (NCIC) — which also serves as the administrative home of the CBCRI — and the federal government (through the participation of the Medical Research Council of Canada and the National Health Research and Development Programme). In addition to the author, a number of other CBCRI staff worked on the project, including Dr. Carmen Tamayo (research associate), Ms. Rebecca McDonald and Ms. Jess Merber. Others contributed to the reviews of specific agents. The task force was chaired by Ms. Donna Cappon. Dr. Kaegi was the Director of Medical Affairs and Cancer Control for the CCS and the NCIC and staff partner with the task force.

**Vitamins A, C and E will be the topic of the next article in the series, to appear in the June 2 issue.**

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Peer-reviewed journals dealing with unconventional therapies:
*Alternative Therapies in Health and Medicine*
*The Journal of Alternative and Complementary Medicine*

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