Hydrazine Sulfate—Dr. Gold Speaks out

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 has not happened; but 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 a *collection*

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 hepato-renal 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*. Have 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 anti-cachexia agent based on its inhibition of the gluconeogenic enzyme, phosphoenolpyruvate carboxykinase (PEP CK). 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.

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, could add to the antitumor effects of chemotherapy drugs, and was free of significant side effects. These results strongly suggested HS as a new means of non-toxic cancer chemotherapy.

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."

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 lympho-granulomatosis [Hodgkin's and non-Hodgkin's lymphomas] and malignant tumors of various localizations, when other measures of specific therapy failed."

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." 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, 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 anti-cachexia 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.

The second, a pharmaceutical-sponsored IND (Investigational New Drug) study of 84 terminal and pre-terminal patients with different types of cancer demonstrated a 59 percent anti-cachexia response and a 17 percent antitumor response.

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). 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. 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.)

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 anti-cachexia response and 44 percent antitumor response. Anti-cachexia 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 is it." (In 1981 the Gershanovich data were published as a full-length paper in the American peer-reviewed journal, *Nutrition and Cancer.*)

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*, 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, 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 Association* 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 reported 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*.

But in this textbook's second edition, published in 1985, 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, 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 anti-cachexia 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 1982 and 1983 — 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, requesting "special funding consideration."

In his letter Dr. Chlebowski, stated: "Our cumulative data are largely in agreement with the over 300 patient Russian experiences 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." 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 February 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 August 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, 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,
(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" (and reaffirming his statement made to the media in 198l: "We throw away drugs that are better than hydrazine sulfate").

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 multi-centric 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
- 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 multi-centric 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, Taiwan), 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 multi-centric 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, and 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, 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, the effect of the editorial (which *preceded* the Chlebowski paper) 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 *JCO*—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 multi-centric (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. 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, 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 data 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."

In the June 1994 issue of the *JCO*, the three NCI-sponsored studies were reported as negative. 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 HS 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 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." 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."

Nevertheless Dr. Friedman would later write to Barry Tice: "That hydrazine sulfate is an MAO inhibitor seems unsupported by our review of the data."

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—NCI submitted to the GAO 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, 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."

On June 5, 1995 the GAO issued its 28-page *Final Draft Report* 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 are 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 "demanding a major rewrite." 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."

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."

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 Action*—whose book he had come across after leaving GAO—asking whether HS was an MAO inhibitor. Tice received a timely reply indicating HS was "an *irreversible* MAO inhibitor" (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 multi-page newsletter on complementary and alternative medicine, discussing HS. Its opening line was: "Hydrazine sulfate is an MAO inhibitor…."

The FDA

On May 7, 1999 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 chapter 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 adversaries 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 studies) 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 editorial alleging that HS caused fatal hepato-renal (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 loved ones would pay if its message were incorrect.

To understand the moral turpitude of the *Annal's* 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* . Have 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. Since HS had been demonstrated to result in serum albumin maintenance and weight gain in late stage cancer paitents, 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." 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.

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." Given the extreme low cost 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. alone each year; more than 600,000 Americans die from this disease annually. The Petrov (Russian) data, corroborated by the Harbor-UCLA data, 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.

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, 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.