COMMENTS AND RESPONSES

Complementary and Alternative Medicine in Cancer

TO THE EDITOR: The informative article by Weiger and colleagues (1) on complementary cancer therapies is an important step in creating dialogue between biomedicine and its alternatives. However, I feel that it repeated certain popular misconceptions about the macrobiotic diet.

The authors describe the diet as “radical” but do not define the scientific baseline from which it is a radical departure. The word radical instead appears to reflect a subjective world-view. I would characterize a diet such as raw-juice fasting as radical because it cannot sustain long-term health and it has never sustained a human community. By these criteria, macrobiotics is not radical. Macrobiotic practitioners argue that their diet resembles traditional diets worldwide, whereas today’s U.S. diet is a radical and unhealthy departure from the human norm.

The risk that the macrobiotic “philosophy” may cause rejection of conventional therapy is not inherent in the diet but could apply to any alternative therapy. I would argue that for every patient with cancer who forgoes standard medical treatment in favor of macrobiotics, perhaps thousands forgo healthy dietary and lifestyle changes and instead rely entirely on biomedical intervention to keep them alive and well. What philosophy is influencing them to do that?

There is no more risk for malnutrition with macrobiotics than with the typical U.S. diet. Only a minority of Americans eat five or more daily servings of fresh, plant-based foods. In fact, every successive revision of the U.S. Department of Agriculture (USDA)’s food guidelines comes closer to macrobiotic recommendations.

Finally, women with reproductive cancer can easily eat macrobiotically without consuming soy phytoestrogens.

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Reference

IN RESPONSE: As Ms. Moliver indicates, there is no single, universally accepted definition of a “radical” dietary regimen, and what is judged as “radical” will depend in part on one’s frame of reference. Our working definition of a “radical” dietary regimen is as follows: 1) Dietary guidelines forbid or substantially restrict consumption of certain food groups that are staples of the U.S. diet, and 2) proponents claim that the regimen is effective in the treatment of specific diseases. By this definition, the macrobiotic regimen is “radical”: It forbids consumption of a food group (dairy) that currently forms an integral part of USDA dietary guidelines and substantially restricts consumption of a second USDA food group (fruits); proponents claim this regimen can effectively treat cancer. Patients can pursue macrobiotic diets while adhering to conventional cancer therapy. However, proponents claim macrobiotics can cure cancer in patients who forgo or discontinue conventional therapy (1). As Ms. Moliver suggests, the risk that patients will refuse conventional treatments applies to any complementary and alternative medical therapy for which similar anecdotal reports of cancer “cures” have been publicized.

We agree that the diet consumed by many Americans is far from ideal and that it is a mistake for patients to rely solely on medical interventions while disregarding potentially beneficial dietary and lifestyle changes. We encourage eating a well-balanced diet, with adequate consumption of fruits and vegetables as suggested by USDA guidelines. As we noted in our article, a carefully formulated macrobiotic diet can provide adequate nutrition, and it seems reasonable, if they wish, for many patients with cancer to use macrobiotics as an adjunct to conventional therapy. However, for cachectic patients who have difficulty maintaining adequate intake of calories and nutrients, we discourage dietary regimens that substantially restrict consumption of food groups that can provide nutritional benefits.

Ms. Moliver states that it is possible to eat macrobiotically without consuming soy phytoestrogens. However, isoflavonoids (derived primarily from soy) are not the only phytoestrogens found at high levels in macrobiotic diets. An analysis of the urine of women following macrobiotic diets showed a mean concentration of lignans (phytoestrogens found in whole grains, legumes, vegetables, and seeds) that was more than 10 times the mean concentration found in women following typical western or Japanese diets (2, 3). Therefore, even with soy-free macrobiotic diets, we remain concerned about the theoretical potential for adverse effects of excessive phytoestrogen consumption on progression of breast or endometrial cancer.

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References

Propensity Scores for Rare Outcomes and Common Treatments

TO THE EDITOR: We describe another use for propensity scores in addition to those reviewed by Braitman and Rosenbaum (1). In a randomized, double-blind clinical trial, some of us were faced with imbalances in baseline variables (2). We sought to use risk differences to summarize treatment effects but needed a method to adjust for the baseline differences. Typically, a multivariable method such as logistic regression or Cox proportional hazards regression is used with prognostic factors and treatment status predicting the outcome of interest. Such an approach typically assumes a constant odds ratio (if logistic regression) or a constant hazard ratio (if Cox regression) and reports an estimate of one of those but does not use a risk difference to summarize treatment effects. The following method yields an ad-
A Lesson in Poverty

TO THE EDITOR: The well-written article by Dr. Das (1) brought to mind several similar situations that we have encountered as both medical students and physicians in India. It is very accurate in its depiction of everyday scenarios that a practicing physician is likely to come across in India, even today, and the confusing gamut of emotions that arises when faced with them.

However, with reference to the man with tuberculosis whom Dr. Das mentioned, we would like to point out that since 1993, India has successfully implemented a national tuberculosis control program using a directly observed treatment, short-course (DOTS) strategy recommended by the World Health Organization. Under the revised program, drugs are provided by the tuberculosis division of the Ministry of Health and Family Welfare of the Government of India and are given free to patients at centers near their homes, according to DOTS strategy. This tuberculosis control program, already one of the largest public health programs in the world, continues to expand, with plans to cover 80% of the country by 2004 and 100% by 2005 (2). The situation described in Dr. Das’s article, in which the patient has no choice and completely gives up hope of receiving antituberculous therapy, is therefore unfair to the colossal efforts (outlined in the National Health Policy 2002 [3]) by the Government of India.

To our minds, the constant challenges faced in most developing countries, with their limitations of poverty and few resources, add an extra dimension to the responsibility of health professionals that extends beyond the delivery of medical care, that is, mere diagnosis and therapeutics. It is imperative that physicians working in these situations be aware of and well-versed in the distribution of health resources and already-functioning health delivery systems, so that underprivileged patients can be appropriately directed and benefit from them.

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References

Herpes Simplex Virus–Associated Sepsis in a Previously Infected Immunocompetent Adult

TO THE EDITOR: Background: Sepsis is a systemic inflammatory response syndrome due to a suspected or proven infection. Bacteria, fungi, and certain viruses can cause sepsis.

Objective: To report a case suggesting that herpes simplex virus (HSV), a common, treatable virus, might cause sepsis syndrome.

Case Report: A previously healthy 37-year-old man presented with fever and dyspnea. He was hypoxic and hypotensive and required immediate inotropic and ventilator support. Acute respiratory distress syndrome (ARDS), hypotension, hepatitis, disseminated intravascular coagulation, and acute renal failure developed. Blood cultures, urine cultures, bronchoalveolar lavage specimens, and cerebrospinal fluid studies before (and after) antibiotic administration were culture negative. Serologic studies and staining for an exhaustive panel of microorganisms were positive only for HSV-1 IgG, suggesting previous HSV-1 infection. Travel, exposure, and occupational history were noncontributory.

Because of a deteriorating clinical course, acyclovir was started on day 7 when oral herpes-like lesions appeared. Thereafter, the patient improved rapidly. Of note, a cell-free serum sample from day
0 revealed an HSV-1 DNA level of 280 copies/mL by quantitative polymerase chain reaction. At 1-year follow-up, the patient is healthy and results of tests for HIV are negative.

**Review of the Literature:** We searched MEDLINE from 1966 to 2002 using the keywords herpes, virus, sepsis, ARDS, and Toll-like receptors. Appropriate articles were obtained and reviewed, as were relevant references in those articles.

**Discussion:** Identification of HSV viremia at presentation, together with rapid recovery only after acyclovir therapy, implies that HSV played a causal role in our patient’s sepsis syndrome. The role of HSV in sepsis and ARDS remains unclear in healthy adults, particularly in the context of previous infection. It is well established that nearly 50% of patients with sepsis have no identified pathogen. Great efforts have been made to diagnose and elucidate the role of bacteria in sepsis, but little attention has been paid to viruses. Perhaps HSV not only can trigger sepsis but may also reactivate from latency and maintain the inflammatory process long after another pathogen-initiated sepsis episode has been successfully treated.

Cook and colleagues (1) demonstrated increased mortality rates in intensive care unit patients with reactive herpes infections. A previous report described a healthy 33-year-old man with HSV-related pneumonia who was intubated for 20 days with sepsis and ARDS, experienced failure of antibiotic therapy, and dramatically improved after acyclovir treatment (2). An 8-year study of 308 patients with respiratory distress reported that viruses were isolated as often as bacteria, and HSV was the most frequently isolated lung pathogen. Of patients with HSV, 14% were immunocompetent (3). Tuxen and colleagues (4) identified HSV from the lower respiratory tract in one third of patients with ARDS.

Bacteria initiate the immune inflammatory response through host recognition via Toll-like receptors. A recent murine study established that double-stranded ribonucleic acid, unique to viral infection, activates B transcription factor activation and inflammatory cascade initiation (5). The pathophysiologic characteristics of viral-induced sepsis in humans may occur by a similar and related molecular pathway, but this remains to be proven.

**Conclusion:** In summary, this case report proves HSV-1 viremia in a patient with ARDS and sepsis syndrome. The viremia preceded the development of oral–labial lesions by 6 days, and HSV-specific therapy was associated with rapid clinical improvement. The literature supports a relationship between ARDS and isolation of HSV. Furthermore, an animal model exists illustrating the molecular pathophysiology of viral sepsis. Currently, a study is in progress using modern molecular diagnostics to evaluate the presence of HSV and other viruses in bronchoalveolar lavage specimens taken from patients enrolled in an ARDS trial. Such systematic studies are necessary to establish whether HSV plays a causal role in the morbidity and mortality of sepsis, especially since effective treatment is available.

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**References**


**The Impact of Methadone Induction on Cardiac Conduction in Opiate Users**

**TO THE EDITOR:** Background: Opiate agonist therapy, specifically levacetylmethadol and high doses of methadone (>300 mg/d), has been associated with QT interval prolongation and torsade de points in two recent reports (1, 2). However, no prospective studies have examined the impact of methadone induction on the QT interval. We therefore sought to determine whether methadone is associated with acquired prolonged QT syndrome. We performed serial electrocardiography (ECG) before and during methadone induction and stabilization in a cohort of opiate users who were newly enrolled in a university-affiliated methadone maintenance treatment program in the Bronx, New York.

**Methods:** Between December 2001 and August 2002, we conducted a prospective cohort study of 132 heroin-dependent adults beginning methadone maintenance treatment. At baseline, before methadone induction, standard 12-lead ECG, medical history, and physical examination were performed. During follow-up, patients were stabilized while receiving a methadone dose ranging from 30 to 150 mg, and ECG was performed at 2 months. QT intervals were measured by using the algorithmic program provided with the MAC 1200 ECG machine (GE Medical Systems, Milwaukee, Wisconsin) and were corrected for heart rate by using the Bazett formula (QTc interval = QT interval/V R-R interval) (3). The mean of the difference between baseline and follow-up QTc intervals was tested for statistical significance by using the Wilcoxon signed-rank test for non-normally distributed data. Separate analyses were performed for the entire cohort and for predetermined subgroups by using SAS software (release 8.1, SAS Institute, Inc., Cary, North Carolina). The Albert Einstein College of Medicine Institutional Review Board approved the study, and patients verbally consented to participation in the study at the time of enrollment.

**Results:** Of the 193 persons enrolled in the study, 132 (68%) completed at least 2 months of follow-up and 61 (32%) discontinu-
used methadone treatment. Patients were predominantly male (66%) and Hispanic (68%); mean age was 40 years. At baseline, 100% reported heroin use, 44% reported cocaine use, 8% reported non-prescription benzodiazepine use, and 17% reported drinking more than 10 alcoholic drinks per week. The QTc interval increased by a mean of 10.8 milliseconds from baseline to follow-up (P < 0.001). No episodes of torsades de pointes were observed or reported during the study period. As shown in the Table, differences in the QTc interval remained statistically significant after stratification by sex, tertile of methadone dose, and baseline heart rate, although men and patients receiving higher methadone doses (110 to 150 mg) had the greatest prolongations.

Discussion: Our study is one of the first to assess changes in the QTc interval of heroin-dependent patients during methadone induction and stabilization. Our analysis demonstrates that, regardless of methadone dose, there is a statistically significant increase in QTc interval during the first 2 months of methadone treatment. A critical question, however, is whether this QTc prolongation is clinically significant. None of the patients exhibited an increase in QTc interval of greater than 40 milliseconds, the generally accepted threshold for an increase that should prompt clinical concern (4). Similarly, although a QTc interval of more than 500 milliseconds is considered a definite risk for torsade de pointes regardless of sex (5), the mean follow-up QTc interval (±SD) observed in this study (428 ± 21 ms) was well below this threshold.

Further research is needed to determine whether changes in QTc interval in patients receiving methadone are in fact associated with adverse cardiac outcomes. Methadone has been used safely for more than 30 years and is widely acknowledged to be the most effective treatment for opioid dependence. Any potential risk associated with its use must be weighed against its substantial demonstrated benefits. In this study, we found that methadone induction and short-term stabilization were associated with a small QT interval prolongation of uncertain significance. Future studies must examine cardiac outcomes among patients who experience QT prolongation while taking methadone and must identify factors associated with clinically significant cardiac dysrhythmias in this population.

References

CORRECTION

Correction: Advising Patients Who Seek Complementary and Alternative Medical Therapies for Cancer

A recent article on complementary and alternative medical therapies for cancer (1) contained an error. Under the heading “Antioxidant Supplementation,” in the section on vitamin E, the first sentence should have read, “One RCT suggests that vitamin E supplementation (at a dose of approximately 1.5 times the RDA) may prevent progression of latent prostate cancer to clinical cancer,” rather than “three times the RDA.”

Reference
Empathy and the Literary Imagination

TO THE EDITOR: I have evidence supporting Dr. Schneiderman’s proposition that the literary imagination and empathy are linked (1). As a medical student, I encountered a caring, thoughtful, and astute attending in nephrology who quickly realized, despite my assertions to the contrary, that I had little interest or talent in renal diseases. He quickly guided our discussions to something of mutual interest—books. Our favorite authors were the same: Conrad, Maugham, Dreiser. We talked vibrantly on rounds for days until I asked him what he was reading now. I was stunned to hear he had time to read only medicine. He hadn’t read a novel in 25 years.

This episode faded but was brought back vividly a few years ago when I happened to see in the newspaper a list of the 100 best novels of the 20th century (2). I was chagrined to note that I had read only about 20, and the last of these I had finished 25 years ago! I cautiously began reading outside medicine again. I’ve now read all of the novels on that list.

My medicine hasn’t suffered. It’s improved. I am a better physician, more understanding, open-minded, and intrigued by the stories behind the patients I meet. When I interview a troubled young man who, despite his youth, has spent years in the criminal justice system, I hear echoes of Richard Wright’s Bigger Thomas (3). A distinguished-looking businessman with elevated liver enzyme levels and a ready denial of problematic alcohol use on his lips—despite the literal presence of alcohol on his breath—calls up the Consul from Under the Volcano (4). The enduring worth of great literature is a character who is presented with compassion. The fact that these people are imaginary is irrelevant. They’re human. As Chief Broom observes in One Flew Over the Cuckoo’s Nest, “It’s the truth even if it didn’t happen” (5).

Given this greater understanding of my patients, I am a better advocate for them. I have also chased down—and confirmed—diagnoses that, before my renewed exploration of the “literary imagination” (1), I would not even have begun to pursue. I am a great proponent of evidence-based medicine. However, I have personal anecdotal evidence of something of which I am certain: Empathy can be taught. Great authors are the teachers, and all of us should be the pupils.

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References

Torsades de Pointes Due to Methadone

TO THE EDITOR: We read with much interest the article by Krantz and colleagues on torsades de pointes associated with long-term, very high doses of methadone (1). We observed two cases of acute methadone intoxication associated with a lengthening of the QT interval and torsades de pointes.

The first patient was found unconscious. Toxicology showed therapeutic concentrations of diazepam, nordiazepam, propoxyphene, and norpropoxyphene. Plasma concentrations of bromazepam and methadone were 277 μg/L (toxic level, >250 μg/L) and 3500 μg/L (toxic level, >1000 μg/L), respectively. Traces of cocaine were in the urine. There were no ionic abnormalities. Electrocardiography showed a sinus rhythm with a corrected QT interval (QTc) of 688 milliseconds, according to the Bazett formula (2). After initial neurologic improvement, the patient experienced torsades de pointes with loss of consciousness. Treatment included an electrical shock of 200 J, isoproterenol, magnesium infusion, and potassium supplementation. The patient recovered, and QTc interval normalized to 440 milliseconds 3 days later.

The second patient was admitted for coma. Electrocardiography showed sinus bradycardia with a QTc interval of 736 milliseconds. Plasma concentrations of methadone and flunitrazepam were 1740 μg/L and 27 μg/L (therapeutic range, 5 to 15 μg/L; toxic level, >50 μg/L). Traces of cocaine were in the urine. The potassium level was 3.6 mmol/L, and supplements were given. The patient experienced ventricular bigeminy followed by torsades de pointes with loss of consciousness. Treatment included an electrical shock of 200 J, lidocaine, and magnesium infusions. The patient recovered, and the QTc interval was 502 milliseconds on day 5.

These two cases suggest that torsades de pointes is also possible in patients with acute methadone intoxication.

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References

Sudden-Onset Thrombocytopenia with Oxaliplatin

TO THE EDITOR: Background: Oxaliplatin is a third-generation platinum compound that has shown activity in colorectal cancer. Although it has been used for several years in Europe, it has been approved for use in the United States only since 9 August 2002. With this approval, widespread use is anticipated. Two previous published reports described thrombocytopenia and hemolytic anemia thought to be caused by oxaliplatin (1, 2).

Objective: To describe a case of sudden-onset thrombocytopenia in a patient taking oxaliplatin.

Case Report: In June 2002, a 70-year-old woman with colon cancer metastatic to the liver presented for her 19th cycle of oxaliplatin. Blood drawn before chemotherapy showed a hemoglobin level of 97 g/L and a platelet count of 432 × 10⁹ cells/L. The patient received a 5-mL heparin flush through her port, and oxaliplatin, 85 mg/m². After approximately three quarters of the oxaliplatin infu-

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sion, she developed chills and hypoxia (pulse oximetry at room air was 90%). The patient received diphenhydramine, 25 mg, meperidine hydrochloride, 25 mg, and intravenous dexamethasone, 20 mg. The symptoms ended within 20 minutes, and she received 250 mg/m² of both 5-fluorouracil and leucovorin without incident.

Approximately 4 hours after cessation of oxaliplatin therapy, the patient noticed a skin rash on her right forearm that was consistent with petechiae. A repeated complete blood count showed a hemoglobin level of 95 g/L and a platelet count of 2 × 10⁹ cells/L. This was confirmed by both a citrate collection tube, rather than EDTA, and a repeated blood draw. Examination of the peripheral smear revealed absent platelets and no schistocytes. The patient was admitted to the hospital for platelet transfusion and observation. The Table displays the patient’s platelet count after the reaction.

Discussion: The patient required a blood transfusion when her hemoglobin level reached 81 g/L. However, the findings of a lactic acid dehydrogenase level of 290 IU/L (normal range, 100 to 200 IU/L), slightly elevated total bilirubin level of 29 μmol/L (1.7 mg/dL) (normal range, 3.4 to 20.5 μmol/L [0.2 to 1.2 mg/dL]), low reticulocyte count (51 × 10⁹ cells/L), and a negative result on a direct Coombs test suggest that significant hemolysis was not present. Antibodies to heparin and platelet factor 4, which cause heparin-induced thrombocytopenia, were not detected by 14C-serotonin release assay. Enzyme-linked immunosorbent assay for heparin antibodies was not performed. AD-dimer level drawn at the time of the event was elevated (12.26 mg/L [normal range, <0.55 mg/L]); however, it is unlikely that disseminated intravascular coagulation can account for the thrombocytopenia because fibrinogen levels were high (6.67 g/L) and prothrombin and partial thromboplastin times were normal (14.5 and 33 seconds, respectively).

The patient reported a similar incident during the 17th cycle of oxaliplatin. She presented to a local emergency department 1 day after chemotherapy with many bruises and a platelet count of 7 × 10⁹ cells/L. Following transfusions, the platelet count increased and the patient was discharged. Results of tests for antibodies to heparin-induced thrombocytopenia were also negative at that time. The 18th cycle of oxaliplatin was administered and received without incident.

Conclusion: To our knowledge, only one case has been reported in which oxaliplatin was thought to cause sudden thrombocytopenia without associated hemolytic anemia (3). Our patient met criteria for a hypersensitivity reaction during the 19th cycle of oxaliplatin (4). It is unclear whether this was associated with the thrombocytopenia, although she received oxaliplatin without incident during the 17th cycle, when thrombocytopenia first occurred. Steroids clearly do not alter the course of this reaction; the patient received intravenous dexamethasone, 20 mg, as a premedication and an additional 20 mg during the hypersensitivity reaction. This case illustrates that physicians should be aware of severe thrombocytopenia occurring immediately after oxaliplatin and that the reaction can recur with subsequent administration.

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References