THE CANCER LETTER

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The Antineoplaston Anomaly: How A Drug Was Used For Decades In Thousands Of Patients, With No Safety, Efficacy Data

Clinical trials of "antineoplastons" therapy are unlike any other in modern medicine.

To begin with, the inventor of antineoplastons, their manufacturer, proprietor of the clinic that offers the alternative therapy, and the principal investigator on clinical trials are all the same man: Stanislaw Burzynski, a Polish-trained physician who initially produced antineoplastons by extracting them from human urine.

Working outside peer review, Burzynski is conducting 71

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Experts Say Interpretable Results Unlikely In Burzynski's Antineoplastons Studies

Clinical trials conducted by Houston physician Stanislaw Burzynski are poorly designed and unlikely to produce interpretable results, three experts in clinical research concluded after reviewing Burzynski's annual report to FDA.

The annual report, which contains the names, diagnoses, and treatment-related toxicities of 963 patients who received intravenous antineoplastons over 12 months ended Nov. 25, 1997, was released to **The Cancer Letter** by Burzynski.

The reviews were conducted by:

—**Howard Ozer**, director of Allegheny University Cancer Center in Philadelphia, a clinical investigator with Eastern Cooperative Oncology Group, former chairman of the biological response modifiers committee and executive committee of Cancer and Leukemia Group B.

—**Henry Friedman,** professor of pediatrics at Duke University and chairman of the brain tumor committee of the Pediatric Oncology Group.

—**Peter Eisenberg,** a community oncologist whose practice in Marin County, CA, offers complementary interventions as well as standard treatment. Eisenberg is the principal investigator of Sutter Health West Cancer Research Group, a clinical trials consortium, and a former member of the executive committee of the National Surgical Adjuvant Breast and Bowel Project.

The reviews represent the first systematic examination of Burzynski's data by independent experts experienced in the design and conduct of clinical trials.

Ozer, Friedman, and Eisenberg agreed on the following points:

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Nearly 1,000 Patients Entered Antineoplaston Trials In 1997

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concurrent, preliminary phase II trials that cover most cancer indications—an unheard of number for a single investigator, and for a drug which is yet to be proven effective for any indication.

These trials are fundamentally flawed in design and execution, said three experts after reviewing the Burzynski Research Institute's 1997 annual report to the Food and Drug Administration. [The reviews begin on page 1.]

An exploration of the structure of Burzynski's clinical trials is by necessity a journey through an intricate, hidden labyrinth of loopholes that proved large enough to allow the controversial doctor to pump a sodium-rich substance into the veins of 963 patients treated in 1997.

Burzynski's motivation for conducting clinical trials is not limited to scientific curiosity. He is under a court order to administer antineoplastons exclusively through clinical trials or through "special exceptions" from FDA.

Though Burzynski says he has a network of physician "co-investigators" who follow his patients, several of these investigators said they did not put patients on the trial, do not administer antineoplastons, have no authority to stop the treatment, and have no knowledge of Burzynski's protocols. These physicians said they had not presented the protocols to their local Institutional Review Boards, which determine whether clinical trials are ethical.

"A Lowered Threshold"

Seven years after antineoplastons became the test case of the capability of the National Institutes of Health to evaluate alternative remedies, answers about the drug's activity are not on the horizon.

In October 1991, a team of National Cancer Institute scientists visited Burzynski's clinic in Houston to review the cases he regarded as the most successful. The team determined that seven of these cases constituted a basis for skipping formal phase I safety testing to move directly to phase II efficacy trials.

This was not done in a political vacuum. In fiscal 1992, Congress mandated NIH to establish an Office of Alternative Medicine that would oversee testing of "the most promising unconventional medical practices." The provision was inserted in the appropriations bill by Sen. Tom Harkin (D-IA), a supporter of alternative medicine.

"Our threshold for doing this has been lowered by a serious instruction from Congress," Bruce Chabner, then director of the NCI Division of Cancer Treatment, said at that time. "I think there is a significant potential downside for Dr. Burzynski here. This trial could put his operation out of business if his agent doesn't work." (**The Cancer Letter**, June 5, 1992)

However, the NCI attempt to test antineoplastons produced more heat than data. First, pediatric oncology cooperative groups said there was no justification for skipping phase I tests and declined to design a trial of the substance.

Advocates of alternative medicine, with backing from Congress, attempted to force the Office of Alternative Medicine to take over the trial from NCI.

For believers in alternative medicine, antineoplastons were an important test case: an alternative medical treatment that claims to produce cures. These members of the OAM advisory board spent much of their time battling the office director, Joseph Jacobs, who saw it as his mission to acquaint alternative practitioners with the principles of sound research.

"OAM was willing to buy the research assistance for [Burzynski] to design a good protocol

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and to set up a data monitoring committee," Jacobs said to **The Cancer Letter**. "There have been plenty of opportunities. And those clowns, his supporters, were doing everything they could to wreck those opportunities."

Ultimately, in late 1993, Burzynski and his supporters gave up on their effort to force the trial into a setting less rigorous than NCI. A trial of antineoplastons, coordinated by NCI, began at Memorial Sloan-Kettering Cancer Center, the Mayo Clinic, and the NIH Clinical Center.

That trial, which tested Burzynski's drug in advanced recurrent malignant glioma, accrued nine patients and was aborted as a result of a dispute. The dispute generated a stack of mutually recriminating memos, in which Burzynski accused the investigators of attempting to scuttle the trial, while NCI officials responded with requests that Burzynski provide the data that would back his accusations.

In August 1995, the studies were ended, generating some data on toxicity, but no conclusion on efficacy.

Another Stab At Clinical Trials

In the fall of 1995, a grand jury charged Burzynski with 75 counts of criminal contempt, mail fraud, and violations of the Food, Drug and Cosmetics Act.

In February 1996, Judge Simeon Lake, of the U.S. District Court for the Southern District of Texas, made Burzynski's "continued pretrial release" conditional on administering his drugs exclusively through "FDA-approved clinical trials." Lake's ruling was based on a 1984 permanent injunction issued by Judge Gabrielle McDonald.

After Lake's ruling, FDA was confronted with an unusual dilemma:

On the one hand, FDA was the client represented by the Justice Department in its prosecution of Burzynski. On the other hand, the agency and Burzynski became involved in negotiations aimed at setting up clinical trials of his remedy.

These negotiations, too, were not happening in a vacuum. Congress and the media were watching. Rep. Joe Barton (R-TX) held a series of hearings that featured patients who wanted to continue receiving the treatment. Burzynski's patients, wielding "Say No To Chemo" signs and chanting, "FDA go away! Let me live another day!" were making news all over America.

Federal prosecutors who were preparing the case against Burzynski told the agency that a deal that would create an appearance of Burzynski's compliance with the law would gut their case.

"We stated that position as forcefully as we could," said Michael Clark, former chief of the criminal division of US Attorney's Office for the Southern District of Texas.

Ultimately, FDA decided to disregard the prosecutors' pleas and make a deal with Burzynski.

Burzynski was allowed to set up nearly identical phase II protocols for every disease he treated. These prospective studies, which Burzynski said he based on the protocol used in the NCI trial, were designed to enroll new patients.

Patients who were getting antineoplastons at that time were placed into a protocol called CAN-1, a retrospective study in which data on non-Hodgkins lymphoma are reported alongside data on brain tumors, prostate cancer, and "adjuvant therapy."

CAN-1 is so distinctly unconventional that frustrated prosecutors promptly began to refer to it as "the garbage can," Clark said.

"When they put the patients into a large clinical trial unlike any other that we have been aware of, it made it very difficult to argue that the clinical trials process was very important in the case," said Clark, an attorney with the Houston firm of Gardere, Wynne, Sewell & Riggs.

In 1997, the government failed in two attempts to convict Burzynski. One trial ended in a hung jury. Another produced a not guilty verdict.

Still No Answer

As a result of his battles with FDA, Burzynski has become something of a folk hero. More importantly, he gained the ability to continue to treat patients legally.

As protocols became central to his efforts to stay in business, Burzynski used the NCI study as a prototype for all his studies.

"We did it this way because we felt that this will give us the best chance to have the right protocol," Burzynski said to **The Cancer Letter**. "[Since] these protocols have been already reviewed by FDA, we felt that FDA should not request many changes."

The purpose of preliminary studies is to ask a single research question. Usually, such studies are done in one—or as many as five—indications that the sponsor regards as the most promising.

"I think the question that needs to be asked is what are the gaps in our surveillance system that would allow someone to do 71 preliminary studies on a single regimen," said Norman Wolmark, chairman of the National Surgical Adjuvant Breast and Bowel Project. "To justify this kind of an effort, the investigator has to have 71 legitimate research questions. I certainly could not come up with that number of questions on a single regimen."

"The problem with 71 pilot trials is that it is so diffuse that it becomes no trial at all," said Robert Young, president of Fox Chase Cancer Center in Philadelphia. "This defeats the purpose of having a clinical trial design."

Generally, peer review—or the cost of conducting a proper trial—prevent investigators from undertaking 71 concurrent preliminary studies. FDA reviews trials for safety, and has no authority to regulate protocol design, the agency said.

"FDA works to ensure that trials are designed to produce clinically relevant results without placing research subjects at unreasonable risk," the agency said in a statement to **The Cancer Letter**. "Although the agency may place an unacceptably designed clinical trial on hold, the ultimate responsibility for designing and conducting trials properly rests with the clinical investigator."

In an interview, Burzynski said he plans to file a New Drug Application for antineoplastons.

"We are retaining two consulting firms which are guiding us through FDA approval process, and they really feel that we have a reasonable chance to get [the] NDA approved, regardless of what the doctors whom you found are saying," Burzynski said to **The Cancer Letter**.

"I Have No Idea Whether He's Got Enough"

Thomas Garvey, one of the consultants retained by Burzynski to compile the NDA, is not quite as upbeat as his client.

"I have no idea whether he's got enough [data]," Garvey said to **The Cancer Letter**. "I have to figure out what the hell is there. Then maybe we can defend it. You don't know until you take a real hard look."

Garvey, a gastroenterologist, is focusing on Burzynski's astrocytoma patients, a cohort in which Burzynski claims to have the strongest response. Burzynski's numbers indicate that 12 of the 28 evaluable astrocytoma patients who had no previous radiation or chemotherapy had complete and partial responses, and another 11 patients had stable disease. The stable disease category is not recognized by FDA as a measure of response.

"The first step is to pull it all together, lay it out, and try to obtain an appropriate historical control against which to compare his results," Garvey said.

Garvey said he is neither "a true believer" nor an "acolyte" of Burzynski.

"Burzynski is a very bright and charming person," Garvey said. "He also appears to be a good doctor. He knows his patients. He takes care of them. He has an unusual, unconventional anticancer therapy, and he has, by-and-large, functioned on the periphery of usual medical endeavors."

Another of Burzynski's consultants, Dieter Schellinger, chief of neuroradiology at Georgetown University Hospital, reviews the scans of Burzynski's patients who are classified as responders. "The majority of the cases I have reviewed were in concert with his assessments," Schellinger said. "In some cases, I rated them higher than he did."

Altogether, Schellinger has reviewed about 40 cases. "I know very little about the drug," he said. "I look only at images."

In an interview with **The Cancer Letter**, and in a follow-up letter, Burzynski said that Robert Temple, director of the FDA Center for Drug Evaluation and Research, encouraged him to file a New Drug Application for antineoplastons.

"Perhaps the reason there is a difference of opinions among experts who reviewed the annual report [for **The Cancer Letter**] and Dr. Temple is that at present we have more extensive data to support approval for Antineoplastons A10 and AS2-1," Burzynski wrote.

Temple said he has not seen the data that would have allowed him to assess the safety and efficacy of antineoplastons. "I don't invite anybody to come to the FDA," Temple said. "We have a standing invitation to anybody who has great data to submit it. I have never seen any favorable data from Burzynski in a form in which we could review it, so I could not possibly have an opinion about the actual data he has."

Burzynski apparently began to count Temple among his supporters after the FDA official commented on brain tumor scans that were presented at a recent meeting on alternative medicine. "My recollection is somewhat dim now, but the specific cases, as described, looked pretty impressive" Temple said. However, scans tell only a part of the story, especially in brain tumors, Temple said.

In a statement, FDA officials indicated that the trials being conducted by Burzynski could not support a New Drug Application.

"The current Dr. Burzynski trials are studies that could provide evidence of activity in a variety of tumor types, but they could not be viewed as definitive themselves," the statement said. "Preliminary trials can therefore be an important step in paving the way to definitive trials. Patients and physicians have no way of knowing whether there is benefit from a product unless that product has been studied in well-controlled clinical trials.

"Perhaps the most unfortunate result of Dr. Burzynski's practice over the past two decades is that he has administered antineoplastons to several thousand patients without, for the most part, gathering enough information to determine whether the product is safe or actually works," the statement said.

"That situation does not help patients, and it does not advance medical science."

Costs And Benefits Of Supervision By FDA

Several observers said the preliminary trials offer one advantage to an investigator: the ability to provide the therapy to a large number of patients.

"It appears that these so-called protocols and the special exception mechanism represent a vehicle for delivery of therapy rather than for answering any meaningful scientific questions," said David Parkinson, head of US oncology research programs at Novartis Pharmaceuticals Inc.

"The reviews suggest that, at best, this extraordinarily large experience of treated patients—approaching 1,000 patients when you combine patients treated under the so-called protocols with special exception patients—is a collection of anecdotes," said Parkinson, former associate director of the NCI Cancer Therapy Evaluation Program.

Janice Dutcher, chairman of the FDA Oncologic Drugs Advisory Committee and professor of medicine at the Montefiore Medical Center, said the Burzynski trials don't appear to be aimed at answering questions about the drug's efficacy.

"From the comments, it seems that it's all commerce: Whoever wants it gets it," Dutcher said. "It's impossible to tell from anecdotal data, without controls, what is happening. The patients and scientific community need to be convinced. The drug needs to be tested."

To date, Burzynski has submitted two annual reports that contain data that can yield a wealth of information about his research methodology and the clinical characteristics of his therapy.

"When fair-minded clinical investigators independently conclude that data are worthless, two options seem available: withdraw antineoplaston therapy from public use, or develop new protocols in conjunction with experts in clinical trials," said Barrie Cassileth, a psychosocial oncologist and author of The Alternative Medicine Handbook.

"The comments reported by Drs. Howard Ozer [of the Allegheny University of the Health Sciences Cancer Center], Henry Friedman [of Duke University], and Peter Eisenberg [of Marin Oncology Associates] cannot be misconstrued as government efforts to impede research," Cassileth said. "The reviews carefully delineate deficiencies in Dr. Burzynski's protocols. The reviews are sufficiently detailed and instructive to enable collaborative development of properly designed protocols."

FDA officials said they have been monitoring the results of Burzynski's trials in order to assess the viability of special exceptions.

"When these trials have shown no responses, we have terminated the expanded access programs," the agency said in a statement. "For example, FDA stopped providing single patient INDs for breast cancer and for non-small cell lung cancer, because Dr. Burzynski's data show that for these conditions, antineoplastons offer no objective benefits and present the risk of significant toxicity.

"Should the trials show similar lack of response for other conditions, FDA would not hesitate to terminate those expanded access programs," the agency said.

"Exceptional Amount Of Sodium"

According to the 1997 annual report to FDA, Burzynski treated 538 patients on protocol and 425 as "special exceptions" last year.

As a clinical investigator, Burzynski enjoys considerable leeway. FDA does not verify whether patients who are enrolled on protocol actually fit the entry criteria.

The agency is consulted when patients request to be treated as "special exceptions." These applications are reviewed by FDA physicians, and exceptions are granted only to patients who are unlikely to be cured by standard treatment.

Burzynski's marketing materials describe antineoplastons as "non-toxic substances."

This claim appears to be at odds with information contained in the protocols, FDA analysis of Burzynski's data, and the data reported by investigators from Memorial Sloan-Kettering, Mayo and NIH, the institutions that conducted the NCI-sponsored trial of the substance.

Under a high-dose antineoplaston regimen, a patient is exposed daily to 2.6 times the total amount of sodium normally found in the body.

In a high-dose regimen, an 88-kilogram patient would get about 147.8 grams of sodium per day, according to a calculation by Helen McFarland, director of oncology pharmacy at Johns Hopkins Oncology Center.

"Certainly, we may have increase of sodium because it's in the formulation, and because patients were dehydrated," Burzynski said. "But also [the therapy] is interrupting signal transduction through RAS oncogene pathway. And the RAS oncogene regulates potassium channels in the cells, which is causing potassium to go inside the cells, and sodium escapes from the cells." [In a telephone interview, Burzynski offered an account of his drug's mechanism of action and its side effects. An excerpted transcript of this discussion appears on page 13.]

Renal specialists and oncologists paint a less optimistic picture.

"This is an exceptional amount of sodium, and no matter what the body's defenses, and no matter what the renal function, first the patient is going to get excessively thirsty, and there is going to be some swelling related to the sodium level," said nephrologist Richard Quigg, associate professor of medicine at the University of Chicago.

Side effects from sodium alone are likely to include hypernatremia, edema, and, potentially, seizures, Quigg said. "A patient who weights 88 kilograms would have to get to about 12 liters of water a day in order not to die," he said. Patients who become incapacitated would be in grave danger, he said.

According to McFarland's calculation, a low dose of antineoplastons pumps 41.4 grams of sodium into the same patient's veins. By comparison, the daily sodium load of phenylacetate or phenylbuterate, two drugs closely related to antineoplastons, is around 8.8 grams.

Even with a sodium content of about one-seventeenth of high-dose antineoplastons, phenylacetate and phenylbuterate are considered high-sodium drugs. Patients currently receiving these drugs in phase I studies are carefully monitored, advised to go on a low-sodium diet, and given diuretics, said Michael Carducci, assistant professor of oncology and urology at Johns Hopkins School of Medicine.

"Infusion of hypertonic saline leads to a shift of fluid from inside the cells to outside the cells," said nephrologist Quigg. "With such massive sodium loads, edema, both cerebral and total body, would occur."

The metabolic consequences of this therapy could be disastrous, said Bruce Chabner, chief of medical hematology and oncology at Massachusetts General Hospital. "As a rational physician I would never do something like this," Chabner said. "This makes no sense."

In a document released at recent hearing held by Rep. Dan Burton (R-IN), chairman of the Government Reform and Oversight Committee, FDA officials said that according to Burzynski's data, 4% of his patients died while on protocol. According to FDA, hypernatremia—an elevation of serum sodium levels—may have been a factor in the deaths of 1.7% of patients enrolled in the studies in 1997 (**The Cancer Letter**, April 24).

Burzynski said his patients are encouraged to drink large amounts of fluid, but sometimes neglect to do so.

"When they stay in Houston, we watch them very carefully, and we monitor fluid in and out very carefully, and we try to convince then that this is important to do," Burzynski said. "But sometimes they don't drink as much fluid as they should, and then they may get dehydrated, and they have an elevation of sodium."

Burzynski said the sodium levels are usually brought down successfully.

"In practically all of these cases except for two cases we were able to reverse hypernatremia and bring this to a normal level, and the patient did not die as a result of hypernatremia," he said. "We had one case when a patient developed hypernatremia and intracerebral hemorrhage, and he died without having a chance to bring hypernatremia to normal. We had another case when a patient who had extensive liver involvement which can cause hypernatremia also developed hypernatremia, and she did not wish to have any treatment for hypernatremia, and she also died.

"So we have two cases in which we couldn't

bring hypernatremia under control," Burzynski said.

Clinical Experience

Independent investigators who worked with antineoplastons confirmed that the treatment was associated with substantial toxicity.

"We found severe toxicity in three of the nine patients, which necessitated stopping treatment," said Mark Malkin, associate attending neurologist at Memorial-Sloan Kettering Cancer Center, an investigator in the NCI-sponsored trial.

"In two of the three patients, we observed somnolence and seizures that resolved by stopping antineoplastons," Malkin said. "The third patient with protocol-ending toxicity developed a general edema of her body, and required stopping the infusion and diuretics to bring her back to normal. This woman had no history of kidney problems, liver problems, heart problems, or high blood pressure."

In two patients, edema appeared to have been attributable to the therapy. "Scans showed that the mass characteristics didn't change, but the edema in the brain went up," he said.

A paper on the trial has been submitted to a peer-reviewed journal, said Jan Buckner, associate professor of oncology at Mayo Clinic, principal investigator on the trial. The third author on the paper is Eddie Reed, chief of the ovarian cancer section of the NCI Medicine Branch.

"I think they were interested to stop this project soon. To prove that this doesn't work," Burzynski said to **The Cancer Letter**. "But we have patients who are now alive who have taken the medicine for a number of years, and these patients have been evaluated by some top neurologists in this country, or neurosurgeons, and they didn't see any toxicities, so to speak, to the treatment."

Hypernatremia was not observed in the NCI-sponsored trial, the investigators said. This is not a surprise for two reasons. First, the sample was small, and second, hypernatremia is rarely encountered in mainstream medicine.

"You can anticipate it, you can monitor it, you can detect it when it starts, and you can treat it, if necessary," Malkin said. "To develop hypernatremia, which can be lethal in patients with hemisphere glioblastoma, as part of their disease or as part of their medical treatment, is just distinctly unusual," Malkin said. "I can't remember the last time I've seen it, and I've been here for 13 years, and have probably treated 1,000 or more glioblastoma patients in that time."

"It's hard to imagine that the risk of death from hypernatremia is still being taken in 1998, when we've known for 20 to 30 years that hypernatremia in the treatment of patients with brain tumors is a contraindication," said Archie Bleyer, head of pediatrics at M.D. Anderson Cancer Center and chairman of the Children's Cancer Group.

Accidental Co-Investigators?

Proper management of Burzynski's patients presents unusual problems.

Since the therapy is administered by the patients themselves, their hometown physicians are often reduced to the role of authorizing blood draws and other routine care. These physicians are listed as "co-investigators" in Burzynski's annual report.

Though many of these physicians filled out standard "1572" forms issued by FDA, their role in taking care of the patients did not conform with the traditional role of co-investigators.

"I am neither honored nor flattered to be listed as a co-investigator by Dr. Burzynski," said Malkin, who is listed as a co-investigator. "I think it's presumptuous to list someone as collaborator in an endeavor when that person has refused to become involved."

"I refuse to become an accomplice after the fact," said Charles Riggs, an associate professor and medical director of the University of Iowa Clinical Cancer Center, after learning from a reporter that he was listed as a co-investigator. "I can't judge the patient for taking antineoplastons any more than I can judge the patient for using illicit drugs. But I will not be a party to either."

Malkin and Riggs said they did not fill out 1572 forms for Burzynski's trial. Virginia Stark-Vancs, a brain tumor specialist in Fort Worth, signed such a form in order to continue routine monitoring of her patient.

"Here is how it's presented: the patient says, 'I need you to authorize local blood draws, so results could be sent to Houston, but I don't want you to interfere,'" Stark-Vancs said. "You don't want to alienate the patient, because you know that inevitably the patient will need to have a local doctor."

The form notwithstanding, Stark-Vancs said she does not consider herself a co-investigator.

"I don't recruit patients to his study; in fact, the opposite is true," she said. "If I were indeed an investigator on his trial, I would have been

administering the drug and doing follow-up. I would have had access to the data. I would have been invited to investigators' meetings. I would have had regular communications with the principal investigator. I would have had the authority to halve the dose or take the patient off therapy unilaterally if I saw major toxicity.

"Finally, I would have had the option of saying, 'I don't want to be a party to what you are doing.'"

The Cancer Letter asked Burzynski to check the forms for nine of the investigators named on the list. Burzynski sent a reporter the forms signed by four of the nine.

Two investigators—Riggs and Malkin—did not return the forms, "but we have correspondences from them indicating that... [they are following] patients," Burzynski wrote. "The person compiling the data was under the impression that in fact they were co-investigators since they agreed to follow-ups and evaluations of these patients," he wrote.

One of the patients was being followed by a physician other than the one named on the list. The remaining two investigators—the father of a deceased patient and an alternative medicine advocacy organization—"were placed on the list by error of the clerk who was compiling the data," Burzynski wrote.

The issue of communications between the principal investigator and co-investigators is not one of mere bureaucratic procedure, said ODAC Chairman Dutcher. If this link does not work properly, important safeguards can be lost, she said.

"When we learn about toxicities, we modify the protocols," Dutcher said. "If we have something that is unusual, like a sodium or electrolyte problem, we have to either add other medications to control it, or change the dosing or schedule, or do whatever needs to be done."

Patient Groups Call For Investigation

While Burzynski's patients have served as their doctor's most effective advocates, patient groups that insist on high quality clinical trials and routinely take part in designing and monitoring protocols have not examined his practice.

In recent years, many patient groups have developed a genuine expertise in the design of clinical trials. Cooperative groups, pharmaceutical companies, and FDA have opened the doors for these patient advocates to take part in peer review of trial design and drug approval. Since Burzynski was not inviting scrutiny by these informed patients, none was being offered. He was simply off the screen.

This is no longer the case.

"It's a travesty of everything we fought for as activists," said Fran Visco, president of the National Breast Cancer Coalition and a member of the President's Cancer Panel. "We've spent years educating breast cancer activists about the importance of quality trials, the importance of research, and advocating for support of research. If this is the type of research that is permitted to go forward, it's a threat to our lives and a threat to continued support for science."

Visco said the reviews by Ozer, Friedman, and Eisenberg point to a breakdown in the system of regulation of clinical research.

"It looks like we have a breakdown on every level of the system that supposedly is designed to advance good science while it protects patients," Visco said. "We supposedly have all these laws and all these regulations in place, so things like this don't happen. How is he getting away with it? There are so many issues here. There is the issue of informed consent. What are these patients being told? What IRBs have been involved in this? What system of checks and balances at the FDA has been called into play here?

"We as activists have to find out where the system broke down. We have to fix it and make certain it never happens again," Visco said. "This clearly warrants an investigation and a response at the highest levels."

Ellen Stovall, executive director of the National Coalition for Cancer Survivorship and president of The March: Coming Together To Conquer Cancer, said Burzynski's supporters in Congress and in the media owe an apology to cancer patients and their families.

"These reviews make it painfully clear that Dr. Burzynski has bastardized the system that patients and their advocates rely on to validate safety and efficacy of cancer therapies," Stovall said.

"The exposure of this information propels us to become actively involved in monitoring Dr. Burzynski's practice. From this moment on, we are not going to let him rest. He is insulting the intelligence of the American people by calling his therapy nontoxic and alternative.

"All the news organizations, all his Congressional supporters—all those who by virtue of giving him a microphone gave him the opportunity

to present himself as a folk hero—now have the moral responsibility to tell the public what the evidence really shows," Stovall said.

"I would like to see Dr. Burzynski's Congressional patrons apologize to the American people. Now that the truth is out, nothing less than an apology will suffice."

Help With Trial Design Is Available

Would it have been difficult—or prohibitively expensive—for Burzynski to design phase II clinical trials that would have provided convincing answers?

"We design trials like this all the time," said ODAC Chairman Dutcher.

The process of designing a proper trial for antineoplastons would have required little more than a one-day meeting involving four experts, said Richard Schilsky, a member of ODAC, chairman of Cancer and Leukemia Group B, and director of the University of Chicago Cancer Research Center.

"If it were just an issue of design, Dr. Burzynski could have brought together four outside consultants—people who have experience and credibility in the clinical cancer research community—and presented his data, and sought their advice on how to design a clinical trial," Schilsky said.

"He could have paid them $1,000 each, and another $1,000 to cover travel expenses, and he would have gotten some very valuable scientific advice," he said.

Had Burzynski invited alternative medicine scholar Cassileth, with whom he is acquainted, he would have saved the honorarium. "If I had known that he needed help in protocol design, I would have offered my assistance gratis," Cassileth said.

Of course, protocol design is just a fraction of the cost of a proper trial. For trials to be meaningful, data have to be properly collected and audited. Such work is performed routinely by institutions, NCI-funded clinical trials cooperative groups, and private clinical trials organizations.

"Had Dr. Burzynski presented his data to CALGB, and had it evaluated by a peer group of investigators, and was able to persuade us that these are exciting data that should be tested fully, CALGB would have been more than willing to do a well-designed clinical trial evaluating these compounds, and that would have been a relatively low-cost effort for Dr. Burzynski to be able to utilize the existing national clinical trials program to evaluate these new agents," Schilsky said.

Government-funded clinical trials groups would not have been the only place available for Burzynski, Dutcher said.

"If he doesn't want the government involved, then he can go to one of the commercial clinical trials groups, and have an external advisory board watching it," Dutcher said.

Reviewers Note Major Flaws In Burzynski's Trial Designs

(Continued from page 1)

—The protocols are poorly designed and data are not interpretable.

—The toxicities of the antineoplastons treatment are significant and life-threatening.

—The data do not justify making antineoplastons available under special exceptions.

—Burzynski is conducting more clinical trials than his data justify.

—Burzynski's claim that antineoplastons produce "stable disease," which he considers a positive result, runs counter to established rules for interpretation of clinical trials data.

—Withdrawal by patients described by Burzynski as having responded is unusual in the practice of medicine.

—If Burzynski wants to convince patients and physicians that his drug works, he will have to accept the established mechanisms of clinical trials.

The reviewers were chosen by **The Cancer Letter**, and were not paid. They worked separately, and did not discuss the materials with each other.

Ozer, Friedman, and Eisenberg received the annual report, a copy of the FDA summary of the report, a detailed letter from Burzynski disputing the accuracy of the FDA tabulation of the data, the address of the Burzynski Research Institute web site which posts the protocols, and a list of questions prepared by **The Cancer Letter**. The reviewers had the option of not answering the questions and addressing any issue they chose.

Burzynski released the annual report last May, when he disputed the accuracy of an analysis of his data by FDA. Testifying before a hostile hearing conducted by Rep. Dan Burton (R-IN), a long-standing Burzynski ally, FDA Acting Commissioner Michael Friedman announced that antienoplastons therapy produced no responses among protocol patients with melanoma, soft tissue sarcoma, as well

as cancers of the breast, colon, lung, prostate and ovaries (**The Cancer Letter**, April 24).

The reviewers did not audit the data in the annual report. The reviewers first assessed protocol design and the quality of data. After enumerating fundamental errors in protocol design and data collection, the reviewers concluded that the studies were so flawed that auditing them was meaningless.

The text of the reviews follows:

Howard Ozer:

Dr. Burzynski is studying a heterogeneous, ill-defined patient population.

He treats patients who come through the door, and only patients who come through the door. He takes patients with bony disease, liver disease, bone marrow involvement, CNS disease. He organizes data by disease site, whatever the patients' stage, and whatever treatment they received prior to walking through the door of his clinic.

What we have here are bad trials that could never get past peer review of any clinical trials cooperative group. It's not in the public interest to conduct trials that are not going to yield clear results. If you are going to test an alternative approach, you need to test it as rigorously as you do mainstream approaches.

Dr. Burzynski's protocols are written with all the trappings of protocols. They look like protocols. They smell like protocols. But they lack the rigor of protocol design that defines the patient population, defines the endpoints, sets exclusion and inclusion criteria, and allows for statistical analysis.

The protocols are evaluating a single statistical endpoint: response. He doesn't evaluate disease-free survival, time to progression, quality of life, or overall survival. With these endpoints not prospectively defined, he has no basis for making legitimate claims regarding these parameters. This is a fundamental problem: You have to set your endpoints prospectively. It's too late to go back and do it after all the patients are treated.

Dr. Burzynski presents no baseline data. He presents no control data. He presents no description of methodology employed to measure active agents in the blood. How are these values affected by other variables, such as how recently these patients have been on other chemotherapy? How many other chemotherapy agents have they had? Is their liver and renal function normal? In the absence of controls, Dr. Burzynski is constructing his controls from memory and experience, which eliminates any possibility of determining a true response rate.

If a fellow brought me these data, I would tell him to choose a tumor—at most three sites—conduct a properly designed phase II trial, and come back to me after collecting adequate data. If this trial were proposed at the Eastern Cooperative Oncology Group, the review committee would lecture the investigator on the perils of employing a "shotgun approach" to clinical trials. Also, the investigator would be told that the proposed trial would subject too many patients to risk without true evidence of benefit.

Moving from protocols to results, I am surprised by Dr. Burzynski's statement that stable disease is a positive outcome. That runs contrary to established criteria for trial design. In the context of phase II trials, which are short-term studies, stable disease is not reported as a positive outcome.

It's possible to set a bar of proving that stable disease is beneficial. However, that bar has to be quite high for a new agent. To demonstrate benefit, the investigator would have to show stable disease not for a month or three months (which is all Dr. Burzynski is claiming at this point), but for six, 12, or 24 months in patients who have truly progressive disease.

For example, if you had a patient with a newly diagnosed acute myelogenous leukemia, and you started treating her with an agent, and her white count remained stable for a year, that would be indeed remarkable. However, if you had a patient with breast cancer in which the natural history of the disease can evolve over a decade, even after metastatic spread occurs, and you do analysis four weeks or even three months apart, and say that's stable disease, your result is not meaningful.

In the annual report to FDA, I see problems of adherence to protocols. While protocols call for evaluation of response every 90 days, in some instances I see Dr. Burzynski making these evaluations monthly.

Looking at Dr. Burzynski's brain tumor data, I don't see a breakdown by histology. It's extremely difficult to evaluate response in brain tumors, and these materials tell me little about how Dr. Burzynski does it. I can't review his scans, his x-rays, or his physical exams to know whether any of his results mean anything.

I do see patients with responses who subsequently withdraw from the study. That means

to me that the patients' perception of their benefit is less than what Dr. Burzynski is interpreting.

In the data presented to FDA, I see a 4 percent death rate that may be attributable to the therapy. That's a very significant grade 5 toxicity rate.

Hypernatremia reported by Dr. Burzynski is serious: as high as 180 mEq/L. A normal serum sodium level ranges between 135 and 145 mEq/L. Generally, the level of 155 to 160 mEq/L would be a big deal on the ward. By that token, 180 mEq/L is truly remarkable. I have never seen it. This would not characterize antineoplastons as very dangerous drugs, but they are certainly drugs that need careful monitoring since patients can be expected to experience life-threatening toxicity. If you are running serum-sodium at that level, it probably means that patients have to be hospitalized.

Dr. Burzynski's pharmacology data presented to FDA leave a lot to be desired. The pharmacokinetic data are reported, but are impossible to interpret. Here, too, I see no homogeneity. Dr. Burzynski presents individual patient kinetics, but I can't make head-or-tails of them, because his methodology is not explained.

In the absence of usable pharmacokinetic data, I can't say whether hypernatremia is caused by huge amounts of saline, or whether the study agents are having a physiological effect of creating hypernatremia.

All of these problems of trial design are real, but even if one assumed a good trial design, there isn't enough follow-up yet in any single group of patients to be able to determine validity of his results.

About 80% of Dr. Burzynski's patient population is too early to evaluate, and yet he evaluates them, and he does include the data from that evaluation. These data could be useful for making preliminary evaluations, but not efficacy claims.

It's not FDA's job to design the trials for Dr. Burzynski. Their job is to monitor safety, and make sure that the trials are ethical.

Based on the data I have seen, I believe that compassionate use of this drug is inappropriate at this time. Compassionate use should be reserved for cases when you know that a treatment is likely to benefit the patient, but the patient doesn't meet the protocol criteria.

I would not allow Dr. Burzynski to continue enrollment of new patients in his study. He has enough patients at this point to demonstrate anything that could conceivably be there. He needs to follow up patients for another 12 to 24 months.

Giving the investigator the benefit of the doubt, I would follow the patients currently under treatment, and over time there will be indicators of activity among some of the larger populations. If the response rate doesn't rise, and stays at about 20 percent or less after sufficient follow-up, then the trials would not be worth pursuing in their present form.

Henry Friedman:

Dr. Burzynski is collecting data in anecdotal fashion.

In the absence of rigorously reported and described results, and in the absence of independent verification of Dr. Burzynski's adherence to his own protocols, these data can never be useful to show true merit or lack of merit of his drug.

I see no data that would support the activity of this agent in brain tumors in any way, shape or form. The biggest problem is that the documents do not reveal that he has the expertise required for meaningful evaluation of radiographic evidence of responses in brain tumor patients. In the absence of peer review, we don't know whether he controls for the many factors that can produce an appearance of a response.

Clinical trials in brain tumor patients require rigorous and controlled review of the scans, because many different things can make an investigator suspect that there is a response when there is nothing. There could be a post-surgical artifact (post-surgery inflammation) that resolves by itself. There could be increases in Dexamethasone, which make the scans look better. There can be changes that are related to other factors, such as concurrent medications that can obscure the results.

If you don't have standardized, rigorous criteria for reviewing MRIs, which is the way you evaluate the responses of brain tumor patients, your data are meaningless. The protocols do not specify who is providing neuroradiologic interpretation of scans. Is it Dr. Burzynski himself? If so, what qualification does he have for interpretation of these results? The absence of requisite expertise to evaluate responses for conditions that produce artifacts in brain tumor scans would render the entire protocol worthless.

Dr. Burzynski reports a significant withdrawal rate of patients who theoretically respond. That has to be explained, because patients who truly respond don't withdraw, unless they have unacceptable

toxicity as part of interventions.

Dr. Burzynski's patients experience hypernatremia levels of about 170 to 180 mEq/L. [The normal level is 135 mEq/L to 145 mEq/L]. This is incredibly dangerous.

Hypernatremia in patients with cancers outside the brain is a problem, but when you have somebody with a mass in the brain, and you've got that kind of a cellular change, you are really asking for a much more pronounced problem because of the fluid shifts that go along with that.

When you correct hypernatremia, you can produce a significant intracranial swelling of the tumor, and—ultimately—kill somebody. When we get a patient who is hypernatremic, he or she is handled incredibly gingerly. Hypernatremia places brain tumor patients in double jeopardy. First, there is the danger from hypernatremia itself. Second, after you correct hypernatremia, a patient can develop cerebral edema.

Cerebral edema normally is a problem. But when you have a brain tumor and you get cerebral edema, it's frequently a lethal event. Anything that has to do with an electrolyte change in a patient with a cancer outside the brain is going to be exacerbated in a patient with a cancer of the brain.

The annual report to FDA and the protocols posted on his web site indicate that Dr. Burzynski is trying his drug in most brain tumors.

After reviewing these documents, I am unable to say what Dr. Burzynski's brain tumor data—or his work—are about. What I see is a waste of an opportunity to help people and advance the field. That's why you do clinical investigations: both to help people and to try to make the field move forward, and what he has done is present such a confusing morass of data that it's uninterpretable.

If Dr. Burzynski wants to test his drug in brain tumors, he is going to have to design a rigorous protocol with one or two histologies, and evaluate those. I personally would not want to be a part of such a trial, because I believe there are a lot more promising interventions than antineoplastons out there to evaluate first. For all brain tumor histologies, there are better questions to ask.

Nonetheless, if Dr. Burzynski chooses to proceed, I would advise him to abandon his claim that stable disease is a meaningful parameter in phase II trials.

It is not.

Peter Eisenberg:

After reviewing materials presented to me, I cannot make any conclusion regarding the efficacy of antineoplastons.

The trials seem to be numerous and unfocused. As a clinical investigator and a practicing physician, I recommend that Dr. Burzynski write a protocol on one or two diseases and treat patients in a rigorous fashion.

The results of his studies should be presented in a peer-reviewed, published paper so that all oncologists would be able to assess the results. This is how all of us who care for patients learn what works and what doesn't:

It is important for me to know that a study is credible:

1. Patients must meet inclusion criteria. Diagnoses must be histologically confirmed malignancy, and tumors must be appropriately staged.

2. Patients must have undergone uniform previous therapy or no therapy at all.

3. Patients must be randomized to receive study drug or placebo so that each treatment group is identical in every respect, except for the treatment to be studied. If the study groups are not identical, this should be acknowledged and explained.

4. Treatments must be given consistent with protocol design.

5. Evaluations of patients must be done in a standardized way so that it is clear what is being measured. Standard definitions for responses should be used. Dr. Burzynski's claim notwithstanding, "stable disease" is not a valid endpoint.

6. Discussions and conclusions should be based on the objective findings and supported by data.

One of the tragedies in cancer care is that not enough people participate in clinical trials. Only 2 to 3 percent of people are treated in a manner that would yield answers about safety and efficacy of treatments.

Dr. Burzynski has studied hundreds of patients without publishing his results, and we still know very little about the efficacy of his treatment.

The results in the annual report are presented in the form of raw data: many, many pages of charts detailing patient names, I.D. number, patient characteristics, name of disease, response to treatment and current status.

I cannot find any helpful summary material or a description of the study, results and discussion.

Also missing is information on whether Dr. Burzynski's patients had been receiving therapies other than antineoplastons and when they were receiving them.

Having gone over volumes of data, I have more questions than answers.

—I am unable to understand why FDA grants "special exceptions" for Dr. Burzynski to treat patients off-protocol. Considering that there is no evidence of efficacy of this drug, it seems unusual to me that Dr. Burzynski has treated 538 patients on protocol and 425 as "special exceptions." The whole notion of using investigational drugs "on protocol" implies a certain degree of rigorous and orderly investigation. I am much more in favor of completing well-conceived, properly designed trials than I am in continuing to provide medications with an unclear efficacy off-study.

—I can't understand why so many of Dr. Burzynski's patients entered in the studies are classified as "not evaluable."

— Dr. Burzynski seems to think that achieving "stable disease" is a good thing. I can say only that stable disease does not a response make. Oncologists use standard measurements for response. A complete response means the complete disappearance of the lesions, and no appearance of new lesions. A partial response refers to shrinkage by more than 50% of the sums of the products of the longest dimension of a tumor and the longest dimension that is at right angles to it. Responses must be documented to persist for more than four weeks.

—Dr. Burzynski's brain tumor data are impossible to interpret since all brain tumors are lumped together into a single category. That's a puzzling choice, considering that brain tumors are usually treated according to their histology.

—I am surprised to see in the FDA summary that half of the 36 patients characterized by Dr. Burzynski as responders withdrew from the study due to patient request, worsening conditions, or growth of tumor. If antineoplastons work, why are these people choosing to stop therapy?

—It is not clear to me why Dr. Burzynski's patients develop hypernatremia. According to the FDA summary, 65% of patients experienced hypernatremia, with 7% having a sodium of 160 mEq/L and higher. This is high incidence, because it's not something we routinely see with standard chemotherapy.

In his letter to the editor in **The Cancer Letter** of May 22, Dr. Burzynski claims that hypernatremia is common in the general populace. This has not been my experience, nor is this supported in the literature.

"We Don't See Any Significant Toxicity," Burzynski Says

In a telephone interview with ***The Cancer Letter*** *Editor Paul Goldberg, Burzynski offered an explanation of his drug's mechanism of action and its side effects. Following is an excerpted transcript of this discussion:*

The Cancer Letter: You say in your promotional materials that antineoplastons are not toxic. How do you arrive at that claim?

Burzynski: It depends on what you are talking about toxicity. In some of the patients who are taking treatment for a number of years, we arrived to the total dose of antineoplaston of about 600 kilograms. And with minimal side effects.

CL: At high dose?

B: It is in the range of 5 to 15 grams per kilogram body weight. The kind of dosage that we are using for A-10 is 25 grams per kilogram body weight daily. We seldom use such high dose, because usually it's not necessary, but that's what we are able to use without really showing any significant side effects in these patients. And, as I've mentioned, for patients who have taken the treatment for a number of years—some of them have taken the treatment for 10 years—we don't see any significant toxicity. Some minor problems, but can you imagine taking any chemotherapeutic drug for 10 years without showing any significant toxicity?

CL: When Mayo, Memorial, and NCI tried it, they found some major toxicities. Of the nine patients, three had to be taken off the study.

B: We can look at this from various points of view. Some of them were taken off because they developed some skin rash. But it happened that the skin rash was due to Dilantin [a seizure medication] that the patient was taking at the same time. I think they were interested to stop this project soon. To prove that this doesn't work. But we have patients who are now alive who have taken the medicine for a number of years, and these patients have been evaluated by some top neurologists in this country, or neurosurgeons, and they didn't see any toxicities, so to speak, to the treatment.

If you take in consideration 20 grams per kilogram body weight, and if you take body weight

of 70 to 80 kilograms, that means that daily you can theoretically administer 20 times 80, around 1,600 grams of the material, which means better than 3 pounds. Okay? So how can you call such material toxic if you can give it in such quantities?

CL: According to a calculation I cite, an 88-kilogram patient on high-dose antineoplastons would get about 150 grams of sodium a day. That's a load of sodium.

B: Of course, there is a substantial amount of sodium here, using a large dose of this drug. We did pharmacokinetic studies, and we were treating a large number of patients with high dosages of antineoplastons, and we were taking blood samples at short time intervals, like after seven minutes, after one hour, two hours, three hours, and so on. And we have seen some fluctuation of electrolytes, but they were within normal limits. We could see sodium levels climbing toward the upper normal limits, but then going back to normal after the infusion was finished. Certainly, we have seen some cases of hypernatremia.

CL: Why do you think it's happening?

B: It may happen for a variety of reasons. Of course, we have a certain content of sodium, and the sodium also causes hypernatremia, sodium which is in the formulation. However, when we did pharmacokinetics, we didn't find any hypernatremia. On the other hand, the medicine has some osmotic effect. The osmolarity is higher than normal. And because of that we see increased diuresis. And increased diuresis may cause dehydration. Typically, in patients we see increased elimination of urine, and we allow them to drink more fluid. We try to accomplish proper fluid balance in these patients, but sometimes they neglect it.

CL: Oh, they do? They neglect it.

B: Sometimes they don't drink such an amount of fluids. When they stay in Houston, we watch them very carefully, and we monitor fluid in and out very carefully, and we try to convince then that this is important to do. But sometimes they don't drink as much fluid as they should, and then they may get dehydrated, and they have an elevation of sodium. In most cases, this is only a minor elevation of sodium, which we may see in the blood test without any symptoms. But in some cases, we may see substantial sodium concentration. We record every instance of elevation of sodium. Even if it's one unit above normal, and we record it. And we report it to FDA. So this way FDA came up with something like 55% of patients have an elevation of sodium, but in most of these cases this was a minor elevation, only evidenced by the blood test.

CL: What kind of elevation?

B: If we see 148 mEq/L, we discontinue the treatment and we report to FDA that the sodium has been elevated. In most of the protocols for chemotherapy they don't pay any attention if sodium is one point above or two points above. They are more concerned when the sodium is too low. Certainly, we have some cases when sodium was very high. In practically all of these cases except for two cases we were able to reverse hypernatremia and bring this to a normal level, and the patient did not die as a result of hypernatremia. We had one case when a patient developed hypernatremia and intracerebral hemorrhage, and he died without having a chance to bring hypernatremia to normal. We had another case when a patient who had extensive liver involvement, which can cause hypernatremia, also developed hypernatremia, and she did not wish to have any treatment for hypernatremia, and she also died. So we have two cases in which we couldn't bring hypernatremia under control.

CL: That's last year, right?

B: Yes. And in the rest of the cases, hypernatremia has been normalized.

CL: Is this only in Houston, or at home?

B: I am talking about all patients, altogether. All patients treated. In most cases these patients were outside Houston when this happened.

CL: So you managed them on the phone?

B: We have a lot of doctors who are involved in the treatment. When a patient is taking high doses of antineoplastons, we have a lot of doctors register as co-investigators. They are managing the patients locally, but we are trying to maintain contact with the patients practically every day. We are more concerned about water toxicity with these patients, because the limiting factor seems to be the volume of fluid which we have to infuse. In most of these patients we are not really reaching the maximum dose of 20 grams per kilograms for adult patients, but they are usually administered the medicine between 5 to 15 grams per kilogram body weight for antineoplaston A-10.

CL: That's a substantial amount of sodium.

B: Yes, sure. In our protocols, we stop the treatment even if we have elevation of sodium by one point. And practically in all of these patients the next day sodium is back to normal, and we don't have

to introduce any treatment, and simply ask the patients to drink more fluids. That's what we normally do in our protocols.

CL: What about cerebral edema?

B: Cerebral edema is usually decreased during the treatment, because we have osmotic effects of the formulation. We have osmotic effects similar to Mannitol. Patients when they are under treatment usually have less chance of cerebral edema. It's like if they receive Mannitol infusions. When we stop the treatment, then they may develop signs of cerebral edema. So they may have a rebound effect. So sometimes with such patients we have to resort to Mannitol, we have to resort to higher doses of dexamethasone to decrease edema. But about 98% of our patients have a tendency to eliminate more than usual amount of fluid, and about 1.5% of patients have a tendency to retain the fluids. This situation seems to be beneficial, because many of cancer patients have problems with fluid retention. If you are talking about patients who also have liver involvement, they usually are coming with ascites. They may have pleural effusions. They may have total edema.

CL: So this is beneficial? I guess intracranial pressure would be increased; wouldn't it?

B: No. It decreases, as a matter of fact. Of course, if you have a high level of sodium, then intracranial pressure may increase because of that. But it takes really a high sodium level to do it. Theoretically, when you introduce osmotic diuresis, then the intracranial pressure is decreasing. That's why we don't really need to use diuretics frequently, because we have diuretic effect of the medicine in the first place. Okay? And also waste products which may be coming up from dying cancer cells, like uric acid, are also eliminated. Before we used high dosages of antineoplastons, and before we used formulations which have such high osmos expression, frequently we have seen high elevations of uric acid in blood, which required, of course, giving them allopurinol, giving them hydration, a proper diet, and discontinuation of the treatment until uric acid stabilized. Now we seldom see this, because uric acid has been eliminated because of this diuresis.

CL: Uric acid in this case occurs because...?

B: Uric acid usually occurs when you have extensive tumor breakdown, or necrosis. So in some cases we experience what is called tumor lysis syndrome, when a high level of uric acid and an elevation of some other laboratory values, and decrease of potassium because of tumor necrosis. And this was when we used lower doses, and not as concentrated formulation. But now we seldom see this, because with the increased diuresis, it has been eliminated.

CL: What effect does the sodium have on the tumor? Does it have any tumor-fighting effect?

B: I doubt it very much. If anything, it may have the opposite effect. Certainly, we try to not have high sodium concentration, and in most of our patients we are able to avoid it through very careful monitoring.

CL: So the sodium is there to get rid of the uric acid from necrosis?

B: There is a more up-to-date explanation why we may have increased sodium in such patients. Certainly, we may have increase of sodium because it's in the formulation, and because patients were dehydrated. But also antineoplaston AS2-1 is interrupting signal transduction through RAS oncogene pathway. And the RAS oncogene regulates potassium channels in the cells, which is causing potassium to go inside the cells, and sodium escapes from the cells.

Child's Treatment Provides Study Of Contrasts: Burzynski Versus Mainstream Medicine

On July 3, 1996, the Burzynski clinic admitted a 4-year-old boy who had undergone a surgical resection of a medulloblastoma, according to the clinic's annual report released to **The Cancer Letter**.

Burzynski's management of the case as well as his stated rationale for medical decisions do not appear to be mainstream, oncologists said. The fact that Burzynski was able to make several treatment choices without running afoul of FDA regulations raises questions about the agency's adherence to the standards of oncology practice, experts said.

In mainstream medicine, early stage medulloblastoma is regarded as a treatable disease.

"Basically, if you treat a kid who has had a resection, and has no metastatic disease, we expect that survival should be at the 70 to 80% level with reduced dose irradiation and chemotherapy," said Larry Kun, president of the American Society of Therapeutic Radiology and Oncology, chairman of radiation oncology, and program leader in neurobiology and brain tumors at St. Jude's Children's Research Hospital.

When the boy was admitted to the protocol, he met the eligibility criteria, Burzynski said.

Indeed, the 1996 version of the protocol states that, "patients who did not receive standard therapy are eligible." FDA requested that the provision be removed the following year, Burzynski said.

The letter of the protocol notwithstanding, the decision to admit a child with a treatable cancer into a phase II preliminary study is problematic, said Norman Wolmark, chairman of the National Surgical Adjuvant Breast & Bowel Project.

"One has to come to grips with what would justify withholding effective standard therapy for a treatment regimen that is undergoing investigation," Wolmark said. "Even if one were to consider clinical trials in such a setting, those trials would have to be rigorously controlled, and the experimental regimen would have to be compared to the standard of care."

Burzynski said antineoplastons offer a reasonable treatment option for medulloblastoma patients. "For such patients, radiation therapy certainly would cause lifelong adverse effects, and certainly mental retardation," Burzynski said. "And, certainly, there was no assurance that this was a curative treatment."

"This statement is entirely false," said Kun. "The current standard for a resected patient is a reduced dose of radiation, in conjunction with chemotherapy, as practiced at every major center in North America now.

"This treatment seems to be associated with rather limited kinds of deficits," Kun said. "The majority of kids will show changes in the order of 10 or less than 20 IQ points. These kids will likely require some assistance with learning, but the early information tells us that they are capable of learning independently at a respectable level and continue to do well."

Burzynski said the boy had some residual tumor. "He had the involvement of the right lateral portion of the fourth ventricle," Burzynski said, reading from a treatment summary. "At that time his tumor measured 2.4 by 1.7 centimeters."

The tumor was evaluated by an in-house radiologist, and Burzynski reviewed the scans himself, he said. "At that time, I was reviewing all of the scans," he said.

Duke oncologist Henry Friedman, who had evaluated the boy prior to initiation of the Burzynski treatment, disagrees with Burzynski's assessment of the patient.

"There was no measurable residual disease at the end of surgery," Friedman said. "There was stuff in the lateral ventricles that was initially interpreted by many institutions, including us, as metastatic tumor, and later was shown to be heterotypia. We had better radiologists look at it over time and realized that this thing was not a tumor."

After eight months on antineoplastons, the child's disease progressed, Burzynski's annual report shows.

"He had progression, because he had some interruption in the treatment program," Burzynski said. "So we said that, perhaps because of the interruption, the tumor was growing. We asked FDA to allow his treatment under a special exception."

Burzynski's letter to FDA dated March 21, 1997, states that the child's tumor had shrunk by 40 percent. However, the scans showed a new nodule of about 1.3 cm. by 0.7 cm.

"There is a good chance that by increasing the dosage of Antineoplaston A10 to the maximum, his new small nodule will also respond to treatment," Burzynski wrote. The letter requested that the child be upgraded to the maximum dosage under the special exception program.

Friedman disagrees with Burzynski's claim that the boy's tumor had shrunk. "This is unequivocally not a kid who would have had measurable disease that one could have said responded to therapy," he said. "It was not a tumor. It was heterotypia.

"All the antineoplastons did was delay the onset of conventional therapy until the kid ultimately progressed," Friedman said.

FDA approved Burzynski's request.

The boy was taken off the treatment eight months later, in October 1997. Burzynski's annual report to FDA notes his reason for withdrawal as "progressive disease."

The child's family remains loyal to Burzynski. "I believe antineoplastons are a potential cure," the boy's mother said to **The Cancer Letter**. "I regret that there wasn't a more concentrated formula available, so he could have a higher dose of the drug without a greater amount of fluid. Without the toxicity of conventional treatment, his body was allowed to recover from the side effects of surgery."

The boy's mother said he has had four resections, the most recent of which was followed by radiation. The boy has responded to treatment, and his intellect has not been impaired, said Thomas White, a pediatrician in St. Petersburg, FL.