SECURING THE HEALTH OF THE AMERICAN PEOPLE

HEARING

BEFORE THE

SUBCOMMITTEE ON
HEALTH AND ENVIRONMENT

OF THE

COMMITTEE ON COMMERCE
HOUSE OF REPRESENTATIVES

ONE HUNDRED SIXTH CONGRESS

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CONTENTS

SECURING THE HEALTH OF THE AMERICAN PEOPLE

WEDNESDAY, SEPTEMBER 13, 2000

HOUSE OF REPRESENTATIVES,
COMMITTEE ON COMMERCE,
SUBCOMMITTEE ON HEALTH AND ENVIRONMENT,
Washington, DC.

The subcommittee met, pursuant to notice, at 10:10 a.m., in room 2123, Rayburn House Office Building, Hon. Michael Bilirakis (chairman) presiding.

Members present: Representatives Bilirakis, Upton, Stearns, Burr, Ganske, Cubin, Bryant, Brown, Waxman, Pallone, Stupak, Green, Barrett and Capps.

Staff present: Marc Wheat, majority counsel; Nandan Kenkeremath, majority counsel; Kristi Gillis, legislative clerk; and John Ford, minority counsel.

Mr. BILIRAKIS. The hearing will come to order. My thanks to all of the witnesses who have taken the time to testify before this subcommittee. This hearing will address, as you know, several pieces of legislation designed to improve the quality of health care.

Today we will hear about H.R. 2399, the National Commission for the New National Goal: The Advancement of Global Health Act. This legislation introduced by my friend, Representative George Gekas of Pennsylvania, would establish a commission to recommend a national strategy to coordinate public and private sector efforts toward the global eradication of disease. The Commission would specifically address how the United States may assist in the global control of infectious diseases through the development of vaccines and the sharing of health research information on the Internet.

Also on the first panel we will hear testimony on H.R. 1795, the National Institute of Biomedical Imaging and Engineering Establishment Act. This legislation introduced by Representatives Richard Burr and Anna Eshoo, members of this panel, would establish a National Institute of Biomedical Imaging and Engineering at the National Institutes of Health.

Finally, our first panel will address legislation introduced my Representative Carrie Meek, H.R. 762, the lupus research and care amendments of 1999, which expands immediate lupus research activities and authorizes the Secretary of Health and Human Services to make grants for the delivery of essential services to individuals with lupus and their families. Congresswoman Meek has been a tireless proponent of this legislation, and I would also be remiss

if I failed to mention the advocacy efforts of Sandy Freer from my area of Florida.

I discussed this legislation at the full committee markup of the minority health disparities bill, and I look forward not only to the testimony today, but to advancing this very important legislation.

Our second panel will include testimony on H.R. 4242, the Orphan Drug Innovation Act. This bill amends the Federal Food, Drug and Cosmetic Act to allow sponsors for a drug for a rare disease or condition, so-called orphan drugs, to ask the Secretary of Health and Human Services to provide written recommendations for the nonclinical and clinical investigations which must be conducted with a drug before it may be approved as a new drug or licensed as a biological product. It also authorizes the Secretary to provide recommendations on whether such a drug is for a disease or condition which is rare in the United States.

I would also like to welcome Mr. Jim Navarro, a concerned parent, to our second panel. He will be discussing H.R. 3677, the Thomas Navarro FDA Patient Rights Act. This bill is named after his son, who was 4 years old when he was diagnosed with a form of cancer known as medulloblastoma. After researching their options, the family decided that the best course of action was through a nontoxic FDA-approved clinical trial. The FDA denied Thomas access to this clinical trial because he had not first undergone and failed treatment by chemotherapy and radiation, which can have, as we all realize, I think, serious side effects for children of that age.

H.R. 3677 precludes the FDA from establishing a clinical hold on the basis that there is a comparable or satisfactory alternative therapy available if a patient is aware of the other therapy and aware of the risk associated with the investigational drug, yet still chooses to receive the treatment.

Finally, in honor of Childhood Cancer Month, we will hear testimony in support of a resolution sponsored by Representative Deborah Pryce on the importance of researching childhood cancer. I think all of us remember that Representative Pryce lost their little daughter a few months ago. The testimony and the resolution focus on the importance of promoting awareness of and expanding research on childhood cancers. The resolution would encourage medical trainees to enter the field of pediatric oncology, encourage the development of drugs and biologicals to treat pediatric cancers, and promote medical curricula to improve pain management. The resolution would also support policies that reduce barriers to participation in clinical trials.

I welcome all of our witnesses, including our colleagues, to this hearing. And to cover as much ground as possible, I would ask members to limit their opening statements. Under the rules, I can limit opening statements other than chairman and ranking member to 3 minutes, and I would appreciate it if you would hold them to within that period of time.

And I would also note that some Members of Congress who are not members of the subcommittee will also give brief introductory remarks regarding their legislation and introduce their witnesses. And I just hope that this hearing will shed light on a number of

important public health issues and that we can devote most of the time to our witnesses.

With that I yield to the ranking member, Mr. Brown.

Mr. BROWN. Thank you, Mr. Chairman. I would like to welcome our witnesses also. Thank you for joining us. We have an ambitious agenda this morning. Among the six bills, we will consider two that would affect access to medications, H.R. 4242 and H.R. 3677.

In the case of both bills, it is likely that today's hearing will not produce definitive answers. The issues involved are simply too complex and the implications of any actions we take too significant. However the questions these bills seek to answer, the concerns they seek to address are important, and it is valuable for the subcommittee to learn about them.

I am also glad we will have an opportunity to review legislation focussing on lupus and childhood cancers. Both types of illnesses devastate and too often take young lives, and neither has received the attention that they both deserve.

But in the interest of time, I want to focus my comments on two of the other bills we will consider this morning, H.R. 2399 and H.R. 1795. I fully support the efforts of my colleague Mr. Gekas to establish the improvement of global health as a national priority, because global health should be a national priority for several reasons.

Global health and the health of Americans are linked. Americans travel abroad, the world travels here. Lethal infectious diseases cross borders. The reemergence of tuberculosis in the United States now in drug-resistant strains that are difficult to treat is a grim reminder that when a disease affects other nations, it is bound to affect us. Tuberculosis last year killed more people than in any year in history; 1,100 Indians die every day from tuberculosis.

A second reason that global health should be a national priority is because the United States is a world leader. We are the wealthiest Nation in the world, we are the most influential force in the world. Our action sets a precedent; our inaction sets a precedent. The United States is in a unique position to save lives, to save families, to save children all over the world.

An investment that is modest by U.S. standards literally can save millions of lives, prevent millions of children from being orphaned, prevent the social, economic and political turmoil these killer diseases too often engender. It is an opportunity and it is a privilege that our Nation should embrace.

The other bill I want to mention briefly is H.R. 1795, which would establish an Institute for Biomedical Imaging and Engineering within the National Institutes of Health. Unfortunately, my colleague Mrs. Eshoo couldn't be here this morning, but I wanted to acknowledge her outstanding leadership and the leadership of Mr. Burr on this measure. I extend a special welcome to Dr. Dunnick from the University of Michigan who is joining us to discuss 1794 at Mrs. Eshoo's request. Adding an institute to NIH is a major step, but Mrs. Eshoo and Mr. Burr make a compelling case for it.

Advancements in medical imaging technology have led to stunning breakthroughs in the early detection and the treatment of many diseases. By identifying these diseases early, and without invasive procedures, patients are often able to receive less painful,

more therapeutic treatments that greatly improve the likelihood that they will live longer and healthier lives. Additionally, when treatment is initiated at the early stage of a disease, doctors are able to rely on less expensive treatment options that reduce overall health care costs.

I am glad we are taking time to access the benefit of establishing an institute dedicated to equipment and techniques that are indispensable to modern health care. I thank the chairman.

Mr. BILIRAKIS. I thank the gentleman.

Mr. Upton.

Mr. UPTON. Thank you, Mr. Chairman. I ask unanimous consent to put my full statement in the record.

Mr. BILIRAKIS. Without objection, the opening statement of all members of the subcommittee will be made a part of the record.

Mr. UPTON. I would just like to say one thing verbally here. I am very glad that we are having these hearings, and I am particularly happy that we are focusing on H.R. 672, the Lupus Research and Care Amendments Act. Sadly, my sister-in-law suffered from this disease and died last year from this illness, so I know how important that it is to commit ourselves to finding a cure for this devastating disease.

I commend my colleague from Florida for offering her bill, and I am delighted to be a cosponsor, and I yield back.

Mr. BILIRAKIS. Mr. Waxman for an opening statement.

Mr. WAXMAN. Thank you, Mr. Chairman.

Let me begin by saying how pleased I am that H.R. 762, the Lupus Research and Care Act, is receiving our attention. It is an excellent bill and deserves our support. Lupus is also one of the dozens of autoimmune diseases which are the subject of my own bill to establish an Office of Autoimmune Diseases at NIH, which has already passed this committee and the House.

But today I am principally concerned about H.R. 4242, the Orphan Drug Innovation Act. As the author with Senator Metzenbaum of the Orphan Drug Act, I care deeply about the issues raised by this legislation.

For many years I have been very gratified by the success of the Orphan Drug Act in stimulating the development of new treatments for rare diseases. I am pleased that we will have Abbey Meyers testify again before our subcommittee on this, and that she is willing to come.

Market exclusivity is the foundation of the Orphan Drug Act. But we created exceptions to that exclusivity in the law. The bill before us would limit the scope of exclusivity granted to drugs proven, "clinically superior," to an existing orphan drug; that is, drugs which are safer, more effective or provide a major contribution to patient care. It has been alleged that the bill is intended to anoint a winner in a commercial dispute, but the bill raises an important and legitimate question: What is the right balance between preserving exclusivity, encouraging competition, and encouraging affordable access to these lifesaving drugs?

As a first step to the best answer, I was looking forward with great interest to the FDA's public clarification of its policy toward clinical superiority. There are questions about its consistency and its relationship to a generic approval process for biotech drugs.

This subcommittee requires some clear answers. They have significant implications for patient health and for access to reasonably priced breakthrough drugs. But this morning I learned that the FDA has withdrawn its witness and testimony. While this may be the result of late notice to the administration, it nevertheless ensures today's hearing will be of less assistance in guiding our deliberations.

I would add that orphan drug policy deserves a hearing on its own. There are 25 million Americans suffering from over 6,000 rare diseases. There is a great deal of unfinished business for Congress. There is the question of how high a bar clinical superiority should be. There are some multimillion-dollar orphan drugs, drugs for which 7 years of exclusivity is unjustified and serves only to boost prices and profits, putting those lifesaving therapies out of the reach of many patients. And just as important, there is the urgent need for more orphan disease research at NIH and FDA.

I sincerely hope that we will have an opportunity early next year to examine these issues in greater detail than will be possible today.

Finally, Mr. Chairman, I would like to submit for the record a series of articles and scientific reviews relating to the alternative cancer treatment offered by Dr. Stanislav Burzynski, the intended beneficiary of H.R. 3677, the Thomas Navarro Patient Rights Act.

Mr. BILIRAKIS. Without objection, that will be the case.

[The information referred to follows:]

CANCER FACTS

National Cancer Institute • National Institutes of Health

National Cancer Institute-Sponsored Clinical Trials of Antineoplastons

Antineoplastons are a group of synthetic compounds that were originally isolated from human blood and urine by Stanislaw Burzynski, M.D., Ph.D., in Houston, Texas.

Dr. Burzynski has used antineoplastons to treat patients with a variety of cancers. In 1991, the National Cancer Institute (NCI) conducted a review to evaluate the clinical responses in a group of patients treated with antineoplastons at the Burzynski Research Institute in Houston.

The medical records of seven brain tumor patients who were thought to have benefited from treatment with antineoplastons were reviewed by NCI. This did not constitute a clinical trial but, rather, was a retrospective review of medical records, called a "best case series." The reviewers of this series found evidence of antitumor activity, and NCI proposed that formal

clinical trials be conducted to further evaluate the response rate and toxicity of antineoplastons in adults with advanced brain tumors.

Investigators at several cancer centers developed protocols for two phase II clinical trials with review and input from NCI and Dr. Burzynski. These NCI-sponsored studies began in 1993 at the Memorial Sloan-Kettering Cancer Center, the Mayo Clinic, and the Warren Grant Magnussen Clinical Center at the National Institutes of Health. Patient enrollment in these studies was slow, and by August 1995 only nine patients had entered the trials. Attempts to reach a consensus on proposed changes to increase accrual could not be reached by Dr. Burzynski, NCI staff, and investigators, and on August 18, 1995, the studies were closed prior to completion. A paper describing this research, "Phase II Study of Antineoplastons A10 (NSC 648539) and AS2-1 (NSC 620261) in Patients With Recurrent Glioma," appears in *Mayo Clinic Proceedings* 1999, 74:137-145. Because of the small number of patients in these trials, no definitive conclusions can be drawn about the effectiveness of treatment with antineoplastons.

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Sources of National Cancer Institute Information

Cancer Information Service
Toll-free: 1-800-4-CANCER (1-800-422-6237)
TTY (for deaf and hard of hearing callers): 1-800-332-8615

NCI Online
Internet
Use http://www.cancer.gov to reach NCI's Web site.

CancerMail Service
To obtain a contents list, send e-mail to cancermail@icicc.nci.nih.gov with the word "help" in the body of the message.

CancerFax® fax on demand service
Dial 301-402-5874 and listen to recorded instructions.

This fact sheet was reviewed on 2/8/99

1: *Mayo Clin Proc* 1999 Feb;74(2):137-45 Related Articles, Books, LinkOut

Phase II study of antineoplastons A10 (NSC 648539) and AS2-1 (NSC 620261) in patients with recurrent glioma.

Buckner JC, Malkin MG, Reed E, Cascino TL, Reid JM, Ames MM, Tong WP, Lim S, Figg WD

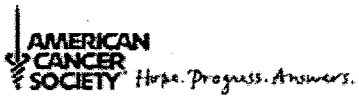
Department of Oncology, Mayo Clinic Rochester, Minnesota 55905, USA.

OBJECTIVE: To assess the pharmacokinetics, toxicity, and efficacy of antineoplastons A10 (NSC 648539) and AS2-1 (NSC 620261). DESIGN: We initiated a phase II trial in order to determine whether evidence of antitumor activity of A10 and AS2-1 could be documented. MATERIAL AND METHODS: Patients with anaplastic astrocytoma or glioblastoma multiforme recurring after radiation therapy were eligible for enrollment in the trial. Patients received escalating doses of A10 and AS2-1 by multiple intermittent intravenous injections with use of a portable programmable pump to the target daily dose of 1.0 g/kg for A10 and of 0.4 g/kg for AS2-1. RESULTS: Nine patients were treated, in six of whom the treatment response was assessable in accordance with protocol stipulations. No patient demonstrated tumor regression. Reversible grade 2 or 3 neurocortical toxicity, consisting of transient somnolence, confusion, and exacerbation of an underlying seizure disorder, was noted in five patients. Mean steady-state plasma concentrations of phenylacetate and phenylacetylglutamine after escalation to the target doses of A10 and AS2-1 were 177+/-101 microg/mL and 302+/-102 microg/mL, respectively. Patients who exhibited confusion tended to have higher phenylacetate levels. CONCLUSION: Although we could not confirm any tumor regression in patients in this study, the small sample size precludes definitive conclusions about treatment efficacy. Antineoplaston-related toxicity was acceptable in most patients with appropriate dose modification, although severe neurocortical toxicity may occur. Steady-state plasma concentrations of phenylacetate with use of A10 and AS2-1 were similar to those reported with use of similar doses of phenylacetate alone.

Publication Types:
- Clinical trial
- Clinical trial, phase ii

Comments:
- Comment in: Mayo Clin Proc 1999 Jun;74(6):641-2

PMID: 10069350, UI: 99166880



ANTINEOPLASTONS

WHAT IS IT?

Antineoplastons are substances that occur naturally in the human body. Dr. Stanislaw Burzynski first discovered and named these substances in the late 1960s. Because antineoplastons were found in the blood and urine of healthy people but not in cancer patients, Burzynski believes that these substances can control the growth of cancer cells.

Burzynski developed a medicine made up of antineoplastons that he claims are effective as a treatment for cancer. Dr. Burzynski reports his greatest success with patients who have certain types of childhood brain cancers and prostate cancer. He also claims to have had good results with non-Hodgkin's lymphoma, pancreatic cancer, breast cancer, lung cancer, and colon cancer.

HOW DOES IT WORK?

According to Burzynski's theory, antineoplastons are a part of what he calls the human body's natural biochemical defense system. He claims that this defense system protects the body from diseases, such as cancer, that involve a breakdown in the chemistry of the body's cells. Antineoplastons work, he claims, by causing cancer cells to grow normally instead of uncontrollably. In 1980, Dr. Burzynski defined the chemicals that make up natural antineoplastons and produced a synthetic version of them.

Dr. Burzynski claims that antineoplastons are not toxic, and that they have few side effects. These side effects include stomach gas, slight rashes, chills, fever, changes in blood pressure, and an unpleasant body odor.

WILL IT HELP?

During the 1980s, NCI studied cases of cancer patients that Dr. Burzynski had treated with antineoplastons. There was no evidence that these patients benefited in any way from the antineoplaston treatment. In 1985, the Canadian Bureau of Prescription Drugs examined records of patients of Canadian doctors treated at Dr. Burzynski's clinic in Houston. It found that of 36 patients, 32 had not benefited from the treatment and had died. Of the remaining four, one died after some slight improvement, one died after stabilizing for a year, and two were still alive, but had widespread cancer.

In 1991, NCI conducted another review of patients treated with antineoplastons, this time involving a series of Dr. Burzynski's best cases. This review showed that seven patients with incurable brain cancer may have benefited from antineoplastons treatment. NCI then proposed

that a formal clinical trial be done to provide a clear and unbiased evaluation of the effectiveness and safety of antineoplastons. The study began in 1993 but closed in 1995 because NCI and Burzynski could not agree on ways to increase the number of patients who could participate in the study.

Dr. Burzynski submitted an application to the US Food and Drug Administration (FDA) requesting that antineoplastons be assigned an investigational new drug (IND) number. Assignment of an "IND" would allow Dr. Burzynski to study the drug. The FDA issued a treatment IND to Dr. Burzynski. Under the IND classification, Dr. Burzynski can use antineoplastons in clinical trials at his clinic to treat patients with several different types of advanced cancers. As patients are treated with antineoplastons in clinical trials and carefully followed, their progress will be reported and solid data about the value of this treatment finally will be available.

RECOMMENDATION

Until there is documented evidence from controlled studies of the drug's efficacy as a cancer treatment, the American Cancer Society urges individuals with cancer to discuss treatment options with their oncologists. Patients who may be considering antineoplaston treatment are urged to do so only in the context of appropriately conducted and independently monitored clinical trials so that the drug safety and effectiveness can be studied.

The Society urges individuals with cancer to remain in the care of qualified doctors who use proven methods of treatment and approved clinical trials of promising new treatments. Patients are encouraged to talk openly with their health care providers about any alternative treatments they are considering, and to consider helpful complementary therapies that can be used effectively along with mainstream (or conventional) treatment.

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REVISED 2/01/99

http://www.cancer.org/alt_therapy/index.html

The Antineoplaston Anomaly: How a Drug Was Used for Decades in Thousands of Patients, With No Safety, Efficacy Data

The Cancer Letter, Vol. 24, No. 36, Sept. 25, 1998.

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 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.

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 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-Vances, 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-Vances 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-Vances 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.

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:

- 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."

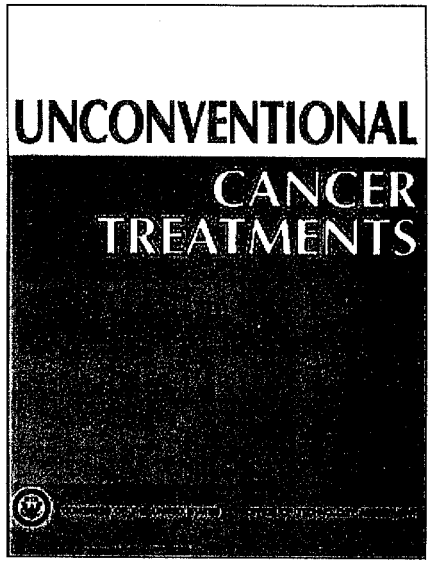
The boy's mother said he has had four resections, the most recent of which was followed by radiation. The boy has responded to treatment, and his intellect has not been impaired, said Thomas White, a pediatrician in St. Petersburg, FL.

Burzynski Response to This Article (to be posted)
Quackwatch Home Page ||| Special Message for Cancer Patients

Unconventional Cancer Treatments

September 1990

OTA-H-405
NTIS order #PB91-104893



Chapter 5

Pharmacologic and Biologic Treatments

A large and diverse group of unconventional cancer treatments has as its central component a pharmacologic or biologic substance, including biochemical agents, vaccines, blood products, and synthetic chemicals. Some of these pharmacologic and biologic treatments are offered at single sites under the direction of a developer or other chief proponent. Others are more widely available, are not necessarily associated with particular proponents, and may be used in combination with a variety of other unconventional and conventional treatments.

Examples of unconventional pharmacologic or biologic cancer treatments associated with a single practitioner include: "Antineoplastons" offered by Stanislaw Burzynski, M.D., Ph.D., at his clinic in Houston; an autogenous vaccine developed by the late Virginia Livingston, M.D., at her clinic in San Diego; "eumetabolic" treatment offered by Hans Nieper, M.D., in Hannover, West Germany; and "biologically guided chemotherapy" practiced by Emanuel Revici, M.D., at his office in New York. Each of these treatments is discussed in detail below. Another pharmacologic treatment, "Immuno-Augmentative Therapy" offered by Lawrence Burton, Ph.D., at his clinics in the Bahamas, West Germany, and Mexico, is discussed in chapter 6.

Examples of pharmacologic approaches offered at a number of places, either singly or in combination, include laetrile, megavitamins, dimethyl sulfoxide (DMSO), cell treatment, digestive enzymes, hydrogen peroxide, ozone, and a variety of other agents. When used in various combinations and with special diets, enemas, and instructions about avoiding substances thought to be harmful, these treatments become part of a general approach often referred to as 'metabolic therapy,' a non-specific term used by many unconventional practitioners to refer to a combination of unconventional approaches aimed at improving the physical and mental condition of cancer patients (96). Many of the best known "metabolic clinics' are located in or near Tijuana, Mexico, not far from the U.S. border, e.g., Centro Medico del Mar, American Biologics, the Manner clinic, St. Judes International, and Hospital Santa Monica. Practitioners associated with these clinics include Ernesto Contreras, Robert Bradford, Jimmy Keller, and Kurt Donsbach. Some of the major components of the 'metabolic' treatments (vitamin C, laetrile, DMSO, cellular treatment, hydrogen peroxide, and ozone) are also discussed in this chapter. The treatments are presented in alphabetical order according to the name of the main practitioner or the substance used.

STANISLAW BURZYNSKI: ANTINEOPLASTONS

In *the late 1960s, Stanislaw R. Burzynski, M.D., proposed that a naturally occurring and continuously functioning biochemical system in the body, distinct from the immune system, could "correct" cancer cells by means of 'special chemicals that reprogram misdirected cells. He called these chemicals 'Antineoplastons, and defined them as naturally occurring peptides[1] and amino acid derivatives that inhibit the growth of malignant cells while leaving normal cells unaffected (124,133). Burzynski developed a treatment regimen for cancer based on the administration of various types of Antineoplastons, which he originally isolated from urine and subsequently synthesized in the laboratory. He currently treats patients with Antineoplastons at his clinic and research facility in Texas.*

Burzynski received his M.D. in 1967 and his Ph.D. in biochemistry the following year, both from the Medical Academy of Lublin in Poland. He moved to the United States in 1970, and obtained a license to practice medicine in Texas in 1973. From 1970 until 1977, he held the positions of research associate and assistant professor at the Baylor College of Medicine in Houston. In 1977, he left Baylor to establish his own research institute. He is now president of the Burzynski Research Institute in Stafford, Texas, where he and his colleagues conduct in vitro and animal research on Antineoplastons. Burzynski's clinical practice focuses on treatment of cancer patients with Antineoplastons, which he administers at his outpatient clinic in Houston. His current regimen for cancer patients includes oral and intravenous use of approximately 10 types of

[1]Peptides are a broad category of molecules, including many biologically active proteins, that are made Up of combinations of amino acids.

Antineoplastons, all of which are manufactured at the Burzynski Research Institute.

From 1974 to 1976, Burzynski received funding from the National Cancer Institute (NCI) for research involving gel filtration techniques to isolate peptides from urine and for testing their ability to inhibit in vitro growth of several types of cultured human cells (142). In 1976, Burzynski applied unsuccessfully for renewal of this grant, although he did receive supplemental finding until July 1977 (245). In 1983, he applied to the Food and Drug Administration (FDA) for an Investigational New Drug exemption (IND), which would allow him to use Antineoplastons in human studies designed to determin e the efficacy and safety of Antineoplastons. That application was put on "clinical hold," the action taken by the FDA in cases where data submitted are insufficient to just@ the investigational use of a substance in cancer patients. In March 1989 the clinical hold was removed for one study, allowing a study of the oral form of Antineoplaston A10 in a small number of women with advanced, refractory, breast cancer (125). That study, which was planned to be conducted at a U.S. medical center, was later "delayed," according to a public notice from Burzynski's staff, "due to the high cost' ' of conducting clinical trials in the United States (858). To date, no form of Antineoplaston has received FDA approval for use on patients outside of that specific study.

Burzynski first isolated Antineoplastons from blood and then the urine of individuals without cancer.[1] He reportedly obtained dozens of fractions (128), each containing many different Antineoplastons (133). Burzynski and other researchers reported testing each fraction for anticancer activity in cultured human cells and then for toxicity in animals. His first fraction, Antineoplaston A, which he used to treat 21 cancer patients at a hospital in Houston (143), was later subdivided into fractions A1, A2, A3, A4, and A5 (132,133). Fraction A2 was reported to contain an "active' ingredient which was named Antineoplaston A10; Burzynski identified the chemical structure of A10 as 3-phenylacetylarnin o-2,6-piperidinedione (131). In addition to using it to treat patients, Burzynski supplies this product to the Sigma Chemical Co., which offers it for sale through its catalogue for research purposes. Two degradation products of Antineoplaston A10, identified as Antineoplastons AS2-1 and AS2-5 (130), have also been administered to cancer patients (see discussion below).

Burzynski believes that a variety of Antineoplastons are present naturally in the tissue and body fluids of healthy people, but that, possibly as a consequence of cachexia (a metabolic process that results in physical wasting), cancer patients excrete excessive amounts in the urine, leaving them with low circulating levels. He states that treatment with Antineoplastons reduces the amount of endogenous Antineoplastons excreted, and that excretion of Antineoplastons decreases with tumor regression (133). Burzynski hypothesizes that Antineoplastons may act by interfering with the action of certain enzyme complexes (methylation complex isozymes) that allow malignant cells to gain a growth advantage over normal cells (546). He has also suggested that Antineoplastons may interact directly with DNA (524).

Burzynski believes that Antineoplastons represent a "completely new class of compounds' (516). It is unclear whether or how Burzynski's Antineoplastons relate to a variety of known growth factors and inhibitors that are the focus of considerable mainstream research in biochemistry and oncology. Burzynski's theory of a biochemical antitumor surveillance system in the body mediated by endogenous Antineoplastons has not been recognized in the broader U.S. scientific community. However, Burzynski has recently supplied some scientists with Antineoplastons which they are testing for biochemical and physiologic properties, particularly antitumor activity, in cultured tumor cells and in animal tumor models (see discussion below).

Burzynski's Treatment Regimen

At present, oral and intravenous forms of 10 types of Antineoplaston are made by the Burzynski Research Institute; most patients reportedly take the oral form (124). Treatment starts with small doses and increases gradually until Burzynski determines that an optimal level has been reached. In some cases, Burzynski also prescribes low-dose chemotherapy (124) and a variety of common prescription drugs (134,136,138). Burzynski claims that following initial treatment with Antineoplastons, some patients produce sufficient quantities of endogenous Antineoplastons and no longer need treatment, while

[1]Burzynski developed the laboratory methodology to make at least one type of Antineoplaston (A10) synthetically.

others continue taking oral doses of Antineoplastons to "guard against future recurrence of cancer" (124).

The patient brochure from the Burzynski Research Institute states that the treatment is "nontoxic" (124), but that a "small percentage of patients had some adverse reaction sometime during the course of treatment." Side-effects cited include "excessive gas in the stomach, slight skin rash, slightly increased blood pressure, chills and fever" (124).

There are no reports of adverse effects from Burzynski's treatment in the published literature. One unpublished report based on a site visit to the Burzynski Research Institute noted two patients who developed sepsis after treatment, one of whom died, although it did not include information confirming the association between the patients' death and Burzynski's treatment. The authors of that report noted that one possible route of infection is through intravenous injections into an indwelling subclavian catheter; infections of the indwelling lines would be likely if aseptic technique is not followed; this is more likely if the patient is not thoroughly instructed in the techniques of aseptic injection (79). Walde, who visited Burzynski's facilities in 1982, also noted this risk of catheter sepsis and air emboli resulting from patients administering their own intravenous doses through indwelling subclavian catheters, but concluded that "the number of complications that [Burzynski and his associates] have been aware of, or have been notified of, have been extremely low" (933).

Claims

While treatment success rates are not specifically cited in the Burzynski Research Institute patient brochure, such rates are widely quoted in the popular literature. An article in Macleans magazine, for example, credits Burzynski with a 46 percent rate of "total remission for cancer of the colon" from the use of one type of Antineoplaston. That article also reports that Burzynski has had the most success with cancers of the bladder, breast, prostate, and bone (291). A recent newspaper article quotes a spokeswoman for the Burzynski clinic as saying that "preliminary studies show that 80 percent of tumor patients respond positively to the treatment" (721).

Burzynski does claim that the 'majority of cancer patients treated at [the Burzynski Research] Institute showed positive response to treatment" (124). His patient brochure states that Antineoplaston treatment makes it "possible to obtain complete remission of certain types of cancer' and that "the number of patients who are free of cancer over five years as the result of Antineoplaston therapy is steadily increasing" (124). In addition to their postulated therapeutic role, Antineoplastons are claimed to be useful in diagnosing cancer. Burzynski believes that measuring the levels of naturally circulating Antineoplastons in blood and urine "may help to identify individuals who are more susceptible to the development of cancer or to diagnose the cancer at the early stages" (129,133).

These claims are based on a number of recent clinical studies in which Burzynski reported favorable clinical outcomes, including complete remissions, partial remissions, and stabilization of disease, in patients with various types of advanced cancer, following injection of Antineoplaston A2 (137), A3 (140), A5 (141), A 10 (138), AS2-1 (136), and AS2-5 (134). Burzynski reported that three of these Antineoplastons (A3, A5, and A10) will be studied in phase II trials.

Burzynski occasionally publicizes his treatment via press releases. In a recent statement, for example, it was announced that "dramatically improved results in the treatment of prostate cancer due to a recent discovery made within the past year' had been obtained through Burzynski's administration of Antineoplastons given orally. It noted that "with this route of administration, some prostate cancer patients, even those whose cancer failed to respond to conventional therapy, have experienced a complete remission of their cancer in as little time as five months" (126). In that press release and another one (127), it was claimed that Burzynski's methods "may also be effective in diagnosing and preventing some types of cancer," citing results from experimental animal studies conducted at the Burzynski Research Institute and at the University of Kurume, Japan.

Published Clinical Studies

Burzynski and his colleagues at the Burzynski Research Institute have a long list of published papers and presentations at meetings in which they report on animal and biochemical studies of Antine-

oplastons, as well as on studies of their use in cancer patients. Most of Burzynski's recent clinical papers (studies of the effects of Antineoplastons on cancer patients, as opposed to laboratory research) appear in supplements to the journal Drugs Under Experimental and Clinical Research, one in 1986 and one in 1987. These supplements were devoted entirely to Antineoplastons and all publication and printing charges for these supplements were borne by Burzynski (840).[7]

Burzynski's list of publications (124) includes a number of "phase I clinical studies," along with several other types of study that also include clinical outcome data, such as "initial clinical studies," and "toxicology studies." Many of these studies are listed as presentations made at conferences outside the United States; these reports are not readily available in the open literature. Many of the published studies appear in the Drugs Under Experimental and Clinical Research supplements, one appears in a journal or a book cited as Advances in Experimental and Clinical Chemotherapy (which is not listed at the National Library of Medicine), and one appears in a book, which presents the same data as a paper in one of the supplements.

Despite the fact that these are reported as early stage studies, which in mainstream research would concentrate on toxicology (i.e., safety more than efficacy), they also report on clinical outcomes, including partial and complete remissions. Burzynski's reputation for success rests at least in part on these reports. OTA's concern with these studies is that, among other problems, Burzynski's definition of a remission, while not stated in any of the papers, appears to be discrepant from the generally accepted definition,[8] making the results difficult if not impossible to understand. Three papers from the 1987 Drugs Under Experimental and Clinical Research supplement are representative ("Initial clinical study with Antineoplaston A2 injections in cancer patients with five years' follow-up" (139), 'Phase I clinical studies of Antineoplaston A3 injections" (140), and "Phase I clinical studies of Antineoplaston A5 injections' (140)). These are discussed below.

These three papers have similar formats and have a similar level of detail, so some general observations can be made about them. First, the reports raise a question about whether these studies were actually planned prospectively, with protocols including patient selection criteria, specific recordkeeping requirements, etc. (a "clinical trial"), or whether they represent groups of patients studied retrospectively. Details concerning a protocol, which would be expected in reporting a clinical trial, are generally lacking. In addition, there is little systematic information about patients' treatment prior to Antineoplastons, except in specific cases, some of which are discussed below. A table with certain information about each individual patient (diagnosis, age, sex, length of Antineoplaston treatment, highest dosage, adverse reactions, desirable side-effects, and anticancer effect) is included in each of these papers.

A particular difficulty with these papers is that some important terms--e.g., "completer regression" and 'partial regression,' terms used to describe the effectiveness of Antineoplastons in these papers—are not used in accordance with their generally-accepted definitions. In the first Burzynski study cited above, six "complete remissions' were reported among 15 patients described as having "advanced neoplastic disease. " Three of these six patients were reported to have non-metastatic transitional cell carcinoma of the bladder, grade II, which would not be described as "advanced" by mainstream definitions. These three patients are described in some detail. Two of them reportedly had no measurable malignant disease when they began Antineoplaston treatment. According to the article:

> Patient D.D., diagnosed with transitional cell carcinoma of the bladder, Grade II, had seven transurethral resections of the tumours and six recurrences in 16 months preceding the treatment with Antineoplaston A2. Her treatment began shortly after the last transurethral resection, therefore she did not have measurable tumour at that time. The patient was incomplete remission and free from recurrences for two years and six weeks as the result of treatment with Antineoplaston A2 intravenous injections. She developed recurrence one year and two months after discontinuation of Antineoplaston A2 injections.

[7] Though most medical journals do not charge authors for publishing papers, it is not uncommon for authors to pay a fee for publication and printing.

[8] In conventional terminology, regressions may occur in patients who initially have "measurable disease," which means that tumors that can either be felt during physical examination or can be seen clearly on some type of diagnostic film or scan, and which can be measured in at least two dimensions. A complete regression is said to occur when the disease measured can no longer be found at all. Partial regression describes the condition where the measurable tumor is reduced by at least 50 percent in size.

> *Patient J.J. . . . underwent transurethral resection of the tumour shortly before the beginning of the treatment with Antineoplaston A2 injections. He was found to have no recurrence after 56 days of treatment and decided to discontinue the therapy at that time. Five months later, he developed recurrence and underwent transurethral resection of the tumour and instillation of Thiotepa. The patient was disease-free for over five years.*

Neither of these patients had measurable malignant disease when treatment began and both had recurrences after treatment. Patient J.J. had curative conventional surgery and chemotherapy as treatment for the recurrence. Burzynski counts both of these patients as complete remissions, and J.J. as a five-year survivor, as a result of Antineoplaston treatment. However, the evidence presented does not substantiate the claimed benefit to either patient from the treatment.

In the second paper, another patientin"complete remission' is described as having "adenocarcinoma of the colon, status post resection,' meaning that the tumor had been removed surgically before the patient started treatment with Antineoplastons:

> *The patient . . . maintained complete remission during the treatment with Antineoplaston A3 . . . After discontinuation of this form of treatment he developed recurrence with liver metastasis, which responded to treatment with different formulations of Antineoplastons and 5-fluorouracil. This patient is alive, well and free from cancer over six years after his participation in Phase I studies with Antineoplaston A3.*

This patient evidently had no measurable disease when Antineoplaston A3 treatment started, but reportedly had a "recurrence," was treated with conventional chemotherapy plus Antineoplastons, and then was reported free of cancer. There is no evidence that this patient was helped by Antineoplastons, and the case does not describe a "complete remission' attributable to that treatment.

Another unusual feature of these studies is the section describing increases in platelet and white blood cell counts as "desirable side-effects." In each case, the post-treatment levels are not just increased, but are abnormally high. In the case of platelet counts, levels are high enough (ranging from about 500,000 to 3.4 million) to lead to possible blood clotting. The authors do not explain why these effects should be considered desirable; physicians would usually consider these levels as indicators of underlying disease or as risks for serious medical complications.

Attempts at Evaluating Antineoplastons

In 1983 and 1985, at the request of the Canadian Bureau of Human Prescription Drugs, NCI tested three of Burzynski's Antineoplastons for antitumor effects in the mouse P388 Leukemia assay, a test that NCI used routinely as a prescreen for antitumor activity until 1985 (2,602) (see ch. 12 for details). No antitumor activity (as measured by a statistical increase in survival) was found for Antineoplastons A2 and A5. Both showed toxicity at the highest dose given, while at lower doses, neither antitumor effect nor toxicity was found. Both Antineoplastons were found inactive over wide dose ranges (602). Antineoplaston A 10 was also tested in a range of concentrations in this mouse system, and the results indicated that there was no increase in survival at any concentration and there was toxicity at the higher dose levels (360).

More recently, Antineoplaston A10 has been studied in several experimental animal tumor systems. Researchers at the Medical College of Georgia reported on results indicating that oral Antineoplaston A10 delayed the development of viral-induced mammary tumors in C3H+ mice and inhibited the growth of carcinogen-induced mammary tumors in Sprague-Dawley rats (393). Eriguchi and colleagues at Kurume University, Japan, presented results suggesting antitumor effects of Antineoplaston A10 on the development of urethane-induced pulmonary adenomas in A/WySnJ mice (275). A second group at Kurume University reported that Antineoplaston A10 reduced the growth of human breast cancer cells in athymic mice (385). Recent experiments using human and mouse tumor cell lines were summarized in an abstract written by researchers at the Uniformed Services University of the Health Sciences, Maryland. It was noted that Antineoplaston AS2-1 promoted cell differentiation in human promyelocytic leukemia HL-60 cells grown in culture and suppressed some of the neoplastic properties of mouse fibrosarcoma V7T cells in culture (775).

A 1981 television news report ("20/20") on Burzynski's cancer treatment, followed by numerous inquiries from patients about the treatment, reportedly prompted David Walde, a physician practicing in Ontario, to visit Burzynski's facilities

in April 1982. In his written report (933), which he sent unsolicited to Health and Welfare Canada and to NCI, Walde described Burzynski's clinical and research facilities and summarized the treatment regimen. He reportedly also reviewed about 60 patient records, but did not report on them in detail. He concluded that there was sufficient information about Burzynski's treatment to warrant evaluating "then nature and action of [Antineoplastons]. . . even if these eventually do not result in any major therapeutic advances" and recommended that Burzynski apply for investigatory new drug clearance in Canada so that Walde could coordinate clinical studies with Canadian health officials. He also suggested that outside funding sources be sought to support clinical studies, and advised against 'sensationalism through the public media,' to avoid disruption to ongoing and future clinical studies.

In November 1982, consultants to the Ontario (Canada) Ministry of Health visited Burzynski's clinical and research facilities in Houston for the purpose of providing information to the Ministry of Health about the treatment because some Ontario residents had sought reimbursement under the Ontario Health Insurance Plan (79). After reviewing Burzynski's published papers and viewing the clinic and laboratories, the consultants, Martin Blackstein and Daniel Bergsagel, asked Burzynski to select examples of patients who he believed had had a good response to Antineoplaston treatment. They specified that each case had to satisfy the following conditions to be considered: 1) proven histologic diagnosis of cancer; 2) complete record of all cancer treatment before Antineoplastons (some of which might be responsible for a delayed response); 3) complete record of additional treatment; and 4) original X-rays, CT, or isotope scans used to document a response.

Burzynski presented them with about 12 cases at the clinic, and sent them additional cases afterward. According to the report, there were original X-rays for only one case; for two others, selected CT scans were available. The case with X-ray evidence was a patient with metastatic nodules in the lung from a colon cancer, which, from his history, appeared to be a slowly progressing disease. The consultants concluded that the X-rays showed no documentable change, though there were difficulties in interpretation because the films were reportedly taken on different machines with different magnifications. They also concluded that the two patients for whom some CT scans were available showed no definite response to Antineoplaston treatment. In those cases, they believed that the views on the scans were not the same, making direct comparison impossible.

In other cases, the consultants reported that Burzynski's patients had had effective treatment for treatable cancers before starting Antineoplaston treatment, and they described two specific examples. The first was a woman who had had radiation treatment for stage III cervical cancer, and had gone to Burzynski when there was still necrotic tumor in the cervix; a cytologist was unsure whether any viable cancer cells remained, but noted extensive radiation changes. The turner gradually disappeared, which the consultants felt could be attributed to the prior radiation, rather than to Antineoplastons. The other patient had prostatic cancer with bone metastases who had had an orchiectomy 3 months before beginning Antineoplastons. His bone scans improved, which the consultants attributed to the delayed effects of the orchiectomy, which commonly takes months for full effects to become evident.

On the basis of the cases they reviewed, Blackstein and Bersagel reported that they found no examples of objective response to Antineoplastons. In addition to reviewing the cases, they asked about four patients reported by Burzynski in 1977 to have had complete remissions with treatment. According to the report, three of those patients had progressed fairly rapidly and died. The fourth patient was still alive at the time of the review (1982), but the consultants felt his disease (a solitary bladder tumor) had been removed during the biopsy. In conclusion, Blackstein and Bersagel's report recommended that the Ontario Health Insurance Plan not cover the cost of Antineoplaston treatment for Ontario residents.

Burzynski wrote a detailed rebuttal (135) to their report, charging that Blackstein and Bersagel "completely distorted the research, production, and clinical data presented to them." He disagreed with each individual assessment, concluding:

> *Out of the initial nine cases presented in the clinic, six patients obtained complete remission and two remaining patients were very close to complete remission. Only one patient was treated with radiation and chemotherapy and one additional patient* received a very small dose of palliative radiotherapy before coming for the treatment with antineoplas-

tons. Two patients died from causes unrelated to cancer like multiple emboli in the lungs and perforation of the stomach ulcer. (135)

Burzynski contested the report's judgments on the quality and content of the clinical data. He cited clinical records (photocopies of which he included) to show that each case was confirmed by biopsy and that "the remission of each of them was confined by at least one other doctor not associated with our clinic. "

In 1985, in a separate and more limited effort to gather information about Burzynski's treatment, the Canadian Bureau of Prescription Drugs reportedly contacted 25 physicians with patients who had visited Burzynski's clinic in Houston for treatment with Antineoplastons. According to a memo summarizing the effort (829), information on clinical outcomes in 36 patients from five provinces reportedly consisted of tumor type and clinical status as reported by telephone from the physicians (actual records were apparently not obtained). Of the 36 patients noted by the physicians, 32 had died with "no benefit" from the treatment, one had died after having a "slight regression for two months," one died after having been stable for a year, followed by progression of disease, and two were alive at the time of the survey. Of the two who were alive, one had metastatic lung cancer and the other had cervical cancer, and both had received radiotherapy prior to Antineoplaston treatment. The memo does not indicate the existence of more detailed data on the clinical course of these patients (including time between treatment and outcome recorded) or the basis for selecting the 25 physicians for the survey. OTA's requests to the Canadian Bureau of Prescription Drugs for further information about this survey have been denied. It is not possible to draw conclusions about efficacy or safety of Antineoplaston treatment from this limited information, since it was a retrospective analysis of self-selected patients and there may have been bias toward reporting poor outcomes.

Despite a substantial number of preliminary clinical studies presented by Burzynski and his associates describing outcomes among the patients he treated with Antineoplastons, and an attempt at a "best case" review, there is still a lack of valid information to judge whether this treatment is likely to be beneficial to cancer patients. Thus far, prospective, controlled clinical studies of Antineoplastons, which could yield valid information on efficacy, have not been conducted.

CELLULAR TREATMENT

Cellular treatment refers to a group of related procedures that may be referred to as "live cell therapy,' "cellular therapy," "cellular suspensions, " "glandular therapy," or "fresh cell therapy." In general, cellular treatment involves injections or ingestion of processed tissue obtained from animal embryos or fetuses. It was developed in Switzerland in the early 1930s by Paul Niehans, M.D., and became widely known when various public figures received the treatment and claimed it restored their youth or extended their lives (26). One of Neihans' colleagues, Wolfram Kuhnau, M.D., introduced the treatment in Tijuana in the late 1970s (238,490). Currently, at least 5 Tijuana clinics offer cellular treatment as a component of "metabolic therapy" (289,968). To OTA's knowledge, cellular treatment is not widely practiced in the United States, although no Federal or State law prohibits physicians from preparing his or her own cellular treatments for patients. FDA has issued an import alert concerning the detention of shipments of foreign cellular treatment products to the United States (887).

Cellular treatment uses a variety of materials, including whole fetal animal cells (derived, e.g., from sheep, cows, and recently also sharks (491)) and cell extracts from juvenile or adult animal tissue. The organs and glands used in cell treatment include brain, pituitary, thyroid, adrenals, thymus, liver, kidney, pancreas, spleen, heart, ovary, testis, and parotid (261). Several different types of cell can be given simultaneously-some practitioners routinely give up to 20 or more at once (489).

A number of different processes are used to prepare cells for use. One form of the treatment involves the injection into the buttocks of fleshly removed fetal animal tissue, which has been processed and suspended in an isotonic salt solution. The preparation of fresh cells then maybe either injected immediately into the patient, or preserved by being lyophilized (freeze-dried) or frozen in liquid nitrogen before being injected. In the latter process, the preserved cells can be tested for pathogens, such as bacteria, viruses, or parasites, before use. Fresh cells, in contrast, are used before such testing can be performed. Other types of cellular treatment may use

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U.S. News 10/5/98

Trials of a cancer doc

Experimental drugs and a 20-year fight with the FDA

BY SHANNON BROWNLEE

To thousands of cancer patients who have failed to benefit from standard medical treatments and who have reached the end of hope, Dr. Stanislaw Burzynski possesses the cure of last resort. Burzynski runs a cancer clinic in Houston, where he has treated at least 3,000 cancer patients with experimental drugs he developed more than 20 years ago. Patients come from as far away as Turkey and Chile for his treatments, and pay up to $14,000 a month, hoping for a cure.

It's a hope that Burzynski himself has fueled assiduously. In appearances on television shows like *48 Hours* he talks of his drugs curing cancer; his Web site claims few side effects. His supporters claim that his drugs can reduce a brain tumor from "the size of a grapefruit to smaller than a pea."

In interviews with the *New York Times* and *U.S. News,* and according to Justice Department papers, the doctor has said his experimental drugs, known as antineoplastons, can help patients with not only a wide array of different cancers, such as prostate, brain, breast and lung, but also a host of other diseases such as multiple sclerosis, arthritis, Parkinson's disease, HIV, and even baldness.

Loyal following. Patients who have taken Burzynski's antineoplastons and gotten better--and there are hundreds of them, he says--compose an intensely loyal following. Pam Murphy, of St. Peters, Mo., believes that antineoplastons have relieved the debilitating symptoms of a rare

connective-tissue disease that afflicted her. The parents of 7-year-old Dustin Kunnari from Aurora, Minn., credit antineoplastons with curing their son's medulloblastoma, a type of brain tumor. Mary Jo Siegel, of Pacific Palisades, Calif., believes that antineoplastons cured her lymphoma in 1993. She is now his most vocal supporter. "Dr. B. is a miracle worker," she says. Without him, she says, "I wouldn't be here today." Some doctors also have been impressed by the apparent results of the treatment. Dieter Schellinger, a neuroradiologist at Georgetown University Medical Center, said he was "surprised" by some responses he saw when he reviewed the MRIs of nearly 40 patients whose brain tumors, Burzynski claims, responded to his drugs. "I don't know of any active agent that produces these results," said Nicholas Patronas, a radiologist at the National Cancer Institute, after reviewing five of Burzynski's brain-tumor cases.

Given such testimonials, the U.S. Food and Drug Administration, the agency that approves drugs for treatment and sale, would like to know if Burzynski is really on to something. But it has yet to see convincing scientific evidence that antineoplastons are either safe or effective. The FDA has spent 20 years and $2 million trying to force Burzynski to put his antineoplastons through standard testing regimens, called clinical trials, which are required to gauge whether drugs work.

These struggles have cost the doctor. The Justice Department prosecuted Burzynski in 1997 on a 75-count indictment for selling and administering antineoplastons without FDA approval. Texas medical authorities threatened to revoke his medical license for illegally marketing his drugs. But Burzynski has fought back with persistence and skill. With supportive patients lining courthouse steps and entreating judges on his behalf, he has beaten federal prosecutors, fended off the state of Texas, and held off the FDA. With new patients walking in the door nearly every day, Burzynski has become the most visible purveyor of an unapproved cancer treatment in the nation, with his clinic grossing, he acknowledges, an amount that "could" approach $9 million last year alone. (He says all revenues are used to run the clinic, and it ran at a loss last year.) Burzynski, says Michael Petty, a former FDA lawyer who now practices in Washington, D.C., "has beaten the system."

But the doctor's long string of successes is now in jeopardy. In August, a Houston judge awarded Provident Life & Accident Insurance Co. $233,044 plus interest in a billing dispute with Burzynski. The judge said Burzynski had "failed to inform Provident of the nature of his treatment, its extraordinary character, or its illegality" and said that it was "unconscionable for him to retain the funds." Burzynski says there was no finding of

fraud and he has filed a notice of appeal.

He has also been hit with his first patient lawsuit: A New York State couple has filed a negligence, fraud, and wrongful-death suit regarding treatment of their 11-year-old daughter, who died in June 1996. "In the opinion of our lawyers, this is a frivolous lawsuit," says Burzynski. Another couple complains clinic doctors misled them about the progress of their 26-year-old daughter, who died on a plane returning from Burzynski's clinic. Burzynski says she died of a stroke and that he had no way of preventing her death.

Whatever the case, Burzynski is enrolling patients in clinical trials per a court order, and has reported interim results to the FDA. This week, however, a respected cancer newsletter plans to publish a review of Burzynski's clinical trials saying that they won't provide meaningful results. The FDA, in a preliminary look at the data, sees no evidence of improvement in eight types of cancer and a response rate in brain cancers that is too small to determine if patients are being helped. The agency also contends that side effects of the therapy contributed to the deaths of seven patients. The doctor challenges the FDA's findings and counters that the agency "doesn't have any evidence that patients died from side effects."

Charismatic. How a Polish-born doctor who came to the United States with $20 in his pocket managed to become so successful is an intriguing tale. Charismatic and self-confident, the stocky, 55-year-old physician posseses a messianic faith in the powers of his drugs. He compares himself to scientific giants like Copernicus and Galileo, whose ideas contradicted accepted axioms of the time. One day, Burzynski boasts, "antineoplastons will be accepted everywhere."

When he arrived in the United States in 1970, Burzynski had a medical degree from Poland's Lublin Medical Academy and an untested idea. From his research, Burzynski believed that bits of *protein found in human urine could fight cancer.* He called these proteins antineoplastons, a word derived from *neoplasm*, Greek for tumor. By 1978, he was extracting them from human urine in a lab set up in a Houston garage and using the drugs in his own cancer clinic. Word of Burzynski's experimental drugs spread quickly; patients soon flocked to his door.

When the FDA got wind of what he was doing, it tried to get him to submit the drugs to clinical trials. In such a regimen, experimenters first give a new drug to animals to test its toxicity. Only after such tests can a drug be given in the clinic to human patients, whose histories are documented closely to determine if the drug's cure rate is as good as or better than existing drugs. "Any doctor can line up

a few successes," says Robert DeLap, who runs an FDA office of drug evaluation. Carefully designed trials are crucial for cancer drugs, because tumors can swell or shrink of their own accord, and cancers can spontaneously go into remission--making it difficult to know if a treatment is actually responsible for a patient's improvement.

In dealing with the FDA, Burzynski took several tacks. Responding to the agency's demands, he sent voluminous letters in reply. He did some pre-clinical animal tests, but they never met the agency's requirements. When the FDA took Burzynski to federal court in an attempt to close down his clinic, a horde of loyal patients pleaded with the judge on their doctor's behalf. The judge allowed the clinic to remain open if Burzynski would test his drugs according to standard FDA procedures. After more wrangling, Burzynski finally was granted permission in 1989 to conduct clinical trials; he sent out press releases announcing that he would begin testing antineoplastons on women with advanced breast cancer. But he never did. "After we got permission, we didn't have the money," Burzynski told *U.S. News*. "It costs millions of dollars to do clinical trials."

While the fight dragged on, Burzynski's business grew, nourished by his flair for publicity. Burzynski distributed fact sheets to patients and owners of his penny stock, attacking the FDA and touting his company's product. An appearance on *Sally Jessy Raphael* in 1988 brought a flood of new customers. Stories about Burzynski soon followed in such publications as *Good Housekeeping*, *The New York Times*, and the *Washington Post*, many of which portrayed him as a victim of an overzealous FDA. Three members of Congress, two critical of the FDA, took up his cause.

Burzynski also benefited from a shift in the regulatory mood. When thousands of frustrated AIDS and cancer patients besieged Congress, the FDA accelerated the process for approving new drugs and allowed patients broader access to experimental medicines. At the same time, the National Institutes of Health began programs for testing alternative drugs. In 1991, the National Cancer Institute sent six scientists, including its own Patronas, to review a "best-case series" of seven of Burzynski's brain cancer patients. In five of those, Patronas said, radiographs indicated that a large tumor had disappeared after treatment by Burzynski. The NCI offered Burzynski the chance to do free trials. He had only to provide the drugs and approve the experiment's design. By the end of the year, however, the collaboration had dissolved in acrimony, and the NCI halted the research.

By 1997, the FDA's struggle with Burzynski reached the federal criminal courts. That year the

Justice Department prosecuted him on behalf of the FDA, charging him with, among other things, mail fraud for illegally shipping his drug across state lines. The trials resulted in acquittal on 35 counts, and the prosecution dropped the other 40.

Still, the FDA got one thing from the court. In 1996, U.S. District Judge Simeon T. Lake III had ordered Burzynski to begin testing his drugs in clinical trials as a condition of his pre-trial release. Burzynski began submitting records for patients already under his care, and he placed new cancer patients in 72 clinical trials.

These trials, if done properly, might finally answer the question of whether antineoplastons really work. Burzynski sent a complete copy of the report he submitted to the FDA to the *Cancer Letter,* a newsletter for doctors, researchers, and patients. Editor Paul Goldberg sent the data to three nationally known oncologists--the first examination of Burzynski's data by independent experts. Among their conclusions: Burzynski's protocols, or trials, are poorly designed, making data impossible to interpret. "They have all the trappings of protocols," Howard Ozer, director of the Allegheny Cancer Center in Philadelphia, told *U.S. News,* "but they cannot be analyzed statistically." They also noted that many patients withdrew from the study, even though Burzynski reported that they were responding to treatment. "Usually, people keep taking medicine that's working," says Peter Eisenberg, a Marin County, Calif., oncologist, "unless the side effects outweigh the benefit."

According to the FDA's analysis of the data, the therapy contributed to the deaths of at least seven people through its most common side effect, hypernatremia--a potentially life-threatening condition associated with high levels of sodium in the therapy. The FDA reported that 65 percent of Burzynski's patients had hypernatremia, a finding seemingly at odds with Burzynski's claim on his Web site that his drugs are "normally free from serious side effects." Burzynski contends the patients died of other causes and when there was hypernatremia, it was "due to the fact that the patient wasn't drinking fluids."

Not all of Burzynski's patients are comfortable with his representations. On July 9, the parents of 11-year-old Christina Bedient, of Lockport, N.Y., filed suit against Burzynski and his clinic, claiming the doctors made misrepresentations to them about the efficacy of antineoplastons, "the effect that the treatment was having on Christina's tumor, and about her prognosis." They say they believed the alleged misrepresentations. They also claim that Burzynski and his clinic were negligent and treated their daughter "in a manner that violated the standards of acceptable medical practice." Christina died June 17, 1996. Burzynski says the

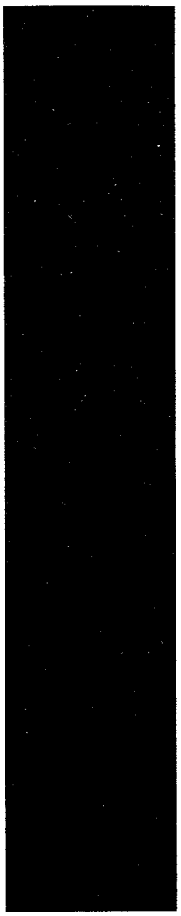
lawsuit is frivolous. "The bottom line is they signed an informed consent form," he says. He says Christina's "big tumor was decreasing" but that another tumor was increasing. "There was no negligence," he says. "There was no treatment for this child. At the same time, we have patients who respond and whose tumors disappear completely, so there was [a] chance."

Another couple has raised similar complaints. In June 1997, 26-year-old Andrea Walsh, a registered nurse from Jordanville, N.Y., was diagnosed with a glioblastoma, the same cancer Christina Bedient had; after surgery, her doctors said chemotherapy and radiation might extend her life a few months, but no more. That August, Andrea's mother, Jean, and her brother Bill took Andrea to Burzynski's clinic, where they say they were told by a clinic doctor that antineoplastons could cure a third of glioblastomas. The Walshes borrowed $16,000 to start treatment.

High fevers. Over the following six weeks, Jean Walsh says, her daughter suffered side effects ranging from disorientation and high fevers to constant thirst. She and her husband, Tom, repeatedly complained to clinic personnel. Each time, she says, "the nurses were jubilant. They said this [side effect] was a sign the tumor was breaking up." On September 22, an MRI scan showed that Andrea's tumor had doubled in size, says her local neurosurgeon, Frank Boehm. He told the parents that Andrea had very little time left. Still, the parents say, a Burzynski clinic doctor insisted that the young woman come to Houston to be examined or she would have to be dropped from the clinical trial. Burzynski says that the clinic has no record of such a conversation. Andrea left on September 28 in the company of Mary Briggs, her best friend.

After they arrived, according to Briggs and the Walshes, another doctor at the Burzynski clinic told the two women the tumor was dissolving. That doctor called Andrea's parents on September 29, telling them the tumor was shrinking and their daughter would be back to work. "I can't tell you how happy we were," says Jean. She and Tom ran up their credit cards to come up with the $7,000 for the next month's treatment.

Andrea never made it home alive. On October 1 her brain swelled massively, just as her flight home was beginning its descent. Henry Friedman, a neuro-oncologist at Duke University, and Victor Levin, a brain-tumor specialist at MD Anderson Cancer Center in Houston, and Boehm, her neurosurgeon, say she should never have traveled any distance from a hospital emergency room. Counters Burzynski: "It's not up to us; that's up to the local physician." Boehm says the Burzynski clinic never called to ask him whether Andrea was



fit to fly.

The patient history in Burzynski's report to the FDA states that Walsh did not die under his care. She is listed as having withdrawn from treatment September 30, two days before she died. But according to the Walshes and Briggs, a nurse, Andrea was still receiving antineoplastons just before she boarded the plane. "If she withdrew, why was she carrying a suitcase full of the medicine?" Tom asks. Burzynski says he listed Walsh as having withdrawn on September 30 because that was the last day she was treated.

The FDA's analysis of Burzynski's records is at odds with Burzynski's interpretations. In a preliminary summary of Burzynski's results released this spring, the agency calculated that the tumors of 36 of Burzynski's 828 patients showed a positive response while on his drugs. The FDA found no apparent effect on breast, prostate, and lung cancer. In brain tumors, the FDA found a 13.5 percent response to antineoplastons--not a 30 percent complete response rate, as Burzynski allegedly told the Walshes and others. (The FDA says that a response rate of 10 percent or less usually means that the drug is not effective.) Burzynski and his lawyer, Richard Jaffe, denounced the FDA for releasing the data and accused the agency of misrepresenting the true figures. In a letter to the *Cancer Letter*, Burzynski complains that the FDA did not count 72 patients who had "stable disease." That, however, is a measure that other researchers say does not necessarily indicate that the cancer has stopped growing. Burzynski told *U.S. News* his latest results are even better: Only 5 percent of brain tumors got bigger, while 60 percent disappeared completely or shrank by more than half.

If true, his data should bear that out. Says Thomas Garvey, a physician and consultant hired by Burzynski to help him present his data to the FDA: "The protocols [Burzynski's] are weird. They are naive, they are flawed, and there are a lot of them. But even a ball of worms can be disentangled. That's what we're trying to do."

Such debate over the meaning of his trials signals that cancer patients will remain in the dark as to whether Burzynski's antineoplastons will be judged more effective than other medicines. Some patient advocates are disappointed by what the oncologists found when they reviewed Burzynski's clinical trials for the *Cancer Letter*. "I am truly aghast because supposedly we have laws and regulations and a legal system in place to stop this from happening," says Fran Visco, president of the National Breast Cancer Coalition. "Resources should be allocated to an appropriate trial run in the right way. While we waste time in these trials, people die."

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Texas cancer therapy useless

Steve Buist
The Spectator

The only independent trial of a controversial cancer therapy being administered to a Stoney Creek girl has shown that the treatment offers no benefit to patients with brain tumours and may, in fact, be harmful.

Dr. Stanislaw Burzynski

The prestigious Mayo Clinic published its findings after it participated in a two-year clinical trial sponsored by the U.S. National Cancer Institute for patients with recurrent glioma, a type of brain tumour.

It's the only independent published examination of the alternative therapy, other than the many ongoing trials being conducted by Dr. Stanislaw Burzynski at his institute in Houston, Texas.

And it raises the agonizing question of whether desperate patients and their families should spend hundreds of thousands of dollars on unconventional treatments that have never passed rigorous scientific study.

Rosemari Brezak, a 12-year-old girl from Stoney Creek, flew to Houston last week to begin antineoplaston treatment for her fast-growing brain tumour, a glioma.

When the Mayo Clinic published its assessment of Burzynski's therapy in February, it was short and sharp.

"The study found no evidence that antineoplastons are beneficial for these patients," the clinic stated. "However, the study did find that they may be potentially harmful.

"Each year, Mayo Clinic cares for hundreds of patients with brain tumours. Mayo Clinic understands and appreciates the problems that these patients and their families face. Mayo Clinic wants to find new treatments that provide real hope, based on solid research, in their fight against cancer."

Lisa Copeland, Mayo Clinic's media relations officer, said that the clinic would not make any further comment on antineoplastons other than the terse, three-paragraph statement issued Feb. 8, 1999, in part because of the sensitivity surrounding Burzynski's unproven treatment.

In the 1970s and '80s, Burzynski began treating cancer patients after developing a synthetic form of antineoplaston -- derived from proteins found in horse urine. The Polish-born doctor has a PhD in biochemistry.

While on staff at Baylor University, in Waco, Texas, in 1967, Burzynski developed his theory that our body can redirect cancer cells back onto their normal path through antineoplastons, chemical substances found in the blood that seem to act as "biochemical microswitches" -- turning off the genes that start cancer and turning on the genes that suppress tumours.

It sounds good in theory. The problem is that there's no concrete proof -- outside of Burzynski's claims -- that it works.

Of the patients who could be properly assessed in the Mayo Clinic trial, almost all suffered some brain-related side-effects, including drowsiness, confusion and an increase in seizures in those patients prone to have them.

Although the results showed no benefits in any of the patients, the study published by the Mayo Clinic also noted that the small size of the trial made it difficult to reach a definitive conclusion about the treatment's effectiveness.

Not surprisingly, Burzynski maintains that the Mayo Clinic conducted the antineoplaston trial improperly.

"The reason why they got such poor results is because they gave a dosage of antineoplastons which was 50 times lower than they should have," Burzynski said. "If you go to a doctor and you have the disease and the doctor gives you a dosage that is 50 times lower, what would they do to such a doctor in Canada? Would he practise medicine any more? I doubt it.

"They know that they were using low dosages. We informed them about it and still they continued to do it.

"Finally," Burzynski added, "when we threatened them and told them that we would inform the American public and I engaged the lawyers, they stopped."

But Dr. Howard Ozer, director of the Medical College of Pennsylvania-Hahnemann Cancer Center in Philadelphia, says the Mayo Clinic used an appropriate dose for the antineoplaston trial.

Ozer is one of three cancer specialists who have conducted an independent assessment of Burzynski's protocols and some of the data that he has been required to file with the U.S. Food and Drug Administration.

Protocols are the scientific recipes that spell out how a clinical trial will be conducted.

In fact, Ozer says that patients could have suffered even more harmful side-effects had the Mayo Clinic used the dosage Burzynski now advocates.

"I think it probably would have made the results that much more horrible and I don't think the Mayo Clinic chose a dose that was too low," Ozer said.

"Part of Burzynski's style has been to constantly change the protocols."

For the type of brain tumour Brezak is suffering from, Burzynski states that his clinical trial shows the two-year survival rate for patients is 40 per cent, compared to 7 per cent for patients who receive the best-available standard treatment.

U.S. agency battled cancer doctor

Joanna Frketich
The Spectator

Dr. Stanislaw Burzynski has broken every rule of American research.

His controversial Houston clinic and unproven cancer treatment has been the target of federal authorities for almost 20 years.

The United States Food and Drug Administration (FDA) has fought vigorously to shut him down for refusing to abide by the standards every other researcher in the country has to follow.

Controversial cancer doctor Stanislaw Burzynski, during his 1997 trial for violating U.S. Food and Drug Administration regulations.

He has been dragged into court at least three times and faced 75 criminal charges over his experimental cancer drugs known as antineoplastons.

But to the astonishment of the FDA, he has walked away from each case and beat every charge.

"We don't have convincing evidence that this product is safe or effective," said Susan Cruzan, spokeswoman for the FDA. "But he won the case and is still allowed to practise."

The long-standing battle between the FDA and the charismatic doctor from Poland has pitted the strict rules of science against the desperate hope for miracle recoveries. At issue is patients' rights to choose their own treatment versus the FDA's responsibility to protect the public and the integrity of medical research.

As far back as the 1970s, the FDA tried to convince Burzynski to submit his remedy to the rigorous testing required in the United States for drug approval.

Under the rules, he should have started with laboratory tests and then moved on to animals to make sure the antineoplastons were safe. Only then, would he be able to apply to the FDA for testing on small groups of patients limited to 20 to 100 people. Next would be clinical trials on several thousand patients. Those trials

would require a placebo, meaning some patients would be given the real drugs and some would unknowingly be given fake drugs to measure the differences in outcomes.

But Burzynski snubbed the FDA's stringent rules and refused to conduct proper trials. Instead he treated cancer patients with his unapproved drug.

By 1983, the FDA was frustrated with Burzynski and gave up trying to work with him. The agency launched a civil suit to shut down his clinic. In what became common at all of his court appearances, hordes of loyal followers showed up at the trial and pleaded with the judge to let the doctor continue giving out his miracle cure.

The FDA was dealt a stunning defeat when the judge ruled Burzynski could keep treating patients. However, he was only allowed to give out his drugs in Texas. The judge forbade him from shipping antineoplastons across state lines because the treatment had not gone through the FDA's approval process.

Burzynski went back to business treating a flood of patients travelling to his clinic from all over the United States and Canada. Meanwhile the FDA and federal prosecutors spent more than a decade building up their next case against him.

It came in November 1995 when Burzynski and his research institute were charged with 75 criminal offences including contempt of court, introducing an unapproved drug into interstate commerce and mail fraud.

Prosecutors accused Burzynski and his staff of breaking the 1983 court order by shipping the drugs to patients in other states. In addition, the doctor was accused of of sending false and misleading billing statements to insurance companies to get them to pay for his patients' experimental therapy.

In February 1996, a U.S. District Court Judge demanded Burzynski set up FDA-approved drug trials as part of the conditions for his pretrial release. This ruling backed the FDA into an uncomfortable corner. Federal prosecutors told the agency it would severely hurt their case against Burzynski if the FDA approved testing for the experimental drug.

At the same time, the FDA was feeling public pressure to allow the trials. Members of congress were taking Burzynski's side and media were broadcasting across the country devoted cancer patients chanting: "FDA, go away. Let me live another day."

In the end, the FDA allowed Burzynski to set up 72 clinical trials for his drugs -- an unheard of amount for one researcher. The approval meant Burzynski could start sending his drugs across the country, but also required him to report yearly to the FDA.

When Burzynski's criminal trial started two years ago this month, he brought him with one of the best defence lawyers in the United States. While the prosecution tried to paint Burzynski as a greedy snake-oil salesman, lawyer Michael Ramsey

paraded a stream of grateful patients in front of the jury. Each told stories of miracle recoveries such as brain tumours shrinking from the size of a golf ball to a mere grain of rice.

The trial ended in March 1997 with a hung jury in a 6-6 deadlock. The judge ordered a direct acquittal on 34 counts of mail fraud and a mistrial on the other 41 charges.

The prosecution decided to drop the 41 charges except for one count of contempt of court. The case was heard in May 1997 and ended in a jury acquittal for Burzynski.

Specialists reject Burzynski's testing methods

Steve Buist
Science Reporter

This is a sad story. In all likelihood, it will have a sad ending, despite the best intentions of those involved, despite the incredible unfairness of the situation, and despite the progress that modern medicine has made.

Rosemari Brezak is a very sick young girl from Stoney Creek who must battle a tumour inside her brain. It's a fight with long odds.

At the tender age of 12, when she should be worrying about boys and pimples and French homework, she is being forced to understand her own mortality, an eventuality that many people can spend long lifetimes contemplating and never come to accept.

In late October, Brezak and her parents learned she had a tumour in the left side of her brain.

Three weeks later, the tumour had doubled in size, and doctors at Toronto's Hospital for Sick Children told the family there was no guarantee that aggressive radiation therapy would work. The treatment might also cause severe side effects that could leave Rosemari developmentally delayed and with permanent hair loss.

To choose that path meant the Brezaks might bring horrible suffering to their daughter with no guarantee of her survival. Even if conventional treatment succeeded, the little girl they knew and loved might be replaced by a stranger.

To do nothing, barring a miracle, meant certain death.

The Brezaks chose a third path. They opted to take Rosemari to the Burzynski Research Institute in Houston, where Dr. Stanislaw Burzynski has treated thousands of cancer patients with a controversial, unconventional, unproven therapy using chemical substances that he calls antineoplastons.

Cancer cells are sometimes described as neoplastic, so Burzynski, a medical doctor with a PhD in biochemistry, christened his chemical warriors

"antineoplastons."

While at Baylor University in 1967, Burzynski came up with his theory that our body can redirect cancer cells back onto their normal path through antineoplastons, chemical substances found in the blood that he says act as "biochemical microswitches" -- turning off the genes that start cancer and turning on the genes that suppress tumours.

In the 1970s and '80s, Burzynski began treating cancer patients with a synthetic form of antineoplaston -- derived from proteins found in horse urine.

Burzynski is currently running 74 different clinical trials using antineoplastons, all with the approval of the U.S. Food and Drug Administration. The FDA is allowing Burzynski to administer the substances for investigational uses only.

The objective of clinical trials is to measure a new treatment in a group of patients and compare its effectiveness against a control group of patients receiving established treatments.

When asked to cite results from his clinical trials, Burzynski rhymes off some impressive statistics.

One recently concluded trial of 36 patients with brain tumours showed a complete or partial regression in 45 per cent of the patients and no progression of the disease in another 27 per cent, according to Burzynski.

Brezak is now enrolled in one of the clinical trials, and Burzynski says that 36 per cent of the patients in that trial have shown a complete or partial response and another quarter of the patients have shown no progression of the disease.

When it comes to survival rates, Burzynski is even more optimistic.

For the type of glioma that Brezak suffers from, Burzynski claims 40 per cent of his patients survive two years, compared to just 7 per cent who receive the best available conventional treatments.

But there is no independent, peer-reviewed evidence to support the Houston doctor's claims.

Only one independent trial has ever been conducted using Burzynski's treatment by a nationally recognized institution. Last February, the prestigious Mayo Clinic in Rochester, Minn., published the results of a two-year clinical trial sponsored by the U.S. National Cancer Institute for patients with glioma, a type of brain tumour.

The clinic's assessment of the antineoplaston treatment was brief, unequivocal and unflattering.

"The study found no evidence that antineoplastons are beneficial for these patients," according to the clinic's statement. "However, the study did find that

they may be potentially harmful."

It's one of the few objective lights that has ever been shined on Burzynski's treatment, not counting the Polish-born doctor's own unsubstantiated claims and the testimonials of his followers.

But it's not the only attempt to separate fact from fiction in the antineoplaston saga.

In 1997, a well-respected cancer publication called The Cancer Letter asked three U.S. specialists, independent of each other, to review Burzynski's protocols as well as some of the data he was required to file with the FDA. Protocols are the scientific recipes that spell out how a clinical trial will be conducted.

The conclusions reached by the three cancer specialists were nearly unanimous, and offered a very harsh assessment of Burzynski's methods and his claims of success.

They found:

* The protocols are poorly designed and Burzynski's data cannot be interpreted.

* The harmful effects of the antineoplaston treatment are significant and life-threatening.

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

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

One of the three cancer specialists was especially blunt in his review.

"What we have here are bad trials that could never get past peer review of any clinical trials co-operative group," Dr. Howard Ozer wrote. "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," Ozer continued. "They look like protocols. They smell like protocols. But they lack the rigour of protocol design that defines the patient population, defines the endpoints, sets exclusion and inclusion criteria and allows for statistical analysis."

Ozer is the director of the Medical College of Pennsylvania-Hahnemann University Cancer Center in Philadelphia.

About a decade ago, according to Ozer, the FDA was being pressured by the U.S. Congress and vocal American citizens to look at Burzynski's treatment.

"They said, 'Let this guy test his hypothesis,' and I don't think anyone would argue with that," Ozer said.

In turn, the FDA began pressuring Burzynski to study antineoplastons in a legitimate manner. The FDA also asked the National Cancer Institute to get involved, and the NCI agreed.

In 1991, Burzynski was asked to supply the medical records of seven of his best cases to the NCI for review as a first step -- patients who were thought to have shown the greatest benefit from antineoplaston treatment.

Based on that review, the NCI decided to work with Burzynski to develop two formal clinical trials of antineoplastons for adults suffering from advanced brain tumours.

The participating centres began recruiting patients in 1993 but after two years, only nine patients had entered the trials.

At that point, Burzynski and the NCI began squabbling and eventually parted ways. The two sides could not agree on a way to increase enrolment, so in August 1995, the NCI shut down its trials.

The results from the two years' worth of trials eventually became the report published last February by the Mayo Clinic.

Burzynski, however, made an end run around the National Cancer Institute and opened up his own clinical trials with the blessing of the FDA.

Ironically, those trials, thanks to the FDA's stamp of approval, have provided Burzynski's treatment with one of its few shreds of legitimacy.

It's the mechanism that allows him to continue administering the therapy, even though there is no scientific evidence in any respected publication to prove the effectiveness of antineoplastons.

According to Ozer, Burzynski simply uses his clinical trials as a revolving door to treat any and all comers.

"That's how I read it," Ozer said. "What had blocked him temporarily a decade ago was that he wasn't doing these clinical trials. Now he says everybody is part of a clinical trial.

"He doesn't screen any patients. There is nobody who shows up who doesn't get treated. Basically, he takes anybody with the ability to pay and he doesn't report the results."

Ozer was then asked whether there's any reasonable expectation that Burzynski's trials will someday come to an end and the results held up to scrutiny.

"Not in my mind," Ozer said simply. "I think he's just going to milk this as long as he can."

Burzynski quickly dismisses the criticism of Ozer and his two colleagues, saying they did not review the results of his trials.

"They reviewed the protocols and some of them didn't like the protocols," Burzynski said. "I can't blame them. You can read a book and you may like the style and others may not like the style.

"Our protocols have been prepared by Memorial Sloan-Kettering Cancer Center, which is reputed to be the best cancer institute in the country. If some people don't like protocols prepared by Sloan-Kettering, well ...

"If you don't like the style of the protocol but 40 per cent of the patients instead of 7 per cent are alive, then to hell with the style," Burzynski added. "I think it's important that these people are alive."

But Memorial Sloan-Kettering didn't prepare the protocols, Ozer points out.

"One guy gave him a fairly simplistic phase II trial design," Ozer said. "They didn't actually write the protocol for him nor did they become co-investigators.

"From that time on, Burzynski has said 'I have an NCI-designed trial, a Sloan-Kettering designed trial.'

"That's not true," Ozer said. "What he got was a consultant who gave him a few pointers. He didn't get a Sloan-Kettering designed trial, he got some advice."

Burzynski also dismisses the findings of the Mayo Clinic, saying that the dosage of antineoplastons being administered was 50 times lower than it should have been.

"If you go to a doctor and you have the disease and the doctor gives you a dosage that is 50 times lower, what would they do to such a doctor in Canada?" Burzynski asked rhetorically. "Would he practise medicine any more? I doubt it."

There are a number of striking parallels between the controversy surrounding Burzynski and the similar hysteria that erupted two years ago over Professor Luigi Di Bella and his anti-cancer cocktail.

Both treatments avoided objective scrutiny for many years and both were boosted by the near-fanatical devotion of believers, who relied on anecdotal claims as scientific proof.

And when antineoplastons and the Di Bella treatment eventually failed to pass the rigours of independent clinical examination, both Burzynski and Di Bella attacked the scientific community for not properly administering the unconventional therapies.

Burzynski, however, is confident his treatment and his methods will one day be vindicated.

"Certainly, there's not even a shred a doubt in my mind about it," Burzynski said. "Justice will finally come."

Man alive 20 years after Houston 'cure'

Carolynne Wheeler
The Spectator

It's been 20 years since Al Swaisland left a sunny Texas cancer clinic with his bladder cancer in remission.

Hamilton cancer survivor Al Swaisland won't support or condemn Houston doctor Stanislaw Burzynski.

It was a measure of victory for the then 40-year-old man.

He had endured surgery to remove tumours from his bladder, but he had defied doctors when they wanted to remove his bladder completely and to follow that with a gruelling regime of chemotherapy.

Once back home in Hamilton, he continued six years of follow-up maintenance treatment, as he continued injecting himself with the prescribed cocktail. He returned to the clinic three or four times for check-ups.

And then the bubble burst.

"You have to believe him when you're there. And when I went there, I believed. I believed for many years.

"But it (the bladder cancer) came back," he said.

Swaisland returned to regular treatment, this time accepting chemotherapy and radiation. And he's been in remission for 14 years, much to his oncologist's surprise.

Today, Swaisland will neither promote nor condemn Dr. Stanislaw Burzynski's clinic in Houston, the same clinic now used by Hamilton residents Georgina and Steve Brezak, whose 12-year-old daughter Rosemari has an inoperable brain tumour.

In Rosemari's case, aggressive radiation is not guaranteed to work, and could leave her developmentally delayed with permanent hair loss. She might never go through puberty.

"I don't want to be judge and jury for anybody else," Swaisland said. "I think they're doing what they think they should do, whether it costs $30,000 or $30. They have to do it for their child. Whether Burzynski is the man or not, I couldn't say."

Neither Swaisland nor the Brezaks are alone. The Canadian Cancer Society estimates more than 50 per cent of cancer patients have looked at some sort of alternative therapy to either supplement their conventional treatment or replace it completely. The society has put out an information sheet to help patients analyse the flood of options that fall outside the conventional medical system.

Such therapy can include everything from psychotherapy and large doses of vitamins to more extreme cocktails made of shark cartilage or -- in Burzynski's case -- synthetic antineoplaston, a protein derived from horse urine which is supposed to "turn off" rapidly multiplying cancer cells by mimicking a substance found naturally in the body.

The problem is, few, if any, of these treatments have proof derived from clinical trials to show their effectiveness. Most are promoted by testimonials from previous patients, which isn't enough to convince the medical community of their benefit.

"Any time you hear someone saying 'move away from conventional practice, move away from radiation, move away from chemotherapy,' that is cause for concern for the medical community," said Margaret Fitch, the provincial co-ordinator of supportive care for Cancer Care Ontario.

Fitch says more and more people are asking questions about such treatments, whether out of curiosity or to regain control over their care in a system that seems cold and brisk. And she says patients should keep in mind what it is they're looking for -- to be cured, or to make their last months more comfortable.

"The whole field is quite intriguing and some of the anecdotal evidence is captivating," Fitch said.

"(But) I have to take a back seat and say at this point no, I don't see the evidence."

Brenda and John Taylor of Stoney Creek, who took their son Derek to Houston five years ago for treatment, made their decision after radiation failed to eradicate his fast-growing brain tumour.

"I can tell you it was well worth going," said Brenda of her son, who was just seven when he died the year after his 1993 diagnosis. "The treatment did nothing for him because he didn't get a proper dose.

"If we were to do this all over again, with our son in our arms, that's what we would do, go there right away. No radiation, no chemo, nothing."

His catheter, which was supposed to be used to deliver Burzynski's prescription 24 hours a day, was also the only way to deliver food and medication to treat pneumonia and other illnesses in Derek's body. They never did manage to get a continuous flow of the prescription into him for the required six weeks.

"The problem is that people go down there on their last legs and so it gives him a bad rap," Taylor said. "I'd like to see more people go."

Swaisland, looking back, says he understands how a family feels. He says Burzynski didn't seem to be in it for the money; he forgave Swaisland a few thousand dollars over the course of his treatment that then cost $200 a week.

But he also knows that of all the people he met while in treatment there 20 years ago, none is alive today. He wishes Burzynski would produce some concrete evidence from his ongoing clinical trials.

And he can't say he'd entrust his own children to the clinic in the event they took ill.

"It's a tough call," he says slowly. "If it was the same place as that young girl (Rosemari Brezak), probably. But if it was a different type of cancer, probably not."

A battle with cancer changes the whole family

Suzanne Morrison
The Spectator

"Courage is not freedom from fear, it's being afraid and going on."

-- Quote in a letter to Gwen George from McMaster University's school

of nursing during her cancer

treatment in the United States.

Life for Jane George changed forever after she walked side-by-side with her mother as she was dying of cancer.

The former director of public relations in McMaster University's faculty of health sciences says that because of this experience, she will "never again take things for granted" as she did before her mother, Gwen, got sick.

Jane George looks over her diary in the room at the Henderson Hospital named for her late mother, Gwen George, whose photo is on the wall behind her. She kept the diary during her mother's illness.

The journey was so life-altering that Jane turned to a new career as executive director of Wellwood Resource Centre so others suffering through cancer would not endure the pain her family did. Wellwood, located at Henderson Hospital, offers information, counselling, support -- and hope -- to cancer patients and their families.

"My mother always said we were so lucky because it wasn't me or my children -- and she had had a really good time. I also remember how difficult it was for her that there weren't resources available that she felt would ease her emotional challenges in dealing with her disease."

Gwen, a registered nurse, was best known by staff and students at McMaster University as the wife of president Peter George, but everyone throughout Hamilton knew her for her consulting business and as a founding partner in both the Centre for Integrative Change and Wellwood.

She was diagnosed with primary peritoneal cancer -- cancer of the lining of the stomach -- in February 1995, just three months after Peter, whose longtime passion was McMaster, had been appointed its president. She died two years later on March 18, 1997.

Jane and her brother Michael and his wife had six children between them. "It was such a time of hope and optimism and fun because of the children. But it was such a devastating time because Mom knew she would never be able to enjoy any of them. It was really sad."

Gwen underwent conventional chemotherapy. "I can remember being up at the Henderson nine months pregnant, with my mom's head on my lap, while she was throwing up. She weighed two-thirds of what she had and had her little bald head."

The cancer briefly went into remission but when it ended, no more treatment options were left in Canada. The family started looking at two centres in the United States, one in Chicago and the other in Denver.

Gwen always believed that treatment decisions should be based on good data. When going to the United States was raised as an option, the family started collecting all the information they could on centres in Chicago and Denver. They also turned to the Internet.

One weekend, the Georges gathered at their cottage to make a decision about what to do next, eventually concluding they didn't have enough information and should collect more.

Jane and Gwen flew to Chicago and turned down that option, partly because the hospital was located in a tough part of town and Gwen worried about Jane walking home alone at night. And they hadn't connected with the caregivers. "We needed to feel safe in their hands."

At the University of Colorado in Denver, the hospital felt right for Gwen's treatment and the family rented a small apartment there.

Gwen underwent a treatment involving an "autologous" bone marrow transplant that is covered by OHIP, recommended by doctors, academically validated, and considered the next wave of traditional treatment. However, it wasn't yet available in Canada. The concept was to put Gwen into a coma for a week and give her high -- almost lethal -- doses of chemotherapy. Some of her bone marrow was taken out before the treatment started and returned to her afterwards.

It wasn't as unorthodox as the "antineoplaston" treatment from horse urine 12-year-old Rosemari Brezak is receiving in Houston, Texas for a brain tumour at

a clinic run by Dr. Stanislaw Burzynski.

'I can't imagine how difficult it is for people who have had no experience with the health care system.'

Jane George

Jane George understands the pain Steve and Georgina Brezak are going through in seeking out an alternative treatment in the United States for their daughter.

"People make decisions that they need to make and they should be supported through whatever road they choose to follow," she said. "People who love someone don't want to lose them and they will do whatever it takes to keep them. The real tragedy is when the family decides (on treatment) but the patient doesn't want it."

Her own family has wondered since if they made the right decision, even though the treatment was based on scientific evidence.

"We felt that maybe she would have lived longer if she hadn't had that treatment. But we also agreed as a family right from the beginning, and she agreed too, that we had to try because it was the only thing that was left."

Jane moved to Denver to become her mother's primary caregiver, along with her father. At the time, her son, Matthew, was three months old, her daughter, Kristen, 3.

Her father had just assumed his new role as university president and flew in on weekends, or for a week. Michael came down a couple of times, as did an aunt.

Jane kept a diary of the family's experiences in Denver which is filled with touching photographs and words: Her mother laughing, dancing and joking with the medical teams; poignant private moments of Peter reading The Healing Garden to Gwen while she was comatose; Jane and her mother watching sunsets together on the roof of the hospital's parking garage.

"There were all kinds of times that we were like Thelma and Louise driving her wheelchair around like maniacs," Jane said. "There were lots of times of joy even though there was great sadness."

What she remembers most is the tremendous sense of isolation that both she and her mother felt -- for different reasons.

"It was the hardest thing personally that I have ever done to watch my mother go through that. I missed my children desperately and I missed the support of my husband (Hamilton gastroenterologist Dr. Bruno Salena) and felt so isolated."

Jane knew they were fine. She sent letters every day, phoned a lot, left tape-recorded bedtime stories in which she talked about being with their granny and taking good care of her, and had family friends look after them.

"When my brother and dad were there, I felt a lot more confident and a lot less alone. My mom was a great support to me, until she couldn't be because of the nature of the treatment, and that was the loneliest time of all."

Jane knows her mother felt isolated and it's an issue Wellwood is addressing.

"She couldn't find a support group that would accept her because she didn't have the right kind of cancer. Even though she had loving, supportive family and friends, she really felt a connection with people who had had a life-threatening illness. She needed to share that with people who understood and who had been there."

Wellwood is gradually bridging this chasm for cancer patients. It offers a range of services free of charge -- yoga, tai chi, help in finding health care resources and a peer support network which matches cancer patients with trained volunteers who have been in the same situation. Work is beginning on a website that will give cancer patients evidence-based information. In two or three years, the centre will have a home -- a kind of haven -- in the community where cancer patients can begin to heal emotionally.

Jane says her family was overwhelmed by their experience and she appreciates how difficult it is for others.

"My husband is a physician, my father sits on the board of a hospital, is president of a university with a faculty of health sciences, and I'm a former director of public relations for the faculty. We were completely overwhelmed. I can't imagine how difficult it is for people who have had no experience with the health care system who try to navigate and understand what resources are there for them and their families."

In the broad scheme of things, the tragedy the Georges lived through is being experienced by nearly 200,000 other Canadians and their families. In 1999, there were an estimated 129,300 new cases of cancer and 63,400 deaths from cancer in Canada.

Last September, Jane's close friend Pat Adams -- a Canadian pioneer in media and public-speaking training who founded the Canadian Association of Women Executives -- died in Hamilton of leukemia.

As she was dying, Jane supported her daughters, one of whom had just given birth, and her husband, explaining death was a lot like birth -- just as awesome and just as intense.

After Jane gave the eulogy at Adams' funeral, one daughter told Jane death is like birth -- and that she is the midwife. "I only wanted to help and to never ever intrude. But I knew that I had learned something that should be shared."

A diagnosis of cancer shatters a lot of lives, not just one, she said.

Many patients are turning to alternative and complementary therapies when conventional medicine no longer offers them any hope as they try to deal with the tragedy of cancer and other life-threatening diseases.

However, there is a move afoot to get valid information to consumers on many of these treatments.

Dr. Alex Jadad, director of McMaster University's health information research unit, is assessing websites to determine which ones offer patients valid health information.

McMaster also has a proposal before Health Minister Allan Rock for a $100 million centre for complementary medicine. If it is approved, the centre will be one-of-a-kind for a Western university faculty of medicine, amalgamating research into Western and Eastern treatments, while investigating the roles lifestyle, diet and stress play in keeping Canadians healthy. It will also have an educational component so consumers can best learn how to take care of their own health.

On Jan. 19, the Institute of Integrated Medicine, a private facility located in the research park at the University of Western Ontario, is linking up with the Mind-Body Health Clinic in Ancaster. The goal is to help patients, their doctors, and complementary health-care practitioners work together to integrate conventional and complementary medicines.

Go to 2000 Special Reports Index
Go to Special Reports Index

Quick Links:

Mr. WAXMAN. As ranking member of the Committee on Government Reform, I have attended that committee's many hearings to defend and endorse alternative medicine and dietary supplements. But I am pleased that this subcommittee, which has jurisdiction over these issues, has finally turned its attention to them.

Developing new forms of cancer prevention, detection, and treatment never ends. Ensuring patients have access and accurate information about their treatments is also vital. So we must keep an open mind about innovative or unconventional approaches to cancer treatment and prevention.

But our first priority must be ensuring access to treatments which are proven to be the best chances of curing patients. And second, our priority must be rigorous testing of new therapies, including complementary and alternative therapies, to determine their safety and efficacy.

The problem with H.R. 3677 is that it undercuts these goals. If research is under a clinical hold, you can be sure that there are unresolved questions about the conduct of that research. But this bill would shield such research from scrutiny, discourage practitioners from cooperating in rigorous research, and lessen our chances of ever knowing for sure whether an alternative treatment actually works or not.

And at a time when research and patients alike complain that IRBs are overburdened and informed consent is not always truly informed, this bill would increase the chances that patients are put at inappropriate risk, not lessen them.

I join my colleagues in welcoming our witnesses, and I look forward to their testimony.

Mr. BILIRAKIS. I thank the gentleman.

Mr. Burr to give an opening statement.

Mr. BURR. I thank the chairman, and I thank the chairman for this hearing. Mr. Chairman, we have a lot on our plate this morning, and it is all extremely important. I will focus just briefly on the NIBIEE bill which Ms. Eshoo and I have introduced, which currently has 169 cosponsors. It is unfortunate today as we meet this morning that Ms. Eshoo is in California under the weather, but I am sure if she were here, she would speak out very loudly in support of this legislation that she and I and others on the Hill and throughout the country have worked on.

I don't think I can sum it up any better than the committee brief for this hearing. In their description of the NIBIEE bill it said: Breakthroughs in imaging such as magnetic resonance imaging and computer tomography have revolutionized the practice of medicine in the past quarter century. But those technologies are inadequate in diagnosing some diseases.

What that statement says is that we have made tremendous progress, despite a lack of a focused effort, on our ability to detect at the early possible point. What we have heard, Mr. Chairman, from people around the country is that we can do better. If you give us the type of focus that it takes in resources, we can come through with an earlier detection of disease, and we can give physicians who are treating disease many more options because of that early detection.

What NIBIEE does is create an institute of health for biomedical imaging at the NIH, the same NIH that every member of this panel and most Members of this Congress are committed to putting new resources into. What we want to make sure when we make that commitment to the American people for additional resources to chase the disease that affects every family in this country, is that biomedical imaging is one of the concentrated focuses of the NIH because we know that early detection will give us more options and will give patients more options.

Mr. Chairman, I would urge my colleagues today to ask as many questions of the witnesses that are here to testify on this bill, but, in the end, to also be supportive of this legislation. This is extremely important that we get it done and we get it done now. We spend a lot of time talking about health care policy. This is a place where we can, in fact, make sure that our options are greater down the road. And I applaud the chairman. And I yield back.

Mr. BILIRAKIS. I thank the gentleman.

Mr. Pallone for an opening statement, going on basis of seniority.

Mr. PALLONE. Thank you, Mr. Chairman. I will limit my comments to the two bills which have I cosponsored, H.R. 3677, the Thomas Navarro FDA Patient Rights Act, and the H.R. 1795, National Institute of Biomedical Imaging and Engineering Establishment Act.

The first of these, the Thomas Navarro FDA Patient Rights Act, deals with the rights of patients and parents to make informed choices about medical treatment. The bill's namesake, young Thomas Navarro, has unfortunately been suffering from the effects of a brain tumor. As any parent with a child in Thomas's situation would, the Navarros researched the treatment options available and found the treatment of radiation and chemotherapy would have extremely debilitating side effects which they did not want to risk. Rather, the Navarros preferred to have Thomas treated with antineoplaston therapy, a therapy surrounded by some controversy that is under clinical trial. The Food and Drug Administration has, however, refused to allow this to happen on the basis that his parents have not yet tried the radiation and chemotherapy path.

I cosponsored the bill because Thomas Navarro's parents should be allowed to decide for themselves whether or not the antineoplaston treatment for Thomas in the setting of a clinical trial is an appropriate path to follow. They researched the issue, and they understand the issue, and I do not believe in light of the circumstances surrounding the case that the Navarros should be denied their right to choose.

The issue is important not just for Thomas, t for other patients in similar circumstances. We shouldn't be restricting the rational choices and measured choices of individuals who choose to pursue alternative medical treatments whose possible outcomes they fully comprehend.

The second bill I want to mention, the National Institute of Biomedical Imaging and Engineering Establishment Act, is an excellent piece of legislation that I hope all of my colleagues on this subcommittee will support. I have discussed the importance of this legislation on a number of occasions over the last 2 years with medical professionals from the radiology department of the University of

Medicine and Dentistry of New Jersey and other medical professionals from my home State. All of them have stressed the importance an institute for imaging research within NIH can play in promoting further breakthroughs in a field that has already vastly changed the practice of medicine for the better.

And I want to thank the chairman for having the hearing on these two bills and the other that we have today. I yield back.

Mr. BILIRAKIS. Mr. Stupak for an opening statement. I am going to try to continue on rather than break, as long as someone gets back in time to spell me.

Mr. STUPAK. Mr. Chairman, I thank you for holding this hearing, and I thank the witnesses for being here. I look forward to their testimony.

I am a cosponsor of H.R. 762 and H.R. 1795, and for the sake of time, and I want to hear the witnesses, I yield back the balance of my time.

Mr. BILIRAKIS. I thank the gentleman so very much.

Mrs. Capps for an opening statement.

Mrs. CAPPS. Mr. Chairman, I thank you for holding this hearing, and I want to thank—extend a welcome to our witnesses. Today we are going to be discussing several worthy pieces of legislation all focused on securing the health of the American people.

Because of the nature of our hearing today, I want to remind you and other members of the bill H.R. 353, the ALS Treatment and Assistance Act. This is a bill that I am offering, enjoying bipartisan support; currently has 280 cosponsors, many of whom serve on this committee. I am so glad that we are having a hearing today on so many important pieces of legislation. I commend you for making that happen, and my hope is that this committee can address H.R. 353 before the 106th Congress is over.

I want to state my strong support in this setting for H.R. 762, the lupus research and care amendments of 1999. I am so pleased that our colleague Carrie Meek is here, the author of this bill, which would authorize the Secretary of Health and Human Services to make grants for the delivery of essential services to individuals with lupus and their families. As a nurse, I know what an insidious disease this is. For many people lupus is a mild disease affecting only a few organs; for others can cause serious, even life-threatening problems.

My district is home to the Scleroderma Research Foundation. Scleroderma is a condition that is closely linked to lupus, and I have seen the work of women like Sharon Monsky in Santa Barbara in my district, who has fought so long to raise awareness of scleroderma and lupus, diseases which disproportionately affect women and can have life-and-death consequences. So I applaud the subcommittee for recognizing this legislation.

I also want to acknowledge the legislation sponsored by my colleague Anna Eshoo which was described by our colleague Richard Burr, H.R. 1795. This legislation will fill a critical void at the NIH by creating an independent institute on this topic of bioengineering. These disciplines have made such contributions to the improvement, as our colleague has said, and have no research home in the current structure of NIH. And I support this legisla-

tion, again commending our colleagues for their leadership in this area.

Finally, I know my statement submitted will be longer than this, but I want to say one word about my good friend and colleague Deborah Pryce and offer my strongest words of support for her resolution. Her resolution focuses on the importance of promoting awareness and expanding research on childhood cancer. This is Childhood Cancer Month, September. It is the second leading cause of death in children past infancy. Many childhood cancers can be cured, but, sadly, dozens still cannot. And I applaud Congresswoman Pryce's efforts in this difficult area and pledge any support that I can give to help get this legislation passed into law.

Mr. Chairman, this is an important topic. Thank you for holding this hearing, and I yield back.

Mr. BILIRAKIS. I thank the gentlewoman.

[Additional statements submitted for the record follow:]

PREPARED STATEMENT OF HON. BARBARA CUBIN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF WYOMING

Our individual health care needs have changed over the years, but the bottom line is we all need care—and we want it to be the best.

That's all the reason we need to make sure we keep moving forward with innovative technologies, new drug therapies, and better standards of care.

We must continue to protect and nurture the different fields of research and development in health care because we live in an unpredictable and sometimes hostile bacterial environment that is constantly reinventing itself.

That means that clinical trials will take on an even greater role in the future as we try to develop new drugs to counteract new diseases.

Giving patients the proper access to these trials is therefore paramount to our success.

Of course, these trials are not possible without the new drug therapies and biologicals that sustain them so supporting drug research and innovation is critical.

By the same token, we're making technological advances that we never thought possible—such as MRIs, Cat Scans, laser devices, telemedicine, and the like.

We must continue to push the envelope in the field of health care technology because it has already proven to enhance the quality of patient care.

There are, no doubt, countless things we have yet to discover about biomedical imaging and we should continue to explore its capabilities.

Today we're discussing specific legislative proposals that are designed to secure the future health of this country. I look forward to the discussion and stand ready to work with all of you.

PREPARED STATEMENT OF HON. TOM BLILEY, CHAIRMAN, COMMITTEE ON COMMERCE

Thank you Mr. Chairman.

I am pleased that you are having this hearing today which continues the extraordinary public health work that Members of the Commerce Committee have done over the past six years.

I would like to take a moment of personal privilege to state how proud the Members of the Committee should be. In the prior two Congresses, this Committee has empowered states and localities to meet the health care and nutritional needs of low-income residents; and provided relief to those hardest hit by the AIDS epidemic.

The Health Insurance Portability and Accountability Act allows working Americans to change jobs without risking the loss of their health care insurance due to a preexisting condition. The law also attacked health care fraud and eliminated tax code discrimination against millions of small businesses and the self-employed. It also provided tax relief for long-term health care needs and terminally ill patients and their families.

The Food Quality Protection Act and the Safe Drinking Water Act Amendments of 1996 modernized programs and enhanced Americans' access to safe, abundant, and affordable food and water.

We established Medicare+Choice and the State Children's Health Insurance Program. Among other bills, we enacted the Food and Drug Administration Moderniza-

tion Act; the Birth Defects Prevention Act; the National Bone Marrow Registry Reauthorization Act; the Mammography Quality Standards Reauthorization Act; the Women's Health Research and Prevention Amendments.

This Congress, we have passed prescription drug legislation and HMO reform. We reauthorized funding to help those suffering from AIDS and moved forward on a major children's health initiative. We also have moved on the Breast and Cervical Cancer Treatment Act, the Health Care Fairness Act, the Cardiac Arrest Survival Act, the Developmental Disabilities Amendments, The Drug Addiction Treatment Act, the Date-Rape Prevention Drug Act, the Health Research and Quality Act, the Pain Relief Promotion Act, the Organ Procurement and Transplantation Network Amendments, and the Nursing Home Resident Protection Amendments. We have also provided new options under Social Security for the disabled.

It is a spectacular record.

Now for the work before us today. I look forward to hearing from today's witnesses and to making even further progress on public health with the Members of this Committee. Today we will discuss global health concerns, new medical technologies, drug approval systems, expanding access to clinical trials, Lupus, and childhood cancers. Some of these efforts may go forward this Congress and others may not. I only ask the Members of the Committee to maintain their workman-like commitment to bipartisan improvements to our public health programs.

PREPARED STATEMENT OF HON. GENE GREEN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF TEXAS

Mr. Chairman, thank you for calling this hearing today. I appreciate the opportunity to examine legislation that has been introduced to improve America's health care programs.

There are several bills being discussed today, two of which I am a cosponsor of, the Lupus Research and Care Amendments of 1999 and the National Institute of Biomedical Imaging and Engineering Establishment Act.

H.R. 762 by Rep. Carrie Meek is a bill that would expand and intensify research at the NIH to diagnose, treat, and eventually cure lupus. It also increases the funding for lupus research and education and establishes a grant program to expand availability of lupus services.

I commend my colleague for introducing this bill and look forward to the testimony on this piece of legislation.

I am also a cosponsor of H.R. 1795 by Rep. Richard Burr. This legislation would create an independent institute to support basic research in medical imaging and bioengineering. These disciplines have made great contributions to the improvement of medical care in the past two decades, yet they have no research home in the current NIH structure. The creation of the National Institute of Biomedical Imaging and Engineering would create a research environment in which new imaging and bioengineering technologies techniques and devices can be developed for clinical use more rapidly than under the present system. This would allow for continued rapid progress in fields such as genetics and molecular biology, which utilize advanced imaging techniques.

I represent the medical center area and I can tell you that this piece of legislation would help advance the technology that can be used for clinical use more rapidly than under the present system.

I look forward from hearing from our witnesses today.

PREPARED STATEMENT OF HON. ANNA G. ESHOO, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF CALIFORNIA

Thank you, Mr. Chairman, for holding today's hearing. With six bills before us today, we have a lot on our plates. However, I'd like to focus my comments on the bill that my colleague Mr. Burr and I have introduced, H.R. 1795 to establish a National Institute of Biomedical Imaging and Engineering at the National Institutes of Health (NIH).

Mr. Chairman, dramatic advances in imaging and bioengineering have revolutionized medical practice in recent years. Development of new, noninvasive imaging techniques, such as Magnetic Resonance Imaging (MRI) and Computed Tomography (CT), has allowed for earlier detection and diagnosis of disease, dramatically improving the quality of healthcare. But, the next generation of breakthroughs will be longer in coming, or in some fields, may not come at all unless we modernize the structure at NIH.

Today, these disciplines, which have made unmatched contributions to the improvement of medical care in the past two decades, have no research home in the current NIH structure. Research at the current institutes at NIH is based on molecular biology, which is fundamentally different from research in imaging and bioengineering. If we are to ensure the continued development of new techniques and technologies, these disciplines require an identity and research home at the NIH that is independent of the existing institute structure.

H.R. 1795 would fill a critical void at the NIH by creating an independent institute to support basic research in medical imaging and bioengineering. It would create a research environment in which new imaging and bioengineering technologies, techniques, and devices can be developed for clinical use much more rapidly than under the present system. By doing so, H.R. 1795 replaces disorganization with efficiency, effective management, accountability, and an improved scientific focus.

At a time when Congress has committed to doubling the NIH budget, we must ensure that research dollars are expended more effectively and efficiently and that the fields of medical science that have contributed the most to the detection, diagnosis, and treatment of disease in recent years receive appropriate emphasis. Establishment of a National Institute of Biomedical Imaging and Engineering at the NIH would accelerate the development of new technologies, improve coordination and efficiency throughout the Federal government, reduce duplication, lay the foundation for a new medical information age, and provide a structure to train the young researchers who will make the pathbreaking discoveries of the next century.

I'm proud to join Representative Burr in sponsoring H.R. 1795 and I'm pleased that the Committee has finally turned its attention to it. I encourage my colleagues' support at tomorrow's full committee markup and I look forward to passage by the full House.

PREPARED STATEMENT OF HON. JOHN D. DINGELL, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF MICHIGAN

Mr. Chairman, we have six bills and resolutions before us today, so I will be brief.

H.R. 2399 would establish a national commission to examine how the United States can most effectively use our scientific and technical expertise to tackle disease on a global basis. This is an ambitious undertaking. A panoply of public and private sector organizations spend considerable time and resources on projects that collectively span virtually all global health issues. Nevertheless, the commission could generate useful information, which in turn could optimize the use of scarce resources and which could lead to improvements in global health.

H.R. 762, the Lupus Research and Care Amendments, is an excellent piece of legislation that has been developed by my good friend and colleague, Representative Carrie Meek. As we will learn, lupus is a debilitating and sometimes fatal autoimmune disease that disproportionately afflicts women, particularly women of color.

H.Res. 576 by Representative Pryce is another measure worthy of our support. Children are not simply "little adults." I note that our colleague, Representative Forbes, has a similar bill, H. Con. Res. 115.

H.R. 1795 would create the Institute of Biomedical Engineering at the National Institutes of Health (NIH). I note the fine work that our colleagues, Representatives Eshoo and Burr, have done on this bill and believe that it deserves our careful consideration, although NIH has some concerns with the bill.

H.R. 3677 causes me great concern, and I can not support it as drafted. This bill would dramatically alter the basic role of the Food and Drug Administration (FDA) in the supervision of human subject protection in the development of experimental drugs. FDA must play a fundamental role in protecting the public in both the development and approval of drugs. The FDA Modernization Act, which has provisions on this matter, is less than three years old, but we should examine the investigational drug process to ensure that it is serving the public in the best possible manner. The moral, ethical, and safety issues presented in the informed consent process are particularly important in the case of experimental drugs and their use on persons with serious and life threatening diseases.

Finally, I oppose H.R. 4242, the Orphan Drug Innovation Act. We will hear testimony opposing this bill from the National Organization for Rare Disorders (NORD). NORD represents approximately 25 million Americans with more than 6,000 "orphan" diseases. The orphan drug law has been a success. Anyone wishing to enact significant changes in this important health statute bears a heavy burden. I do not believe the proponents of this bill have met that test.

Thank you, Mr. Chairman.

Mr. BILIRAKIS. Mr. Gekas and Mrs. Meek are here to testify on behalf of their legislation briefly and also introduce the witnesses. What is your pleasure? Should we go to you now, or would you like to return? I don't want to really rush you, but we do want to make this vote. Would like to return? I will be here.

Mrs. MEEK. With your pleasure and Mr. Gekas's, I would rather go forward, if I may.

Mr. BILIRAKIS. What would you prefer to do?

Mr. GEKAS. I do not mind proceeding.

Mr. BILIRAKIS. Well, then, proceed. The only thing is I am liable to cut you off.

You are recognized, the gentleman from Pennsylvania.

STATEMENT OF HON. GEORGE W. GEKAS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF PENNSYLVANIA

Mr. GEKAS. Thank you. The opening remarks made by the chairman and the ranking member in describing the bill which I have placed before you were more than adequate in describing the purport of the legislation.

I simply want to add to that the fact that the national goal for the 20th century is well-known to everybody. The one that we just completed, that goal was thrust upon us. It was the repulsion of totalitarianism and the reestablishment and preservation of democracy across the globe. That was the national gole thrust upon us.

Now we have an opportunity in the next century to assume leadership in what I envision to be, and others do, the national goal for the 21st century, namely the eradication of disease worldwide. Why is that important? Not only for the humanitarian and altruistic rationale that are the foundation for such a project, but also in the enlightened self-interest of our country, which is the leader in all of these disciplines that are so vital to the health of the world, that enlightened self-interest we not only protect our people in the future from these diseases and other catastrophes that might occur, but at the same time we create jobs, we create interests, we develop new technologies, new pharmaceuticals and all the other necessaries to further envision a world without disease with our country in the forefront.

That is what the purpose of it is. That is why our witness is so important. She has testified before our Biomedical Research Caucus as one of the leading lecturers in her field, and you will see from her testimony that she will be a vital force if we implement the legislation which I have offered.

She is Professor Dyann Wirth, of the Department of Immunology and Infectious Diseases, Harvard School of Public Health, and has a slew of publications which she is the author. She is renowned in her field. She impressed the Members of the Hill, the Capitol, who engaged in the Biomedical Research Caucus series, and I am sure she will impress you. Unfortunately she has impressed me so much that I am leaving right now to go vote, but I know what she will testify and commend her to you.

[The prepared statement of Hon. George W. Gekas follows:]

PREPARED STATEMENT OF HON. GEORGE W. GEKAS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF PENNSYLVANIA

Mr. Chairman, and Members of the Committee, I would like to thank you for giving me the opportunity to testify at this hearing on such an important matter.

The latter part of the twentieth century saw the dismantling of the U.S.S.R., the fall of the Berlin Wall, and a worldwide blossoming of democracy. To many this seemed an impossibility at the time. Most of the world rightly places the credit for these events in the hands of our United States. Our leaders and our government put forth endless efforts to achieve these ends successfully. While these accomplishments are extraordinary, it is time to turn our attention to another seemingly impossible goal.

With the dawning of the new millennium, the time has come to focus our national energy and resources on efforts to eradicate all disease across the globe. This is indeed an awesome goal that may not be attainable in itself, but its purpose could lead to new treatments of diseases, and new approaches to controlling them.

Beyond the humanitarian reasons for promoting this idea, the U.S. has enlightened domestic goals as well. Eradicating global disease would protect American citizens, improve the quality of life worldwide, enhance our economy, and advance American interests across the globe. Achieving this goal would impact every aspect of our society, not just the field of health care.

In order to reach the objective of eradicating disease globally, I have introduced H.R. 2399, the Advancement of Global Health Act, which would establish a commission, the National Commission for the New National Goal: The Advancement of Global Health. The commission's task would be to recommend a strategy for the global eradication of disease. The United States has the resources, through the National Institutes of Health (NIH) and the National Science Foundation, to take the lead in expanding health research information globally, especially with the recent explosion of Internet technology. Additionally, the commission would assist the Center for Vaccine Development at the NIH to achieve global control over infectious disease. A one-time $1 million allocation would be granted to the commission to coordinate and attract other sources of funding both domestically and abroad for the purpose of achieving these objectives.

The fifteen-member commission would be charged with coordinating governmental, academic, and public and private health care entities for the purpose of global disease eradication. The commission would then be required to submit a final report to Congress within one year of its establishment, with its recommendations for legislative, administrative, and other appropriate actions. The wide-sweeping goals of this legislation could encompass ideas like the simple act of teaching a youngster how to properly wash his or her hands, reaching across to the more complex, such as medical advances learned from space exploration.

It gives me great pleasure to have Dr. Dyann F. Wirth here today to further discuss the idea of eradicating global disease. Dr. Wirth earned a Ph.D. in Cell Biology and Biochemistry from the Massachusetts Institute of Technology. She currently serves as a professor at the Harvard School of Public Health in its Department of Immunology and Infectious Diseases. Dr. Wirth is a widely published author in numerous esteemed scientific and medical journals. She also worked for ten years as an NIH Study Section Member on Tropical Medicine and Parasitology, which is Dr. Wirth's particular area of expertise. Again, I am glad to have her with us today.

The intelligence and imagination of American researchers and scientists did not fail us in our attempts to preserve and promote freedom and democracy across the globe. It is now time for us to unleash these same great minds towards the goal of improving the quality of life for everyone. We must summon all of the resources at our command in our efforts to eradicate disease from the face of the Earth.

Again, Mr. Chairman, I thank you for this hearing on this very important matter that can change the lives of countless individuals.

Mr. UPTON [presiding]. I thank the gentleman from Pennsylvania. Now I recognize Mrs. Meek, and I didn't know that you were here when I gave my opening statement, but I commended you for your good bill, and I am delighted to be a cosponsor and delighted to recognize you now.

STATEMENT OF HON. CARRIE P. MEEK, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF FLORIDA

Mrs. MEEK. Thank you, Mr. Chairman. I am pleased to be before the committee again, and I want to thank you for bringing this hearing up again. 762 is an extremely important piece of legislation. It is time that it be passed, Mr. Chairman, and of course I am hoping that this committee will see fit to pass it out and send it to the floor as quickly as possible so that no one else will have to wait for the kind of assistance that this Lupus Research and Care Act will bring.

The Lupus Foundation has really stuck with the Congress through this, Mr. Chairman. They have assiduously watched this bill for many, many years, and I do hope we can get it passed. What it will do is add additional services for lupus victims.

But I am here this morning because I am pleased and privileged and blessed to have a young lady who is sitting at the table, the testimony table, to testify for lupus, a very beautiful, lovely lady, Tomiko Fraser. She is the spokesperson for the Lupus Foundation, and I do not have to take your time to tell you all of the demerits, I would say, or all of the real terrible effects of lupus. I lost a sister to it. I have lost so many friends to lupus. It is a young woman's disease, and as a result of that, I think as this committee you have 243 cosponsors behind this bill.

And I want to have my statement placed in the record, Mr. Chairman, and with your permission.

Mr. UPTON. Without objection, your entire statement will be put in the record, and, again, we thank you for your leadership on this very important issue that touches so many American families in every State.

[The prepared statement of Hon. Carrie P. Meek follows:]

PREPARED STATEMENT OF HON. CARRIE P. MEEK, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF FLORIDA

Good morning, Chairman Bilirakis, Ranking Member Brown and my other colleagues. It's a pleasure to be with you. Thank you for holding this hearing and inviting me to appear before your Subcommittee to discuss my lupus bill, H.R. 762. My bill would authorize additional funding for lupus research and treatment programs. Providing such additional help for lupus victims is not a Democratic issue or a Republican issue. It's an American issue. My bill has broad bipartisan support (243 cosponsors from both sides of the aisle).

I won't take the Subcommittee's time to lay out all of the details of H.R. 762. In a nutshell, this bill would authorize spending of up to $75 million for lupus research and $75 million for lupus care and treatment programs.

I want to recognize and introduce to the Subcommittee the beautiful young women sitting next to me, Tomiko Fraser. Tomiko is a nationally recognized spokesmodel and actress. She is the first African-American women to be a spokesmodel for Maybelline. Tomiko's sister has lupus. Tomiko has seen firsthand the devastation that lupus has caused for her sister and she speaks eloquently about what it is like for her sister to live with lupus. She makes a powerful case for why we need the additional funding for lupus research and treatment that my lupus bill authorizes.

Tomiko, I salute you and your sister for your courage and thank you for your commitment to obtaining additional relief for lupus victims and their families.

As many of you know, I know firsthand the heartache that lupus causes, I lost a sister to lupus and have seen many others suffer from this disease. We all know the debilitating pain and fatigue that lupus often causes, pain and fatigue that makes it difficult for persons with lupus to maintain employment and lead normal lives. We also know the profound impact that this disease has on family members of those with lupus.

Mr. Chairman, lupus victims and their families need more help and they need it now. Congress and the President can provide it by passing and signing H.R. 762. We can do it, and we must do it this year, but, to make this happen, I need your help to persuade the leadership to bring this bill to the floor immediately. I won't be satisfied, and none of us should be, until we get this bill to the House floor, pass it overwhelmingly, pass it in the Senate and have it signed by the President.

I urge the Subcommittee and the full Commerce Committee to mark this bill up immediately and implore the Leadership to bring this bill to the floor on the Suspension Calendar at once so that it can pass the House this Session. Thank you, Mr. Chairman.

Mrs. MEEK. Thank you, Mr. Chairman. And I would love to hear Tomiko, but I must go and vote.

Mr. UPTON. Well, you can come back.

Mrs. MEEK. All right.

Mr. UPTON. At this point, as no members are coming back from the vote that is currently ongoing, I would like to invite the first panel to come to the table. They include Dr. Nick Bryan, professor and chairman of radiology at the Hospital of the University of Pennsylvania; Dr. Reed Dunnick, professor and Chair of the Department of Radiology, University of Michigan. Go blue. Beat UCLA this weekend. Dr. Bruce Hillman, professor and Chair, Department of Radiology, University of Virginia; Ms. Tomiko Fraser, who is, of course, at the table already, and obviously the national spokesperson for the National Lupus Association; and Dr. Dyann Wirth, professor at the Department of Immunology and Infectious Diseases at Harvard.

I just want to say before we start that there are a number of things ongoing this morning, and a number of committees and subcommittees that are meeting. We have a very important issue on the House floor, that being the marriage penalty tax as well, where I am going to have to return to engage myself in that debate a little bit later this morning.

Your statements are made part of the record in their entirety. We would like to keep this to 5 minutes each or less. And Dr. Wirth, we will start with you. Thank you for being here with us this morning.

STATEMENTS OF DYANN WIRTH, PROFESSOR, DEPARTMENT OF IMMUNOLOGY AND INFECTIOUS DISEASES, HARVARD SCHOOL OF PUBLIC HEALTH; N. REED DUNNICK, PROFESSOR AND CHAIR, DEPARTMENT OF RADIOLOGY, UNIVERSITY OF MICHIGAN HEALTH SYSTEM; BRUCE J. HILLMAN, PROFESSOR AND CHAIR, DEPARTMENT OF RADIOLOGY, UNIVERSITY OF VIRGINIA; TOMIKO FRASER, NATIONAL SPOKESPERSON, LUPUS FOUNDATION OF AMERICA, INC.; AND R. NICK BRYAN, PROFESSOR AND CHAIRMAN OF RADIOLOGY, HOSPITAL OF UNIVERSITY OF PENNSYLVANIA

Ms. WIRTH. Mr. Chairman and members of the subcommittee, thank you for the opportunity to testify today. My name, as you already know, is Dyann Wirth. I am a professor at Harvard University School of Public Health and the Department of Immunology and Infectious Diseases, and I am here today on behalf of the Joint Steering Committee for Public Policy, which has worked closely with Representative Gekas in his outstanding efforts in support of biomedical research.

The Joint Steering Committee for Public Policy is a coalition of four life sciences societies representing more than 25,000 researchers. I am here today to support—to express the support of the joint steering committee for Congressman Gekas's bill which we have just heard about on the advancement of global health, H.R. 2399. This bill, if enacted into law, would create a Presidential/congressional commission to investigate how we as a Nation can most effectively seize the scientific opportunities presented by modern advances in research to eradicate many of the diseases that are plaguing millions of the world's people.

We support this bill because we believe that in this next millennium it is within the grasp of human capacity to accelerate the role of basic biomedical research and the translation of that research to the benefit of the world's least fortunate people.

Now is the time. This is an attempt to focus all of the tremendous scientific energy in the United States on fighting diseases throughout the world. This is a noble endeavor for the United States. We have the means to do this, and I believe we should make it a priority.

My particular experience is in malaria, but as devastating as malaria is, it is just one of the several infectious diseases that are not only killing millions, but costing billions. According to the World Health Organization, infectious diseases account for more than 13 million deaths a year. That is 35 percent of the deaths in the world today. That means during the duration of this hearing, 1,500 people will die from infectious disease. Malaria alone kills 2.7 million people each year. Tragically, every 30 seconds a child somewhere in the world, probably in Africa, dies of malaria.

The enormous volume of travel and trade have made infectious diseases blind to national borders, and this has been recognized. The January 2000 unclassified report from the CIA's National Intelligence Council entitled "The Global Infectious Disease Threat and Its Implications for the United States" suggests that in modern warfare infectious diseases are likely to account for more military hospital admissions than battlefield injuries. The report claims, and I concur, New and reemerging infectious diseases will pose a rising global health threat and will complicate U.S. and global security over the next two decades. These diseases will endanger U.S. citizens at home and abroad, threaten U.S. Armed Forces deployed overseas, and exacerbate social and political instability in key countries and regions where the United States has an interest.

Research into prevention, treatment and control of tropical and infectious diseases is now more important than ever. I will talk just briefly about malaria because that is where my interest and passion is. Among adults living in high-transmission areas, malaria is considered a chronic disease. A single bout can incapacitate someone for weeks, and despite massive efforts to eradicate this disease in the 1950's, there is more malaria in the world today than there ever has been in history. One-fourth of the world's population is at risk of infection.

Clearly, we need better implementation of the tools that we have in the short term, but our tools are not adequate. New research interventions are desperately needed. Cutting-edge technology has led to the development of new paradigms. The genome of the most

important parasite is being sequenced. We have DNA vaccines, new technologies. And it is important to seize the opportunities of these scientific advances to accelerate and defeat malaria worldwide.

But equally important as progress in research and public support and awareness of these major health threats, in order to conquer malaria, AIDS, malaria, other infectious diseases, we need a global strategy that includes American leadership and resources to invest in continued research into prevention and treatment.

As we begin the 21st century, we are blessed with unimaginable opportunities to build on breakthrough research to control and prevent global infectious diseases. This is not just altruism to reduce suffering of the world's most needy; this is also a question of national security and health for the United States and its citizens. Renewed investment in the treatment and prevention of global infectious diseases is a win-win for the country. By helping others across the world, we are launching the best defense to protect the health of our Nation's people.

We hope that you will seriously consider passage of H.R. 2399 and thank you very much for the opportunity to present.

[The prepared statement of Dyann Wirth follows:]

PREPARED STATEMENT OF DYANN WIRTH, PROFESSOR, HARVARD UNIVERSITY SCHOOL OF PUBLIC HEALTH

Mr. Chairman and members of the Subcommittee, thank you for the opportunity to testify today. My name is Dyann Wirth. I am a Professor at the Harvard University School of Public Health Department of Immunology and Infectious Disease. I am here today on behalf of the Joint Steering Committee for Public Policy, which has worked closely with Representative Gekas in his outstanding efforts in support of biomedical research.

The Joint Steering Committee for Public Policy (JSC) is a coalition of four life-science societies representing more than 25,000 researchers in the fields of genetics, cell biology, biophysics, biochemistry and molecular biology. The JSC was formed in late 1980s to bring scientists together to advocate for federal funding for basic biomedical research. Eric Lander of MIT chairs JSC, and among its 20 board members are Nobelists J. Michael Bishop, Paul Berg and Harold Varmus.

Founders of the JSC realized that there was a great need for the United States to invest in biomedical research and called for the doubling of the NIH budget. Since that time, Mr. Chairman, the Congress' visionary support of the NIH has lead us to the dawn of a new age in science. I have no doubt that the coming decade will be remembered for major discoveries enabled by the mapping of the human genome which will lead to the prevention and cure of diseases. The JSC also worked with Congressman Gekas to introduce the Congressional Biomedical Research Caucus to the Halls of Congress. Today, the Biomedical Research Caucus has been called by Chairman John Porter and former Speaker New Gingrich among others, "the most influential Caucus in Congress."

I am here today to express the support of the Joint Steering Committee for Congressman Gekas' bill the National Commission for the New National Goal: The Advancement of Global Health Act, H.R. 2399. this bill, if enacted into law would create a Presidential/Congressional commission to investigate how we as a Nation can most effectively seize the myriad scientific opportunities presented by modern advances in genomic to eradicate many of the diseases that are plaguing millions of the world's people. We support this bill because we believe that in this third Millenium it is within the grasp of human capability to accelerate the role of basic biomedical research and the translation of that research to the benefit of the world's least fortunate people. Now is the time: scientific potential is there; it requires only political will to make it reality.

My particular experience is malaria, but as devastating as malaria is, it is just one of several infectious diseases that are not only killing millions but costing billions. According to the World Health Organization, infectious diseases account for more than 13 million deaths a year. That means that over the duration of this hearing 1,500 people will die from an infectious disease—over half of them children under five.

According to the WHO the seven infectious diseases that caused the highest number of deaths in 1998 are AIDS, TB, malaria, hepatitis B and hepatitis C, diarrheal diseases, and measles. Of these, TB and hepatitis are renewed threats because they are becoming increasingly resistant drug resistant. But, malaria alone is estimated to cause up to 500 million clinical cases and 2.7 million deaths each year, representing 4 percent to 5 percent of all fatalities globally. Tragically, every 30 seconds a child somewhere in the world dies of malaria. As you know, most of these deaths occur in developing countries where extreme poverty and lack of access to basic health care, adequate sanitary and essential drugs can seal the fate of children before they're born. However, the enormous volume of travel and trade today have made, infectious diseases blind to national borders.

A January, 2000, unclassified report from the CIA's National Intelligence Council, entitled "The Global Infectious Disease Threat and Its Implications for the United States," suggests that in modern warfare infectious diseases are likely to account for more military hospital admissions than battlefield injuries. The report assesses claims, and I concur, that "New and reemerging infectious diseases will pose a rising global health threat and will complicate US and global security over the next 20 years. These diseases will endanger US citizens at home and abroad, threaten US armed forces deployed overseas, and exacerbate social and political instability in key countries and regions in which the United States has significant interests."

Research into the prevention, treatment and control of tropical and infectious disease are now more important than ever to the US and the world. I will address malaria as an example because I know more about malaria than about other global health threats.

Among adults living in areas of high transmission, malaria is best thought of as a chronic, debilitating illness that robs its victims of years of productivity. A single mosquito bite can transmit one of the four parasites that cause malaria, setting in motion bouts of fever, chills, and nausea that can recur for weeks. According to a 1993 World Bank Report, malaria represents a global public health burden second only to tuberculosis among infectious diseases of the 2-3 million children who die of malaria each year, most of them live in Africa, continent already overwhelmed by poverty and internal conflict. Those who survive can suffer chronic anemia and/or immune suppression that leave victims vulnerable to other fetal diseases.

Despite massive efforts to eradicate in the 1950s, today than at any other time in history. More than 500 million people are infected with malaria worldwide; one-fourth of the world's population is at risk for infection. Better implementation of currently available control measures, including the use of insecticide, and better and more rational use of existing drugs, should be the goal in the short term; in the long-term, new research interventions are desperately needed. Cutting-edge technology has led to the development of new paradigms—the genome of the most important malaria parasites is being sequenced, DNA vaccines are being developed and tests of methods to prevent transmission by the mosquito are being explored. We must seize the opportunity presented by these scientific adversities to accelerate the defeat of malaria worldwide. But equally important as progress in research is public support and awareness of this major health threat. In order to conquer malaria, we need a global strategy that includes American leadership and resources to invest into continued research into prevention and treatment. I must also point out the great need for action with regard to HIV/AIDS in Africa. Africa remains the epicenter of the pandemic, bearing the largest disease burden, with 70 percent of people living with AIDS worldwide, 83 percent of global AIDS deaths, and 95 percent of the world's AIDS orphans. AIDS is reversing decades of progress from important public health efforts, lowering life expectancy, and significantly affecting daily life form millions of Africans. This situation cries out for leadership.

The JSC supports efforts to encourage research and development on vaccines to combat malaria, tuberculosis, AIDS and other infectious diseases causing and to ensure that existing vaccines are accessible to populations in developing countries most impacted by these diseases. These efforts will require partnerships among federal agencies, industry, non-profit foundations and other NGOs, the World Bank, and international organizations to combat the scourge of infectious diseases. This Commission could vastly accelerate the pace of these efforts.

Specific mechanisms might include, enhanced R&D tax credits and new tax credits for sales of vaccines, contributions to international organizations such as the Global Alliance for Vaccines and Immunizations (GAVI) for the purchase and distribution of vaccines in developing countries, and measures that will improve the public health infrastructure in developing countries in order to expand immunizations, prevent and treat infectious diseases, and build effective delivery systems for basic health services.

As we begin the 21st century, we are blessed with unimaginable opportunities to build on breakthrough research to control and prevent global infectious disease. This is not just altruism to reduce the suffering of the world's most needy: this is also a question of national security and health for the United States and its citizens. Renewed investment in the treatment and prevention of global infectious disease is a win-win for the country: by helping others across the world we are also launching the best defense to protect the health of our Nation's people. We hope you will seriously consider passage of H.R. 2399.

Thank you for the opportunity to present the views of the Joint Steering Committee for Public Policy. I would be happy to answer your questions.

Mr. UPTON. Thank you, Dr. Wirth.

Dr. Dunnick, welcome to Washington's version of the "Big House."

STATEMENT OF N. REED DUNNICK

Mr. DUNNICK. Thank you. Good morning. Thank you for this opportunity to share my support for H.R. 1795 with you. I also appreciate the leadership shown by Mr. Burr and Ms. Eshoo in support of this legislation.

I am Reed Dunnick. I currently serve as the Chair of the Department of Radiology at the University of Michigan. Prior to coming to Michigan in 1992, I served on the faculties at Stanford and at Duke. In addition, I spent 4 years as a staff radiologist in diagnostic radiology at the National Institutes of Health.

The Congress has recognized the structural impediments to imaging research that exist at the NIH in the conference report on H.R. 3194, the Consolidated Appropriations Act for Fiscal Year 2000. The language in that conference report is a good summary of the current situation at the NIH.

Continued advances in biomedical imaging and engineering, including the development of new techniques and technologies for both clinical applications and medical research, and the transfer of new technologies from research projects to the public health sector are important. The disciplines of biomedical imaging and engineering have broad applications to a range of disease processes and organ systems, and research in these fields does not fit into the current disease and organ system organizational structure of the NIH.

The present organization of the NIH does not accommodate basic scientific research in these fields and encourages unproductive diffusion of imaging and engineering research. Several efforts have been made in the past to fit imaging into the NIH structure, but these have proved to be inadequate.

This congressional report is correct. The current structure of the NIH does not promote basic research in medical imaging and bioengineering, two disciplines that have become critical to improving health care. The next logical step suggested by this congressional finding is the creation of a National Institute of Biomedical Imaging and Bioengineering as proposed in H.R. 1795.

The imaging science community has worked with the NIH leadership for three decades to fit imaging into the existing NIH organizational structure of individual institutes dedicated to specific disease processes and organ systems. However, nothing short of an institute will be effective in stimulating and coordinating biomedical research to the extent that it is needed.

The imaging community has not proposed the establishment of a new institute lightly. We recognize and agree that the bar for structural change should be set high. For that reason we looked to the National Academy of Science's Institute of Medicine in their 1984 report titled Responding to Health Care Needs and Scientific Opportunity: The Organizational Structure of the National Institutes of Health.

They recommend a new institute when each of the following five criteria are met: One, the activity is compatible with the mission of the NIH; two, the research area in question is not receiving adequate attention; three, there are reasonable prospects for scientific growth; four, there are reasonable prospects of sufficient funding; and five, the proposed structural change will improve communication, management, priority setting and accountability.

The proposed National Institute of Biomedical Imaging and Bioengineering is consistent with these criteria. In identifying imaging as one of its top research priorities, the NCI has stated that this field is compatible with the mission of the NIH. The NCI has indeed increased its level of support for biomedical imaging in recent years. However, even with this increase in resources, the amount of moneys carried out by radiology departments throughout the country account for less than 1 percent of the NIH budget.

Finally, the proposed institute, which would include a division to coordinate imaging research throughout the Federal Government, would certainly improve communication and management in a field in which these qualities are sorely lacking.

Mr. Chairman, breakthroughs in medical imaging have revolutionized the way in which physicians detect, diagnose and treat disease. Imaging holds the promise of further advances that will move us into an era of noninvasive medicine. To reach that goal, however, we need to create a climate that promotes discovery and innovation in imaging just as the NIH provides such a climate for other fields.

For that reason I urge the committee to support the establishment of the National Institute of Biomedical Imaging and Engineering. Thank you.

[The prepared statement of N. Reed Dunnick follows:]

PREPARED STATEMENT OF N. REED DUNNICK, PROFESSOR AND CHAIR, DEPARTMENT OF RADIOLOGY, UNIVERSITY OF MICHIGAN HOSPITALS

Good morning. Thank you for this opportunity to share my support for H.R. 1795 with you. My name is Reed Dunnick, and I chair the Radiology Department at the University of Michigan. Prior to coming to Michigan in 1992, I served on the faculties at Stanford and Duke. In addition, I spent four years as a staff radiologist in the Diagnostic Radiology Department at the National Institutes of Health.

Like everyone in my discipline and throughout the imaging sciences, I was extremely pleased that the Congress recognized the structural impediments to imaging research that exist at the NIH in the Conference Report on H.R. 3194, the Consolidated Appropriations Act for Fiscal Year 2000. The language in that Conference Report is a good summary of the current situation at the NIH:

"Continued advances in biomedical imaging and engineering, including the development of new techniques and technologies for both clinical applications and medical research and the transfer of new technologies from research projects to the public health sector are important. The disciplines of biomedical imaging and engineering have broad applications to a range of disease processes and organ systems and research in these fields does not fit into the current disease and organ system organizational structure of the NIH. The present organization of the NIH does not accommodate basic scientific research in these fields and encourages unproductive dif-

fusion of imaging and engineering research. Several efforts have been made in the past to fit imaging into the NIH structure, but these have proved to be inadequate."

This Congressional report is correct. The current structure of the NIH does not promote basic research in medical imaging and bioengineering, two disciplines that have become critical to improving health care. The logical next step suggested by this Congressional finding is the creation of a National Institute of Biomedical Imaging and Bioengineering as proposed in H.R. 1795. Like my colleagues Dr. Hillman and Dr. Bryan, I have been involved in imaging research at the NIH for many years. The imaging science community has worked with the NIH leadership for three decades to fit imaging into the existing NIH organizational structure of individual institutes dedicated to specific disease processes and organ systems.

During that period, numerous plans have been tried. In 1982, for example, most extramural research in imaging was transferred from the National Institute of General Medical Sciences to the National Cancer Institute with the understanding that NCI would support imaging research beyond that related to cancer. However, the NCI has focused almost exclusively on cancer imaging.

On the intramural side, the Laboratory of Diagnostic Radiology Research (LDRR) was transferred from the Office of the Director of the NIH to the Clinical Center a couple of years ago. This move was an improvement but far from a solution because the Clinical Center lacks the research mandate and resources to allow LDRR to achieve its full promise.

Despite good will on both sides, these initiatives did not solve the problems faced by either extramural or intramural imaging investigators. Only after such repeated efforts failed did the imaging community conclude that the NIH structure is not compatible with an effective imaging research program and that creation of a new institute is justified and necessary. Nothing short of an Institute will be effective in stimulating and coordinating biomedical research to the extent that is needed.

The imaging community has not proposed the establishment of a new institute lightly. We recognize and agree that the bar to structural change at the NIH should be set high. For that reason, we looked to neutral, expert guidance, which we found in the National Academy of Sciences' Institute of Medicine. In a 1984 report titled *Responding to Health Needs and Scientific Opportunity: The Organizational Structure of the National Institutes of Health,* issued in response to a Congressional directive, the IOM concluded that new institutes should be created only in unique circumstances when the following five criteria are met:

(1) the activity is compatible with the mission of the NIH;
(2) it can be demonstrated that the research area in question (defined either as a disease or health problem or as a biomedical or behavioral process related to a health problem) is not receiving adequate attention;
(3) there are reasonable prospects for scientific growth in the research area;
(4) there are reasonable prospects of sufficient funding for the new organization;
(5) the proposed structural change will improve communication, management, priority setting, and accountability.

The proposed National Institute of Biomedical Imaging and Bioengineering is consistent with these criteria. In identifying imaging as one of its top research priorities, the NCI has stated clearly that this field is compatible with the mission of the NIH and that there are reasonable, even extraordinary, prospects for scientific growth. The NCI has increased its level of support for the Biomedical Imaging Program in recent years. Even with this increased commitment of resources, however, extramural support for imaging research carried out by Radiology Departments continues to account for substantially less than one percent of the NIH budget—a level that is inadequate for an "Extraordinary Opportunity for Investment." Finally, the proposed institute, which would include a division to coordinate imaging research throughout the federal government, would certainly improve communication and management in a field in which these qualities are sorely lacking.

Two years ago, again in response to a Congressional mandate, the IOM issued another report that addressed the question of structural change. In its 1998 report titled *Scientific Opportunities and Public Needs: Improving Priority Setting and Public Input at NIH,* the IOM recommended that "The U.S. Congress should use its authority to mandate specific research programs, establish levels of funding for them, and implement new organizational entities only when other approaches have proven inadequate." The imaging community agrees with this recommended limitation on Congressional action and believes firmly that the proposed National Institute of Biomedical Imaging and Bioengineering is consistent with it.

In addition, and just as important, the proposed institute is also completely consistent with the NIH's own rationale for the elevation of the National Center for Human Genome Research to institute status in 1997. According to the statement issued by the NIH to announce the creation of the National Human Genome Re-

search Institute, "As an institute, NHGRI can more appropriately interact with other Federal agencies, and develop collaborations with industry, academia, and international organizations."

The same is true for imaging. The proposed institute would coordinate imaging research throughout the federal government, a mission that cannot be accomplished successfully by a lower level office or organization lacking sufficient institutional stature and authority to deal effectively with cabinet-level departments. Similarly, industry-government collaborations are essential to the development of new imaging technologies. The proposed institute would assist industry in setting research priorities and assessing potential fields for development. The National Electrical Manufacturers Association, which represents the companies that produce imaging devices, supports this proposal.

This matter of coordinating imaging outside the NIH is important. Other federal agencies such as NSF, NASA, the intelligence agencies, and the Departments of Defense, Commerce, and Energy all support imaging research. There is little or no coordination of these efforts. In one key area, telemedicine, the General Accounting Office found a couple of years ago that more than 35 separate federal organizations in nine different departments have sponsored telemedicine initiatives. Despite a major federal investment of $646 million over three years, the GAO found that "no formal mechanism or overall strategy exists to ensure that telemedicine development is fully coordinated among federal agencies to serve a common purpose." According to the GAO, the Joint Working Group on Telemedicine, created in response to a directive from the Vice President, encountered serious difficulties even in developing a federal inventory of telemedicine programs.

This lack of coordination not only encourages duplication and inefficiency, it impedes the transfer of imaging technologies from research projects to the public health care sector. The proposed institute could do much to ensure that federal research dollars are expended more efficiently and productively.

The National Institute of Biomedical Imaging and Bioengineering would also provide a focused effort to meet the medical needs of the information age. It has been estimated that computerization requirements in the coming decade will double just to keep pace with developments in all segments of society. The largest component of that need will be in the area of medical imaging information. In addition to the enormous amount of imaging-related, unprocessed information generated, there will be a need to process and analyze the huge date sets produced by medical imaging to improve the medical value of those data to the referring physicians who will access the network. An imaging institute would support research focused on the acquisition, transmission, processing, and optimal display of images.

Mr. Chairman, breakthroughs in medical imaging have revolutionized the way in which physicians detect, diagnose, and treat disease in the past two decades. Imaging holds the promise of further advances that will move us into an era of noninvasive medicine. To reach that goal, however, we need to create a climate that promotes discovery and innovation in imaging just as the NIH provides such a climate for other fields. For that reason, I urge the Committee to support the National Institute of Biomedical Imaging and Engineering Establishment Act.

Mr. UPTON. Thank you very much.

Dr. Hillman.

STATEMENT OF BRUCE J. HILLMAN

Mr. HILLMAN. Good morning. I am Dr. Bruce Hillman, Chair of the Department of Radiology at the University of Virginia, and I am also a Chancellor of the American College of Radiology. I am grateful to the committee, especially to the bill's sponsors Mr. Burr and Ms. Eshoo and my own Congressman Chairman Bliley, for the invitation to testify in support of H.R. 1795, the National Institute of Biomedical Imaging and Engineering Establishment Act.

Medicine now stands at the threshold of a new and exciting revolution in how we think about disease. It is the molecular revolution wherein we will develop the tools needed to diagnose and treat disease at its earliest stages when the chances of success are likely to be much greater than currently.

Medical imaging must be a critical element in this new paradigm. Medical imaging is the noninvasive biopsy that will detect al-

terations in the genetic or molecular makeup of cells that have the potential to progress to disease. Imaging technologies will precisely determine what faction of cells are affected. Finally, medical imaging technologies will be integrated with new therapeutic methods to either guide or monitor treatment so that only diseased cells are treated while preserving normal tissue.

The basic knowledge exists to begin to implement this vision; however, the current means by which the NIH institutes address imaging research is as a stepchild, a part of the research portfolio of nearly all of the institutes, but the principal focus of none. As a result, basic research into the development of new imaging technologies has been subject to overlap and duplication, inefficient use of resources and lost opportunities.

The initial invention of and basic research into new technologies that have emerged in recent times such as CAT scanning, MRI, and image-guided interventional methods have most frequently occurred outside the U.S. where the logistics and funding of basic research into medical imaging can be handled in a more straightforward and integrated fashion.

The establishment of a new Institute of Biomedical Imaging and Bioengineering would correct many of these structural problems. The institute would address the needs of imaging research directly and comprehensively. It would provide a home and focus for the fundamental disciplines of computer sciences, physics and engineering that are so inextricably connected to progress in imaging research. It would foster basic imaging research lacking in the current NIH structure that would lead to the more efficient development of the new broad-ranging technologies applicable to my vision of molecular medicine.

Through relationships the new institute will develop with regulatory agencies and industry, it would facilitate technology transfer, allowing important innovations to more rapidly be employed in medical care. And very significantly the new institute would foster the more rapid assessment of new technologies as they enter practice to ensure that their use is appropriate and cost-effective.

This last aspect of the institute's proposed functions is critical and is yet another example of how the current institutional structure insufficiently addresses the needs of the American public.

Among my other responsibilities, I am Chair of the American College of Radiology Imaging Network, or ACRIN. ACRIN is a National Cancer Institute-funded cooperative group that through clinical trials gathers information to extend and improve the quality of lives of cancer patients.

ACRIN is a remarkable endeavor that evaluates the effectiveness of imaging technologies in improving health outcomes for individual patients and measures the balance of benefit and costs the American public receives for its expenditure on cancer imaging.

The results of major definitive ACRIN trials of such technologies as digital mammography, a screen for breast cancer, and CAT scan for the detection of early lung cancer will guide medical practice and reimbursement in the years to come.

The National Cancer Institute should be applauded for its vision in establishing ACRIN less than 2 years ago. Yet again, these same technologies that ACRIN will study and many other current and

future technologies are broadly applicable to diseases other than cancer.

There is no counterpart to ACRIN at any of the other institutes. Even if there were, the fragmentation of imaging technology assessment on such arbitrary grounds would be wasteful, inefficient and leave important gaps.

The structural inadequacies that hinder imaging research can be rectified only through an institute. Institutes are the standard NIH administrative units for areas of such significant scientific research. Any entity devoted to biomedical imaging, bioengineering, and related fields will necessarily be of the size that will make any organizational unit short of an institute inappropriate.

Related research occurs in numerous Federal agencies such as the Departments of Defense and Energy, and the National Science Foundation. A subordinate administrative unit would lack the stature necessary to coordinate research involving imaging outside of NIH. For these reasons and for those I have detailed in this testimony, I hope you will vote favorably on H.R. 1795 and pass it on to the full House of Representatives for its consideration. Thank you.

[The prepared statement of Bruce J. Hillman follows:]

PREPARED STATEMENT OF BRUCE J. HILLMAN, CHAIR, DEPARTMENT OF RADIOLOGY, UNIVERSITY OF VIRGINIA SCHOOL OF MEDICINE

Good morning. I am Dr. Bruce Hillman, Chair of the Department of Radiology at the University of Virginia School of Medicine and a Chancellor of the American College of Radiology. I greatly appreciate your invitation so that I may testify in support of H.R. 1795, the National Institute of Biomedical Imaging and Engineering Establishment Act.

During the past thirty years, no specialty of medicine has advanced technologically so much as medical imaging. And no specialty of medicine has so drastically and positively changed the way we detect, diagnose, stage, and treat disease. The introduction during that time period of such computer-based technologies as CAT scanning and MRI, and the use of imaging to guide a host of interventional procedures has revolutionized medicine. As a result, the preferred diagnosis and treatment methods for a broad range of diseases—cancer, heart disease, orthopedic injuries, and infectious diseases, to name just a few—has become less invasive, less expensive, and less risky for patients.

Medicine now stands at the threshold of a new and exciting revolution in how we think about disease. It is the molecular revolution, wherein we will develop the tools needed to diagnose and treat disease at its earliest stages, when the chances of success are likely to be much greater than currently. Virtually everyone agrees that medical imaging must be a critical element in this new paradigm.

Medical imaging is the "non-invasive biopsy", the method of disease quantitation, the guidance for new treatments still to be developed that will form the underpinnings of molecular medicine. Under this scenario, new medical imaging technologies will detect alterations in the genetic or molecular makeup of cells that have the potential to progress to disease. We then will employ imaging technologies to precisely determine what fraction of cells are so affected. Finally, medical imaging technologies will be integrated with new therapeutic methods to either guide or monitor treatment, so that we can much more precisely than ever before ensure that only diseased cells are treated while preserving normal tissue.

The basic knowledge exists to begin to implement this vision. However, for this optimistic and exciting prophecy to come to fruition, we will need to invest in the development and assessment of new imaging technologies. We are ill-equipped to do so under the current NIH organizational structure that focuses the work of existing institutes on specific organ systems and diseases.

Imaging technologies, with few exceptions, are multi-potential. They are applicable to many organ systems and diseases. Their value in detection, diagnosis, staging, and treatment of disease cuts across traditional institute lines. The leadership of existing institutes do not generally have training or expertise in imaging. The requests for applications and the public announcements that are the principal instru-

ments used by institutes to guide research in their respective fields view imaging more as a tool to address disease-specific questions than as a focus for research in its own right. The critical research training of new young imaging investigators, when it is supported at all, is forced into unnatural pathways that address imaging technology research obliquely rather than head-on.

Thus, the current means by which the NIH institutes address imaging research is as a "stepchild"—a part of the research portfolio of nearly all of the institutes but the principal focus of none. As a result, basic research into the development of new imaging technologies has been subject to overlap and duplication, inefficient use of resources, and lost opportunities. The initial invention and basic research into new technologies that have emerged in recent times—such as CAT scanning, MRI, and image-guided interventional methods—have most frequently occurred outside the U.S. where the logistics and funding of basic research into medical imaging can be handled in a more straightforward fashion.

The establishment of a new Institute of Biomedical Imaging and Bioengineering would correct many of these structural problems. The Institute would:

- address the needs of imaging research directly and comprehensively;
- provide a home and focus for the fundamental disciplines of computer sciences, physics, and engineering that are so inextricably related to progress in imaging research;
- provide a home for basic imaging research—lacking in the current NIH structure—that would lead to the more efficient development of the new, broad-ranging technologies applicable to the vision of molecular medicine that I have detailed earlier;
- through relationships the new institute will develop with regulatory agencies and industry, facilitate technology transfer, allowing important innovations to more rapidly be employed in medical care;
- and very significantly, foster the more rapid assessment of new technologies as they enter practice, to ensure that their use is appropriate and cost-effective.

This last aspect of the Institute's proposed functions is critical and is yet another example of how the current institutional structure insufficiently addresses the needs of the American public.

Among my other responsibilities, I am the chair of the American College of Radiology Imaging Network, or ACRIN. ACRIN is a National Cancer Institute-funded cooperative group that conducts clinical trials of medical imaging technologies at community practices and academic health centers across the country. The overriding goal of ACRIN is, through clinical trials, to gather information that will extend and improve the quality of the lives of cancer patients.

ACRIN is a remarkable endeavor that evaluates the effectiveness of imaging technologies in improving health outcomes for individual patients and measures the balance of benefit and costs the American public receives for its expenditures on medical imaging. The results of major, definitive, ACRIN trials of such technologies as digital mammography for screening for breast cancer, CAT scanning for the detection of early lung cancer, and the use of PET scanning for patients' response to chemotherapy will guide medical practice and reimbursement in the years to come.

The National Cancer Institute should be applauded for its vision in establishing ACRIN less than two years ago. Yet again, these same technologies that ACRIN will study, and many other current and future technologies, are broadly applicable to diseases other than cancer. There is no counterpart to ACRIN at the National Heart, Lung, and Blood Institute, or the National Institute for Neural Diseases and Stroke—institutes whose purview includes organ systems and diseases where imaging plays a large and critical role—nor, for that matter, at any of the other institutes. Even if there were, the fragmentation of imaging technology assessment on such arbitrary grounds would be wasteful, inefficient, and leave important gaps.

The unification of imaging technology assessment activities under the aegis of the proposed Institute obviates these concerns. It ensures that assessment activities critical to both the health and financial well-being of the American public will be orderly, strategic, coherent, and efficient and that they will best advise us on how to most wisely expend our resources on imaging technologies as they are employed in medical practice.

The structural inadequacies that hinder imaging research can be rectified only through an institute. Institutes are the standard NIH administrative units for areas of such significant scientific research. An entity devoted to biomedical imaging, bioengineering, and related fields would necessarily be of a size that would make any organizational unit short of an institute inappropriate. Related research occurs in numerous federal agencies, such as the Departments of Defense and Energy and the National Science Foundation. A subordinate administrative unit would lack the stature necessary to coordinate research involving imaging outside of NIH.

For these reasons and those I have detailed in this testimony, I hope that you will vote favorably on HR 1795 and pass it on to the full House of Representatives for its consideration.

Mr. BILIRAKIS. Thank you, Dr. Hillman.

Ms. Tomiko Fraser is the national spokesperson for the Lupus Foundation of America.

Thank you very much for being here today.

STATEMENT OF TOMIKO FRASER

Ms. FRASER. Good morning, Mr. Chairman and members of the subcommittee. I appear before you today representing the Lupus Foundation of America on behalf of the 1.4 million Americans who have lupus erythematosus, a devastating disease that causes the immune system to attack the body's own cells and organs. Unfortunately, one of the victims of lupus is my younger sister Shneequa, who has a very serious case of lupus that affects her brain. The disease has been so devastating to Shneequa that she must receive around-the-clock care at a skilled nursing facility.

That is why I have agreed to serve as the national spokesperson for the Lupus Foundation of America. I want to help educate all Americans about the devastating impact lupus has on its victims.

I urge Congress to pass H.R. 762, the Lupus Research and Care Amendments Act of 1999. Congresswoman Carrie Meek, who lost a sister to lupus, introduced this legislation. Two hundred forty-three Members of the U.S. House of Representatives are cosponsors of H.R. 762.

The legislation authorizes a $23 million increase to the current funding level for lupus medical research supported through the National Institutes of Health. It also authorizes $75 million to fund a grant program. This program would provide local governments, community hospitals, and other nonprofit health care facilities with a pool of funds so they could offer lifesaving medical care to the poor or uninsured people with lupus.

This grant program will help local communities hardest hit by lupus, especially in medically underserved areas including rural and urban communities where often there is a shortage of medical facilities to treat people with lupus.

Lupus deserves special funding consideration. Lupus is the prototypical autoimmune disease. Research on lupus benefits all autoimmune diseases that disproportionately affect women. Autoimmune diseases are the fourth leading cause of disability among women.

Lupus is an expensive disease to treat. The cost to provide medical care for a person with lupus averages between 6- and $10,000 annually. The Lupus Foundation of America estimates the economic impact of lupus on the Federal Treasury to be several billion dollars every year. These costs include disability income payments to the tens of thousands of lupus victims disabled every year by the disease. They also include the cost of government-sponsored medical care provided through the Medicare and Medicaid programs and uncollected tax revenue due to lost wages when individuals with lupus are unable to work.

The Lupus Research and Care Amendments Act of 1999 is a bipartisan effort to address an urgent national health care crisis that

inflicts an enormous burden on individuals, families, the business community, the Federal Government and society. Many scientific opportunities exist, but current funding levels can support only one in four of the promising studies submitted for funding that eventually lead to a cure for lupus. By accelerating medical research for lupus now, Congress will reduce future health care costs and save billions of dollars for the Social Security and Medicare Trust Funds in future years.

Lupus is a complicated and mysterious disease that needs extensive study. Presently there is no cure for lupus, nor do researchers fully understand what causes the disease. We do not know why lupus alternates between periods of remission and periods of disease activity called flares. We do not know why the disease can remain mild in some individuals and become life-threatening in others. What we do know, Mr. Chairman, is that lupus has a devastating impact on its victims and their families. We know that lupus causes debilitating health effects including extreme joint pain and swelling, constant fevers, overwhelming fatigue, horrible skin rashes, organ failure and a host of other devastating symptoms.

Lupus destroys the quality of life for many of its victims. The disease can severely damage the kidneys, heart, lungs and other vital organs. Lupus disables one in five of its victims, often at a very young age, and tragically every year thousands of lupus victims die from complications of the disease.

Lupus is not an equal opportunity disease. Ninety percent of the victims of lupus are women. Also, lupus is more common among women of color. Lupus is two to three times more likely to affect African Americans, Hispanics, Asians and Native Americans than Caucasian women. Lupus also appears to be more serious among African American women.

Approximately 20 percent of lupus cases begin in childhood. Unfortunately, lupus is more severe in children. Nearly 70 percent of children with lupus have kidney disease as opposed to 30 percent of adults who develop lupus. Whereas half of those with adult onset lupus have organ-threatening disease, nearly 80 percent of those with childhood onset lupus go on to develop organ-threatening conditions.

Lupus strikes women in the their childbearing years between the ages of 15 and 44. This is one of the most devastating realities of lupus. It destroys the quality of life during a time when young women should be enjoying their best health.

Many people with lupus suffer 3 to 5 years, visiting 5 or more doctors before they receive a correct diagnosis. Many medical schools do not provide family physicians with sufficient training to diagnose lupus. By the time some lupus patients are diagnosed, especially in poor or rural communities, irreversible damage to vital organs may have already occurred. This increases the need for expensive treatments such as kidney dialysis or transplantation.

Medical researchers have made progress, and there is great hope for new discoveries. Still, most lupus patients are frustrated that the disease remains incurable.

As you can imagine, Mr. Chairman, lupus is not an easy disease to live with. Over a million American families are struggling to

cope with lupus every day of their lives. I know this personally from watching my sister suffer from the devastating effects of the disease.

It is time for action. A majority of Members of the U.S. House of Representatives, a total of 243, are cosponsor of H.R. 762. I urge that this legislation be brought to the floor of the House for a vote as soon as possible.

Thank you for the opportunity to represent the victims of lupus at today's hearing, and I will be happy to answer any of your questions. And thank you for the extra time.

[The prepared statement of Tomiko Fraser follows:]

PREPARED STATEMENT OF TOMIKO FRASER, NATIONAL SPOKESPERSON, LUPUS FOUNDATION OF AMERICA

Good Morning Mr. Chairman, and Members of the Subcommittee. I appear before you today representing the Lupus Foundation of America on behalf of 1.4 million Americans who have lupus erythematosus, a devastating disease that causes the immune system to attack the body's own cells and organs.

Unfortunately, one of the victims of lupus is my younger sister, Shneequa, who has a very serious case of lupus that affects her brain. The disease has been so devastating to Shneequa that she must receive around-the-clock care at a skilled-nursing facility.

That is why I have agreed to serve as a National Spokesperson for the Lupus Foundation of America. I want to help educate all Americans about the devastating impact lupus has on its victims.

I urge Congress to pass H.R. 762, the Lupus Research & Care Amendments Act of 1999. Congresswoman Carrie Meek, who lost a sister to lupus, introduced this legislation. *243 members of the U.S. House of Representatives are cosponsors of H.R. 762.* The legislation authorizes a $23 million increase to the current funding level for lupus medical research supported through the National Institutes of Health. It also authorizes $75 million to fund a grant program. This program would provide local governments, community hospitals, and other non-profit health care facilities with a pool of funds so they could offer life-saving medical care to poor or uninsured people with lupus.

This grant program will help local communities hardest hit by lupus, especially in medically under-served areas, including rural and urban communities where often there is a shortage of medical facilities to treat people with lupus.

Lupus deserves special funding consideration. Lupus is the prototypical autoimmune disease. Research on lupus benefits all autoimmune diseases that disproportionately affect women. Autoimmune diseases are the fourth leading cause of disability among women.

Lupus is an expensive disease to treat. The cost to provide medical care for a person with lupus averages between six and ten thousand dollars annually. *The Lupus Foundation of America estimates the economic impact of lupus on the federal treasury to be several billion dollars every year.* These costs include disability income payments to the tens of thousands of lupus victims disabled every year by the disease. They also include the cost of government-sponsored medical care provided through the Medicare and Medicaid programs, and uncollected tax revenue due to lost wages when individuals with lupus are unable to work.

The Lupus Research and Care Amendments Act of 1999 is a bipartisan effort to address an urgent national health care crisis that inflicts an enormous burden on individuals, families, the business community, the federal government, and society. Many scientific opportunities exist, but current funding levels can support only one in four of the promising studies submitted for funding that eventually will lead to a cure for lupus. By accelerating medical research for lupus now, Congress will reduce future health care costs and save billions of dollars for the Social Security and Medicare trust funds in future years.

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We do not know why lupus alternates between periods of remission and periods of disease activity, called flares. We do not know why the disease can remain mild in some individuals and become life-threatening in others.

What we do know, Mr. Chairman, is that lupus has a devastating impact on its victims and their families. We know that lupus causes debilitating health effects including extreme joint pain and swelling, constant fevers, overwhelming fatigue, horrible skin rashes, organ failure, and a host of other devastating symptoms. Lupus destroys the quality of life for many of its victims. The disease can severely damage the kidneys, heart, lungs, and other vital organs. Lupus disables one in five of its victims, often at a very young age. And tragically, every year thousands of lupus victims die from complications of the disease.

Lupus is not an equal opportunity disease. Ninety percent of the victims of lupus are women. Also, lupus is more common among women of color. Lupus is two to three times more likely to affect African-Americans, Hispanics, Asians and Native-Americans than Caucasian women. Lupus also appears to be more serious among African-American women.

Approximately 20% of lupus cases begin in childhood. Unfortunately, lupus is more severe in children. Nearly 70% of children with lupus have kidney disease, as opposed to 30% of adults who develop lupus. Whereas half of those with adult-onset lupus have organ-threatening disease, nearly 80% of those with childhood-onset lupus go on to develop organ-threatening conditions.

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Medical researchers have made progress; and there is great hope for new discoveries. Still, most lupus patients are frustrated that the disease remains incurable.

As you can imagine, Mr. Chairman, lupus is not an easy disease to live with. Over a million American families are struggling to cope with lupus every day of their lives. I know this personally from watching my sister suffer from the devastating effects of this disease.

It's time for action. *A majority of members of the United States House of Representatives—a total of 243—are cosponsors of H.R. 762.* I urge that this legislation be brought to the floor of the House for a vote as soon as possible. Thank you for the opportunity to represent the victims of lupus at today's hearing. Now I will be happy to answer your questions.

Mr. BILIRAKIS. Thank you very much, Ms. Fraser.

Dr. Bryan.

STATEMENT OF R. NICK BRYAN

Mr. BRYAN. Good morning. My name is Nick Bryan. I currently serve as professor and Chairman of the Department of Radiology at the University of Pennsylvania. I really appreciate this opportunity to share some of my experiences as an imaging researcher and a former NIH staff member with you and to express my support for H.R. 1795.

I would like to thank you, Mr. Chairman, and the committee leadership for holding this hearing, and I would like to thank the sponsors of the bill, Mr. Burr and Mrs. Eshoo, for their leadership and efforts on this issue.

You have already heard about the importance and uniqueness of biomedical imaging and engineering, and I will not belabor the point. I will instead focus on what I view as current structural inadequacies to support this field in NIH.

Prior to coming to Penn, I served for 2 years as Director of Diagnostic Radiology and Associate Director, Imaging Sciences Program, at the Warren G. Magnuson Clinical Center at the NIH. During my tenure, and with superb support from Dr. John Gallen, director of the clinical center, we were able to consolidate several

disparate imaging departments into a unified imaging sciences program, which elevated the status of imaging research on the NIH campus and began to lay a foundation for an advanced research program.

In the final analysis, though, I felt the imaging sciences program could not be wholly successful mainly because the very structure of the NIH makes such an endeavor problematic. Research authority and resources reside in the institutes, not in programs at the clinical center. As a result, the success of our imaging research was ultimately dependent on the ability of me and my colleagues to convince one or more of the institutes, institutes whose primary missions and priorities are in areas other than imaging, to divert funds from their main activities and commit those funds to imaging research.

I accepted the position at the clinical center knowing that it involved a significant challenge, but in the hope and in the belief that an effective imaging research program could be developed within the parameters of the NIH structure. In fact, at that time I was skeptical about the need for a new institute. My experience, however, gradually changed my opinion and convinced me that the existing NIH organization will not work optimally for imaging in bioengineering.

Ultimately, my decision to leave the NIH owed much to the inherent obstacles to imaging research that are built into its structure. It should be recognized that the NIH does acknowledge the importance of imaging and has taken steps to make imaging research a more visible part of its portfolio, as you heard. And, for instance, the National Cancer Institute has authorized significant expansion of the extramural biomedical imaging program.

The NIH Biomedical Engineering Consortium, known as BECON, sponsored a conference in 1999 entitled Biomedical Imaging Symposium: Visualizing the Future of Biology in Medicine. This year the NIH, in response to a congressional mandate, has begun to organize a new Office of Bioimaging, Bioengineering and Bioimformatics in the Office of the Director of the NIH. The new office is to provide focus for and facilitate work in our fields.

Unfortunately, all of these initiatives suffer from major flaws. First, the NCI program applies real resources to imaging, but the research is limited to cancer imaging. Cancer imaging is clearly important and should be extremely high priority, but imaging, as I have said, is not disease- or organ-system-specific. It has applications far beyond cancer, applications that are neglected when the research focus is on cancer or any other individual disease.

Initiatives such as BECON and OB3, as it is called, the new office, constitute a useful effort to identify research opportunities and focus attention on imaging, but they bring little in the way of actual research dollars to imaging research. They represent a strong commitment by the NIH to identify potentially fruitful areas of research, but no commitment at all to supporting that research.

The Director of the OBBB will have to do what I did. He or she will have to pass the hat by the current institutes for contributions, and I am certain that the donations will be insufficient to support a robust imaging research program.

In fact, it is unrealistic and perhaps even inappropriate to expect existing disease and organ system institutes to divert resources from their primary missions in order to support basic research to advance the science of imaging. For these reasons I believe that the creation of a National Institute of Biomedical Imaging and Bioengineering is essential to promote the development of new imaging techniques and technologies.

In order to flourish and grow consistently at the NIH, a scientific field requires organizations with the mandate, the responsibility, the authority, and the resources to direct and drive investigation in that field. In the NIH structure, institutes possess those attributes.

I would like to conclude by noting that my opinions are not alone. Nearly all of radiology and bioengineering supports this is initiative. During the current year, I am also privileged to serve as Chairman of the Board of Directors of the Radiological Society of North America. The RSNA is the largest radiological organization in the world, with a membership of more than 30,000 radiologists, physicists, and allied scientists. The RSNA and more than 40 other professional organizations representing physicians, radiologic technologists, bioengineers and imaging scientists have joined coalitions that support H.R. 1795. The total individual membership of these organizations is well over 100,000.

All of us believe that this is the time to create a National Institute of Biomedical Imaging and Bioengineering to support a field of inquiry that is central to continued progress in advanced research in biomedicine as well as the development of better systems for delivery of health care. This institute would be good for patients, physicians, and the NIH itself.

I urge the subcommittee to approve this bill. I would be pleased to answer any questions.

[The prepared statement of R. Nick Bryan follows:]

PREPARED STATEMENT OF R. NICK BRYAN, CHAIRMAN, DEPARTMENT OF RADIOLOGY, UNIVERSITY OF PENNSYLVANIA HEALTH SYSTEMS

Good morning. My name is Nick Bryan. I have been a radiologist specializing in neuroradiology for more than 25 years. I currently serve as Chairman of the Department of Radiology and Eugene P. Pendergrass Professor of Radiology at the University of Pennsylvania. Prior to coming to Penn, I served for two years as Director of Diagnostic Radiology and Associate Director, Radiologic and Imaging Sciences Program, at the Warren G. Magnuson Clinical Center at the National Institutes of Health.

During the current year I am also privileged to serve as Chairman of the Board of Directors of the Radiological Society of North America. The RSNA is the largest radiological organization in the world, with a membership of more than 30,000 radiologists, physicists, and allied scientists.

I appreciate this opportunity to share some of my experiences as an imaging researcher and NIH staff member with you and to express my support for H.R. 1795, the National Institute of Biomedical Imaging and Engineering Establishment Act. I would like to thank you, Mr. Chairman, and the Committee leadership for holding this hearing and the sponsors of the bill, Representatives Burr and Eshoo, for their leadership and efforts on this issue.

It is important to note that all of radiology and imaging supports this initiative. More than 40 separate professional organizations representing physicians, radiologic technologists, bioengineers, and imaging scientists have joined coalitions that support H.R. 1795. The total individual membership of these organizations is well over 100,000.

This is perhaps the most exciting time in the history of medical imaging and, indeed, all of medicine. Breakthroughs in imaging have allowed physicians to elimi-

nate much surgery, including virtually all exploratory surgery, and to diagnose disease at earlier and earlier stages of development, when treatment is most effective. Because of advances in imaging, patients receive more effective treatment, avoid painful, expensive, and often dangerous surgical procedures, and live longer.

The National Institutes of Health is the premier medical research institution in the world and has been at the center of pathbreaking research in most areas of medicine. In imaging, however, the NIH is not—and under its present structure cannot be—the catalyst of imaging innovation. The various institutes are focused on specific disease processes or organ systems, but imaging cuts across those lines and is broadly applicable to virtually all diseases and organ systems. Consequently, imaging is used as a tool in all the institutes, but there is no home at the NIH for the basic research that is essential to develop new imaging techniques and technologies for the 21st century.

The basic science of imaging and bioengineering, it must be remembered, is fundamentally different from that of the existing institutes at the NIH. Imaging is based on mathematics and physics, not the biological sciences that underly most of the research in the current institutes. Imaging and bioengineering are unique scientific fields at the NIH and are also critical to future advances in the delivery of high quality health care.

While at the NIH, I directed intramural research efforts in imaging in the Clinical Center. During my tenure, we were able to consolidate several disparate imaging departments into the unified Imaging Sciences Program (ISP), which elevated the status of imaging research on the NIH campus and began to lay a foundation for an advanced research program.

In the final analysis, though, the ISP could not be wholly successful, mainly because the very structure of the NIH makes such an endeavor problematic. Research authority and resources reside in the institutes, not in programs at the Clinical Center. As a result, the success of imaging research proposals was ultimately dependent on the ability of ISP researchers to convince one or more of the institutes—institutes whose primary missions and priorities are in areas other than imaging—to divert funds from their main activities and commit those funds to imaging research. Even when imaging researchers are successful, which sometimes requires artificially tailoring proposals to create the appearance of disease- or organ-specific research, the institutes are likely to assume practical control of projects and, in all probability, recast the research to fit their own missions.

I accepted the position at the Clinical Center knowing that it involved a significant challenge but in the hope, and in the belief, that an effective imaging research program could be developed within the parameters of the NIH structure. In fact, at that time I was skeptical about the need for a new institute. My experience, however, gradually changed my opinion and convinced me that the existing NIH organization will not work for imaging. Ultimately, my decision to leave the NIH owed much to the inherent obstacles to imaging research that are built into its structure.

It should be recognized that the NIH has taken steps to make imaging research a more visible part of its portfolio. The National Cancer Institute, for example, has designated imaging as one of only a few "Extraordinary Opportunities for Investment" and has authorized significant expansion of the extramural Biomedical Imaging Program. The Biomedical Imaging Program at the NCI, under the extremely able leadership of Dr. Dan Sullivan, has benefited from growing staff resources and new research initiatives.

In addition, the Bioengineering Consortium, known as BECON, sponsored a conference in June 1999 titled "Biomedical Imaging Symposium: Visualizing the Future of Biology and Medicine." Participants produced an ambitious research agenda for imaging science that calls for focused efforts in a number of fields:

—multidisciplinary research;
—imaging technology, probes, and contrast agents;
—education and training;
—clinical trials and informatics
—greater cooperation among the NIH, the Food and Drug Administration, the Health Care Financing Administration, and private industry to improve the speed with which new imaging technologies, probes, and contrast agents are transferred to clinical practice.

The 1999 BECON symposium was actually the second NIH-sponsored conference in recent years devoted to imaging research. In 1994, the NIH brought together more than 40 top researchers from inside and outside government at a Conference on Developing a Long-term Plan for Imaging Research. Conference participants developed a set of recommended research goals in 33 separate areas of basic science, basic and applied technology, and organ-based clinical research.

Finally, this year the NIH, in response to a Congressional mandate, has begun to organize a new Office of Bioengineering, Bioimaging, and Bioinformatics in the Office of the Director, NIH. According to the Vacancy Announcement seeking candidates to direct the OBBB, the Director of the new Office "will provide a focus for stimulating and coordinating the development of biomedical engineering, bioimaging and bioinformatics activities among the 25 Institutes and Centers (ICs) at the NIH; and will facilitate the overall planning, development, and implementation of NIH biomedical engineering, bioimaging and bioinformatics research programs and activities."

Unfortunately, all of these initiatives suffer from one of two fatal flaws. First, the NCI efforts apply real resources to imaging, but all of the research is on cancer imaging. Cancer imaging clearly should be an extremely high priority, but imaging, as I have said, is not disease- or organ-system specific. It has applications far beyond cancer—applications that are neglected when the research focus is on cancer or any other individual disease.

ACRIN, the cooperative clinical trials group chaired by Dr. Hillman, offers a clear example of the shortcomings of this approach. ACRIN represents a significant and wise investment, but this application of resources could produce so much more if imaging technologies beyond cancer were included.

The ACRIN approach, valuable as it is, actually shortchanges cancer research as well as the broader field of imaging. Evaluating the use of existing techniques and technologies for the diagnosis and treatment of breast, prostate, and other cancers will produce important knowledge that will result in incremental improvements in patient care. But the real breakthroughs that will produce quantum leaps forward are likely to occur through the development of wholly new imaging modalities that do not result from disease-specific research.

The second group of NIH initiatives—the 1994 conference, the BECON symposium, and the creation of the OBBB—represents the second fatal flaw. These initiatives constitute a useful effort to identify research opportunities and focus attention on imaging, but they bring little in the way of actual research dollars to imaging. They represent a strong commitment by the NIH to identify potentially fruitful areas of research but no commitment at all to supporting that research.

The Director of the OBBB will be, as I was as Director of the Imaging Sciences Program, dependent on the goodwill and interest of the other institutes. Again, these are institutes that do not have imaging as primary missions and which are faced continually with competing claims for scarce resources from within their primary research constituencies.

The disciplines represented in the existing institutes use imaging, but they cannot accommodate the basic science of imaging itself. It is unrealistic, and perhaps even inappropriate, to expect the existing disease and organ system institutes to divert resources from their primary missions in order to support basic research to advance the science of imaging.

Without grant-making and decision-making authority, these NIH efforts to improve coordination can be marginally successful at best. No one would suggest that the search for better treatments for cancer, diabetes, or other diseases should be undertaken by organizations that lack the capability to make research grants—or that progress in these vital areas should be dependent on the ability of researchers to convince other institutes to divert a portion of their resources away from their chief responsibilities. Yet that is precisely the approach the NIH has taken to imaging. In consequence, while the NIH might consider the recommendations from the 1994 and 1999 imaging conferences to be priorities, there is not much evidence that significant action has been taken on this research agenda. The present organization of the NIH makes such action unlikely.

For these reasons, I believe that the creation of a National Institute of Biomedical Imaging and Bioengineering is essential to promote the development of new imaging techniques and technologies. In order to flourish and grow consistently at the NIH, a scientific field requires an organization with the mandate, the responsibility, the authority, and the resources to direct and drive investigation in that field. In the NIH structure, only institutes possess those attributes.

Institutes, for example, can issue Requests for Applications (RFAs) and Program Announcements (PAs) to initiate research projects and direct resources toward investigations on specific subjects that offer particular opportunities for scientific advances. Such institute-initiated research projects represent a substantial portion of the institutes' extramural research portfolios. Even smaller and mid-sized institutes can exert considerable influence on the direction of research. A recent analysis showed that the National Institute on Aging (NIA), with only the 10th largest budget among the institutes and major centers at the NIH, issued seven RFAs covering a wide variety of topics with a total price tag of more than $16 million in Fiscal

Year 1999. In the same year, the NIA collaborated on 16 additional RFAs in which other institutes were the primary sponsors. Without an institute, imaging lacks this fundamental capability to guide and support the research in this field.

Research training is another key issue. Training grants ensure the continuity of a pool of trained researchers in the institutes' fields of research. Under the current structure, training opportunities in imaging are generally limited to grants that focus on the use of imaging in connection with specific diseases and organ systems rather than on training imaging scientists to conduct the basic research that will produce new modalities. An analysis of NIH data on T32 grants, the most common NIH training awards, found only three imaging awards of the 148 active T32 grants in the National Heart, Lung, and Blood Institute. Moreover, the National Institute of Neurological Disorders and Stroke (NINDS), which is the institute most closely related to my work in neuroradiology, had no active imaging grants among its 44 T32 awards.

The National Institute of Biomedical Imaging and Bioengineering would help to ensure that the brightest young radiologists and imaging scientists have opportunities to obtain research training. Such opportunities are largely non-existent under the present system.

For all of these reasons, I believe that this is the time to create a National Institute of Biomedical Imaging and Bioengineering to support a field of inquiry that is central to continued progress in advanced research in molecular biology as well as to the development of a better system for the delivery of health care. The proposed would be good for patients, physicians, and the NIH itself. I urge the Subcommittee to approve H.R. 1795, and I would be pleased to answer questions.

Mr. BILIRAKIS. Thank you so much, Dr. Bryan.

I will start off the questioning.

Ms. Fraser, why does lupus seem to affect women of color more often than Caucasian women?

Ms. FRASER. Well, this is a subject of a research project currently under way by the NIH Lupus and Minority Studies, or LUMINA. We believe lupus has a genetic basis, and it appears that the gene suspected of causing lupus may be more prevalent among women of color.

Mr. BILIRAKIS. So we sort of know that or have come to that conclusion on the basis of studies that are taking place?

Ms. FRASER. Yes. That is correct.

Mr. BILIRAKIS. We do not know of any other reason, though, other than the fact?

Ms. FRASER. Not yet, we are still checking.

Mr. BILIRAKIS. In terms of the administration's support or nonsupport of the legislation, my understanding—and I may be wrong, and if I am, I wish to be corrected, but I think it is significant—that they have problems with title 2. The administration has problems with title 2. Are you aware of that?

Ms. FRASER. I would be happy to answer that, but I would like to submit a written response to that question, if that is okay with the chairman.

Mr. BILIRAKIS. Okay. Yes, we would like to have that from you, by all means, because it would be very helpful in terms of not only moving the legislation through, but we also try to work with the Minority in most cases to work things out ahead of time, and that would be very significant.

Dr. Wirth, can you tell us the organizations, or at least some of the organizations, you are familiar with that are working on the issue of global disease eradication?

Ms. WIRTH. Well, there are several organizations in the world. The World Health Organization is very active in this area, but the World Health Organization is more of an implementation organiza-

tion rather than a research organization. They have a very small research arm.

Really the United States is really the only—the United States National Institutes of Health and to a certain extent the NSF are really the only organizations that have the knowledge base and the research base to bring that to bear on these important tropical diseases. There is some work in Europe funded by the European Union, but, again, I think the United States really has the leadership role, and we need to maintain that.

Mr. BILIRAKIS. I know—I am a Rotarian. Do not attend very many meetings these days for business reasons, but in any case they have worked on eradicating polio around the world, as you know.

Ms. WIRTH. That is correct.

Mr. BILIRAKIS. And that is working and has worked very well; has not it?

Ms. WIRTH. Uh-huh. Polio actually will be eradicated in this hemisphere this year. And there have been many groups involved in that, and certainly the Rotary has been involved particularly in the last several years.

And, again, I think that is implementing a very important step, implementing the sort of research in discoveries that have been made over the years primarily here in the United States. So I think there are many steps to eradicating global disease. We have to get those vaccines and drugs that we have to the people who need them, and that is very important. But we also need for many of these diseases to develop new interventions. The tools we have just aren't working.

Mr. BILIRAKIS. Okay. So the World Health Organization is just not doing the job, and you feel that the national commission that Mr. Gekas is a proponent of would do the job?

Ms. WIRTH. I think so. And it would particularly establish the United States in its natural leadership role in this area. I think that we need political leadership at this point to bring to bear on this problem. We have the skill set in the United States to develop these interventions and to implement them, but we need to take that leadership role in the world.

Mr. BILIRAKIS. Do we have now—and if not, is that the reason maybe for the national commission—do we have the proper coordination? For instance, I don't know, how has Rotary gone about it all to know exactly where to go? Have they coordinated?

Ms. WIRTH. That is right. I think one of the things that the National Commission could do is to have a focus point for this kind of work in the United States. I think in the case of Rotary and other nongovernmental organizations, they have sort of gone about it themselves, having to go to different agencies, to different interest groups to begin to find out about it, and then to become involved with the implementation.

Mr. BILIRAKIS. Well, let me ask you this. If this commission is formed, the administration feels that CDC and NVPO, the National Vaccine Program Office, should be included in the composition of the commission's membership. And also that the FDA, as the agency overseeing vaccine safety and approval of new vaccines, should also have a role in it if the bill is enacted. Your opinion?

Ms. WIRTH. I think that those, particularly the CDC and the FDA, would be appropriate to become involved in this. They have implementation roles. And I think the national vaccine program is also one that certainly could be involved. They are dealing very specifically with vaccine issues. As you know, there are broader issues of implementation including drug development and development of other controlled, measured environmental and insecticides at some point.

Mr. BILIRAKIS. Any other opinions regarding that particular legislation that you all may want to offer?

All right. That being the case, the Chair yields to Mr. Brown.

Mr. BROWN. Thank you, Mr. Chairman.

Dr. Wirth, I am sorry I missed your testimony. I was voting. But I read your testimony, and you said, as we begin the 21st century, we are blessed with unimaginable opportunities to build on breakthrough research to control and prevent world disease.

Dr. Gro Brundtland of the World Health Organization—I would argue that the World Health Organization has done phenomenal work over the last 20 years. Nonetheless, she said talking about tuberculosis—and I know your expertise is more malaria, and I want to get to that in a second, but she said it is not medical eradication—dealing with tuberculosis is not a medical problem, it is a political problem. But—and I think back just less than a year ago in December 1999, the Government of India, working with nongovernment organizations around the world, including the World Health Organization, including all kinds of groups from this country, had a national immunization day and immunized 134 million children in 1 day, which tells me that Mr. Gekas's bill goes in the right direction in this country. Our country should show a great deal more leadership in dealing with issues that surely we can.

Tuberculosis and malaria both do not get the attention from the big drug manufacturers in their research arms that they should. The drug companies seem much too interested, in my mind, in "me too" drugs, in drugs that are more cure for baldness than for tuberculosis, malaria, lupus, a whole host of diseases where there simply is not the moneys, potential profit available. There is not a lot of profit in malaria or TB especially, diseases that hit this country not very hard and hit the poorest countries with the poorest citizens especially hard.

Shift gears to Walter—Walter Reed has done especially and the Defense Department has done especially good research in malaria. We underfund Walter Reed. We fund organizations like NIH, a wonderful government agency. We want to double its budget in the next 5 years, yet we do not fund CDC very well, which its budget is about one-sixth of the NIH. And we do not fund the Walter Reed research arm of the Defense Department particularly well, putting it mildly.

Is the only real hope for a malaria vaccine, TB vaccine, better treatment of those diseases—TB, as you know, you need to take a pill every day for 6 months, which in countries with military occupation, in places like Chiapas in southern Mexico, people are afraid to go by the military checkpoint to get their TB pills every day. And even though we can cure it, it is difficult because of that. Is the only hope for a TB vaccine or malaria vaccine better medicines

to treat those two diseases? Must there be government funding because the drug companies won't do it? And what do we need to do? Talk about malaria. What do we do with Walter Reed in the Defense Department, and what do we do with NIH and CDC on malaria? Even though it is not a great issue for me to go back to my district in Ohio and say, I am working on malaria and TB, it does not matter much directly today to citizens of this country, it will down the road, and that is a whole other issue. But what do we do with places like Walter Reed?

Ms. WIRTH. I share your respect for Walter Reed and the work they have done over the last several years in developing antimalarial drugs. They really are the only group that has consistently maintained a research program, even in spite of very limited funding.

And, in fact, I think that the solution to these diseases is going to require a very large governmental component because the pharmaceutical industry, as you say, is driven by developing drugs that are important for this country. These are important drugs for this country, but the diseases of tuberculosis and malaria and many other diseases found in tropical countries just will never have profits like drugs for diseases in this country. The drug companies will not develop them. And I think we are going to have to—it is going to require governmental intervention and governmental funding.

I recommend that Walter Reed certainly receive funding, that the NIH receive funding for basic research and for translational research, something I think that the NIH has become very interested and very active in.

And in terms of CDC, CDC is our implementation arm; once we have these tools, we have to get them out. And, in fact, for many diseases we could certainly improve the situation today just by better implementation of the tool we have. We still face the challenges, but certainly better implementation through CDC is important. So I recommend support for all of these organizations, and let me correct myself if I misspoke. I certainly have a great deal of respect for the World Health Organization, but I think they need help and they need leadership from the United States. Their budget is very small compared to the budget of the NIH, for example, and I think they provide a forum, but I think they need help from us, and I think we can assume the leadership role in these diseases.

Mr. BROWN. Thank you.

One last brief question. Should Walter Reed and the CDC be included in this bill, both?

Ms. WIRTH. Yes. I think that is an excellent idea.

Mr. BROWN. Okay. Thanks.

Mr. BILIRAKIS. Mr. Burr to inquire.

Mr. BURR. Thank you, Mr. Chairman.

Dr. Wirth, I don't know that you misspoke, I don't think you need to apologize. Sherrod and I participated in the same hearing in International Relations on the threat of global infections, a debate over whether it was a public health issue or whether it is a national security issue, and I think we can all agree it is probably (d) All of the above.

Clearly the World Health Organization and other international organizations that are targeted toward health issues have been effective on some things. Clearly there are other things where health care professionals have pointed out the deficiencies that exist; and with deficiencies in place, we cannot be assured of successful immunization or successful eradication of diseases that ultimately we see as a threat, not only here but spreading throughout the globe.

And your reference to AIDS in Africa is a very good one. It is important that we recognize that that spread, as it begins to happen in Asia, is of a magnitude that we have never seen before, potentially; and that every effort that we can make, not relying on any one entity, is in fact the policy that we should adopt.

And I appreciate your allowing me to editorialize just a little bit.

Let me move to some of the other witnesses if I can because I do have some real interest in another piece of legislation. Let me turn to you, Dr. Bryan.

Who benefits? Who benefits from the creation of an institute for biomedical imaging?

Mr. BRYAN. Well, the people who benefit the most will be the patients.

Mr. BURR. Isn't that who it is all supposed to be about?

Mr. BRYAN. That is exactly right.

Mr. BURR. For any person who is on the fence about this issue as to whether we should create this, if they stopped for a minute and thought, who is this about; if their answer was, the patients, then the answer is, vote for this bill.

Mr. BRYAN. I would agree.

Mr. BURR. Is it safe to say—and I open this up to anyone—as we identify breakthroughs in technology, that we can also expect health care costs to possibly decline because if we detect earlier, our treatments may be less intensive as it relates to a period of time; and if you looked at the patient from that standpoint, the quality of the care we deliver might in fact be better because we have put them through less?

Mr. HILLMAN. That has been the history of the development of imaging technologies: that, in fact, they do detect disease earlier, they do replace more morbidity-inducing, more illness-inducing technologies. And over time I believe that imaging technologies have been cost-saving and also improve patient outcomes.

Mr. DUNNICK. I would like to make two comments in response to that. First, when the DRGs were established a number of years ago, my assumption was that the medical centers would try to reduce the number of ancillary tests being performed. In fact, just the opposite occurred. We went to more ancillary testing in an effort to get to the answer faster, which in the long run will reduce the cost of medical care.

My second comment is a reflection of my own experience. When I was a medical student, my first research project was with influenza, and we tried to use immunization to protect against that disease.

We use death as the end point. Fortunately, we were using mice as an animal model to test that. As we move along, radiology has become very good at identifying disease processes being able to

quantify them in many cases. And so we can use changes in imaging assessment as the end point for testing this.

We are now in what we call the era of molecular imaging or functional imaging, where we can actually detect changes before they become manifest with routine testing. This allows us to see the changes, see whether treatment is effective before the disease has gotten out of control. I think these will make dramatic changes in decreasing the cost of health care.

Mr. BURR. Can any of you address a specific disease where, say, in the last decade the imaging improvements have changed in——

Mr. DUNNICK. Absolutely. Trauma would be the first response to that. The patient comes into the emergency room, and in fact it does not even have to be a traumatic injury. It can be a patient with abdominal pain and the conventional way to treat that would be first to do an operation to open the abdomen and find where the pathology is.

We can do that noninvasively. In the trauma setting specifically, we can now identify not only the problem, but in many cases, quantify it, which enables more conservative therapy.

So it has resulted in a dramatic decrease in the number of patients that have to go to the operating room.

Mr. BURR. Let me ask one last question with the chairman's indulgence.

One of the fears that I have is that we are successful and that not only in imaging, but in other areas of medical breakthroughs, we are successful. Technological improvements have not necessarily been rewarded through the reimbursement process in this country, specifically Medicare.

If, in fact our reimbursement system does not recognize the cost of technology and the cost of this research, what will that do to further development of new innovations, new treatments, new imaging that might detect disease earlier?

Mr. BILIRAKIS. Important question, but brief answers, please.

Mr. HILLMAN. Yes, there are two things that this new institute will be able to do better than we are currently: One, as I indicated, that it will have an assessment component that will run clinical trials in a timely fashion to provide the information to guide reimbursement. In fact that has been problematic under the current NIH structure.

The other is that we will develop relationships directly with the regulatory agency and payers to quickly move these technologies into practice.

Mr. BURR. I thank the witnesses. I thank the chairman. I yield back.

Mr. BILIRAKIS. Dr. Ganske.

Mr. GANSKE. Thank you, Mr. Chairman, for having this hearing. I think there are several bills that we are talking about that have merit, and while they may not be the biggest health care issues that Congress is facing, such as prescription drugs or patient protection legislation or even, for that matter, a bill that this committee will be doing shortly on providing relief for Medicare, in particular, I hope, relief for rural hospitals.

I just completed my series of town hall meetings back in the district, and I get asked a lot about the high cost of prescription

drugs, and I find that there is one of these bills that I think relates to that and that is the Orphan Drug Act which created incentives for drug companies to develop therapies for rare diseases by awarding a period of 7 years of market exclusivity to a product approved for an orphan indication.

I find the testimony of Mr. Thomas Lang to be convincing. He says in his testimony, recently FDA has adopted a policy position related to the scope of a clinically superior orphan drug's exclusivity that actually undermines the incentives for companies to continue to innovate for additional improvements in these areas. As noted earlier, FDA's policy also raises questions of fairness, alternate product availability and patient and physician choice of therapy.

Now, after approval an original orphan drug, whenever a subsequent orphan drug with a clinically superior improvement has also been approved and awarded exclusivity, FDA totally restarts the 7-year exclusivity clock for the drug as a whole, and in this way the improved drug shields the original drug from competition, even when—after the original drug's exclusivity period is over. In these instances, companies that have developed new competing versions of the same drug to treat the disease in anticipation of the expiration of the original 7-year exclusivity are unfairly denied access to the market for an additional 7-year period.

I think this has pertinence to the high cost of prescription drugs. And Congress, even in the short time period that we have left, should significantly look at the Thornberry bill, H.R. 4242, because I think that additional extensions of exclusivity will surely keep prices higher. That is why I and others have been fighting an extension of—patent extension for the drug Claritin.

And so, Mr. Chairman, I again thank you for holding this hearing. I thank the people for testifying. I have another hearing that is ongoing at this moment that I will be going to and I will yield back.

Mr. BILIRAKIS. And I thank the gentleman. If he would yield to me maybe 30 seconds of his time before me yields——

Mr. GANSKE. I will.

Mr. BILIRAKIS. You know we have a dilemma here in terms of, let's say, NIH funding. Let's just talk NIH funding, and the dilemma is, should we in this so-called ivory tower determine the amount of money for research that ought to go to specific diseases? I mean, the experience that we have had on this committee has been just amazing, the number of diseases that I am sure most of us, if any of us, although some are medical doctors, were not even aware of.

Just some terribly sad stories that we are going to hear, and we are going to hear certainly even on the next panel, and the plea for more funding for Parkinson's, more funding for lupus. We can just go on and on. Mohammad Ali was here pleading for more funding for Parkinson's.

So the thought has been that we just do not know enough of actually what is taking place up there in terms of research and how close they may be to a breakthrough and that sort of thing; and should we be telling them, rather than just giving the money or doubling the money as Mr. Brown has indicated?

Any opinions in that regard, because I consider that quite a dilemma. We have come to maybe a conclusion.

I have not talked with Mr. Brown on his feelings on that subject. I don't remember that we have in any case. But any feelings in that regard? Just very quickly, please.

Mr. BRYAN. Mr. Chairman, I think you do have indeed a major challenge, and that is the responsibility you all accept as our public representatives. I think that your directive is to provide broad strokes of direction to institutes such as the NIH. And I do think you have to leave some of the details to them.

Mr. BILIRAKIS. Yes, sir?

Mr. DUNNICK. I think in terms of H.R. 1795, what we are really talking about is not necessarily more funding, but reorganization to establish focus and priority setting.

Mr. BILIRAKIS. Which is basically what Ms. Fraser has testified to and what Mrs. Meek's bill does, right?

Ms. FRASER. Yes. I just want to say that we just want to level the playing field pretty much. Lupus, I did not really know a lot about it before my sister was infected with the disease. And as I learned more about it and I learned that there are so many Americans, 1.4 million infected with it, I think it is a disease that should be on the forefront right now.

Not putting anybody else's cause down or their testimony, but we just want to level the playing field is why we are here.

Mr. BILIRAKIS. I just wanted to sort of share with you the dilemma that we have and the difficulty sometimes. Did you want to add something quickly?

Ms. WIRTH. Yes. Very quickly, I come from the sort of training where I feel getting basic training and understanding fundamental mechanisms is very important to understanding disease. So, in general, I think it is very important that NIH be given as much free rein to follow the advances as they come.

But I also think it is important that the interests of individuals, who perhaps cannot sit at a table like this, are represented in the area of biomedical research. And I think without influence from the public to help direct the NIH to areas of importance—I mean, the area of importance I clearly consider very important is global health; and rarely is there anyone sitting at this table with direct experience in it.

So I think it is very important that that be heard at NIH at least in an advisory and perhaps not absolutely directive way.

Mr. BILIRAKIS. Thank you. I see that Mr. Bryant, who was here earlier and had to leave, has returned. Did you have any questions of this panel, Ed?

Mr. BRYANT. Mr. Chairman, thank you. Just some very brief statements and perhaps a question of Dr. Bryan. I think I am thinking more of the medical research at Pittsburgh, and you are down the road a little bit I guess in the other direction. But perhaps you know something about this.

I agree with Dr. Wirth in terms of that NIH ought to be given a broad rein—range, I guess, in which to make their decisions and less input from those of us who come into contact with a lot of these difficult situations and have to—can't really pick and choose. We are not knowledgeable either to make those determinations.

But on the other hand, I think there is some need for input from outside, as you point out, some representation, and I guess to a degree we do that.

It seems to me—and maybe I am not using the setup of NIH correctly, but I have heard the representation on their board or perhaps the doctors' panels that help set these priorities. Perhaps maybe we could have a better play in what groups are represented there—what specialties, what doctors, what diseases are represented there. And that would be a way of again giving them broad powers, but yet we in Congress being able to make sure that one disease is not given priority over another one for the wrong reasons.

Second—and my last comment in this area, and I am going toward something that I just mentioned earlier—I have been working really closely with a group in Memphis in terms of a disease that again does not address a large part of our population, but a lot of our—a percent of our young children. It is Duchenne's muscular dystrophy; I was at a fund-raiser for them about a week ago in Memphis, and I am told that that is a disease in which there have been great advancements made, and I think a lot of that has come out of the University of Pittsburgh or the Pittsburgh area.

I think our priorities also ought to be, in addition to all the other priorities, trying to find cures for those diseases regardless of the size of the population affected; those diseases that are getting close to being solved, cured. That, to me as a layperson, a nonmedical person, makes some sense, that if we are getting close—because that can open the doors to other related diseases, I would think. I would think Duchenne's muscular dystrophy would have some very close cousins in terms of diseases that could be affected in a positive sense.

So, Dr. Bryan, I am asking you cold, do you know anything about that particular disease in terms of are we making progress there?

Mr. BRYAN. I am familiar; I am not an authority on that disease. But you are correct, it is a disease that affects a relatively small population, but in a devastating fashion. And remarkable advances have been made, mostly in understanding the genetics and etiology of the disease.

I think the dilemma is one that is difficult. Your committee has to face the public needs, define areas where you think emphasis should be placed. But then I think, to be honest, one has to defer to our peer review system which—the NIH has a superb peer review system, where the experts have to adjudicate whether, in fact, it is time, whether the knowledge is there, the technology is there, the feasibility is there, to actually, at that time, fund the additional research in that area.

So I think you all have to define priority from a public perspective, but then I think you have to take into account the experts and the peer review system to help decide when you actually support a particular research project area.

Mr. BRYANT. Quickly, does anyone have an additional comment? Thank you for being here and thank you, Mr. Chairman.

Mr. BILIRAKIS. And I thank the gentleman.

We will excuse this panel at this time. We customarily furnish written questions, and we request written responses. We would ap-

preciate your assistance if you are all willing, to do that in a timely fashion, Ms. Fraser, sooner rather than later, particularly on the question that I raised——

Ms. FRASER. That will not be a problem.

Mr. BILIRAKIS. Thank you very much.

The second panel consists of—was scheduled at least—Mr. Jack McCormick, Deputy Director of the Office of Orphan Drugs for the Food and Drug Administration. Is Mr. McCormick here? No? Is someone else going to be here to represent FDA on this matter?

Mr. DOLESKI. I work for the FDA.

Mr. BILIRAKIS. Well, you do not want to testify at all? Technical responses?

In any case, you will be here for the testimony and the questions so that you can take those back too? I appreciate that.

Why don't you give us your name, sir, for the record?

Mr. DOLESKI. Dave Doleski, D-O-L-E-S-K-I, Legislative Analyst with the FDA.

Mr. BILIRAKIS. I am going to introduce Mr. Robert Brady, a partner with Hogan & Hartson. They are here on behalf of Biogen; Ms. Abbey Meyers, President of the National Organization of Rare Disorders; Mr. Thomas A. Lang, Senior Vice President, Strategic Product Development, Serono Laboratories, Rockville, Maryland, and he is accompanied by Nick Ruggieri, Vice President of Governmental Affairs; Ms. Catherine Bennett, Chair, Board of Directors, Cancer Research Foundation of America.

And I would now yield with the committee's indulgence to Mr. Dan Burton, who is not on this committee, but who chairs of course another very significant committee, who will introduce Mr. Navarro and at the same time take 2 to 3 minutes to talk about his legislation. You are recognized.

STATEMENT OF THE HON. DAN BURTON, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF INDIANA

Mr. BURTON. Thank you, Mr. Chairman. And I hope you will grant me just a minute or 2 latitude because I think some of the things that I would like to say are very important.

To my classmate and chairman of this committee, Chairman Bilirakis, it is nice to be with you. I think it is the first time in the 18 years that we have been here that I have appeared before your committee.

Mr. BILIRAKIS. I am sure that is true. And, Dan, I am sure the thought has crossed your mind, there are not too many of us left.

Mr. BURTON. No, and unfortunately we just lost one of our classmates.

Mr. BILIRAKIS. Yes, we just lost one of ours.

Mr. BURTON. Anyhow, I appreciate your holding this hearing and allowing us to testify on H.R. 3677, the Thomas Navarro FDA Patient Rights Act.

The United States of America is a country based on freedoms, and among the freedoms guaranteed through our Constitution are freedom of speech, freedom to practice the religion of our choice and a free press. However, we are not, as individuals, guaranteed the freedom to make a life-and-death decision in the area of medicine.

Imagine our own government forbidding your child access to a nontoxic treatment, a nontoxic treatment with full human subject protection through clinical trials that has already saved the lives of other children. Imagine being told that you must subject your child to treatments that may cause him to be blind, to be deaf, to make him sterile, to stunt his growth, to give him hormonal deficiencies, to lower his IQ and to give him secondary cancers.

Imagine having your choices reduced to chancing no treatment and possibly death or toxic treatment and possibly creating a special-needs child with no guarantee of success, all at a time when another treatment is available.

Imagine learning that the treatment that the FDA wants your child to receive, that two of the three drugs in the, quote, "standard protocol" of approval drugs, clearly state on their package inserts, "Not proven safe or effective in the pediatric population."

Now, that is exactly what Donna and Jim Navarro have been faced with. Imagine being a doctor who has treated cancer patients successfully for over 20 years. Imagine being repeatedly attacked by the FDA in an attempt to stop your work. Attacked by the very agency that is supposed to encourage and promote research.

Imagine submitting the BT-29 protocol so that a 4-year-old boy can be treated with a nontoxic cancer therapy whose safety has been established. A treatment which has saved the lives of other children with the same type of cancer. Imagine this government agency putting that protocol on hold because of other existing treatments. That is exactly what has happened to Dr. Burzynski down in Texas.

Many have heard the story of little Thomas Navarro. You may have seen his story in "People" magazine, in the New York Post or on CNN. His father, Jim Navarro, is here today to testify, and I will leave the full story of Thomas' specific condition for Mr. Navarro to talk about.

Two years ago the parents of another little boy, Dustin Kunnari, testified before our committee, the Government Reform Committee, about FDA's gatekeeping on clinical trials. Dustin had the same form of cancer as little Thomas Navarro. Dustin was the last person the FDA allowed to receive antineoplastons without having first failed chemotherapy and radiation. He is healthy and cancer-free today and without the devastation of chemotherapy and radiation side effects.

Over the last 3 years, the Committee on Government Reform has conducted five hearings looking at cancer treatments and access to care. Unfortunately, Thomas Navarro is just one of thousands of Americans who have been excluded from clinical research because of the FDA. He is just one of the thousands of children who are denied access to the parents' treatment of choice because the government's agency has made a life-or-death decision for the family and not allowed them the freedom to choose.

The heart of this whole issue, Mr. Chairman, is, who decides? Is it the role of the U.S. Government to make a treatment decision? Or is it the right of the patient and the family to make an informed treatment choice?

H.R. 3677, the Thomas Navarro FDA Patient Rights Act is the first step in restoring medical freedom. It is the first step in taking

the decisionmaking out of the hands of the government and putting it back in the hands of the individual where it belongs, an informed decision.

Mr. Chairman and members of the committee, H.R. 3677 has 43 cosponsors from both sides of the aisle, Democrat and Republican. I respectfully request your help in getting this bill passed during this Congress.

I am now pleased to introduce Jim Navarro, Mr. Chairman. And once again I want to thank you very much, my colleague, for holding this hearing.

Jim testified at our June hearing and shared with us the challenges that they faced as a family dealing with a cancer diagnosis and the Federal agency that has forced them into a corner. They have spent almost all of their money—I think they sold their house. They completely depleted all of their resources—in trying to solve the problem of their boy. And it is a heart-rending story and I know Jim is going to go into it in detail. He is here to testify about this bill.

Jim and Donna Navarro are intelligent, conscientious parents. They love their son. They stood firm in the battle to find the best and safest treatment for their child. And Jim is a brave man fighting a battle on two fronts. While he is in the battle for his son's life, he is in a battle for his own life. Several months ago Jim was diagnosed with prostate cancer. So, Jim, we wish you the best. And we pray for you and your boy.

And with that, Mr. Chairman, I would like to yield, if you do not mind, to Mr. Navarro.

Mr. BILIRAKIS. Thank you, Dan. Thanks for your interest in this subject, all issues in America.

The Chair will now yield to Mr. Navarro, who uses as his address: Ronald McDonald House, Room 1101, 405 East 73rd Street, New York, New York.

Mr. Navarro, please proceed, sir.

STATEMENTS OF JAMES NAVARRO, FATHER OF THOMAS NAVARRO; ROBERT BRADY, PARTNER, HOGAN & HARTSON, ON BEHALF OF BIOGEN, INC.; ABBEY MEYERS, PRESIDENT, NATIONAL ORGANIZATION FOR RARE DISORDERS; THOMAS A. LANG, SENIOR VICE PRESIDENT, STRATEGIC PRODUCT DEVELOPMENT, SERONO LABORATORIES, INC.; AND CATHERINE P. BENNETT, CHAIR, BOARD OF DIRECTORS, CANCER RESEARCH FOUNDATION OF AMERICA

Mr. NAVARRO. That is home, as you stated because as the chairman stated, there is no longer a home for us.

Good morning, Mr. Chairman, my name is Jim Navarro and I am the father of 5-year-old Thomas Navarro for whom this bill is named.

I have been asked to speak on the benefits of this bill, and I would like to first go on record saying that my son's health has not stood still while the slow wheels of government move, and thus this bill will not help my son. It is too late to bring hope to our family, hope that the FDA would stand down and allow my son access to our first choice of treatment.

We were forced to begin the FDA's preferred treatment this summer. This bill will, however, help thousands of others. This bill was conceived as a result of the FDA's unwillingness to allow Thomas access to a treatment which had a higher rate of success than the treatment offered through conventional means.

This bill will, however, bring hope to others, others who, like us, have been denied access to treatments that show promise and give a chance of survival, treatments which are good or greater than those treatments currently available for treating pediatric cancer.

We were faced with a decision almost a year ago, which changed our lives forever, when our son Thomas was diagnosed with medulloblastoma, which is a nonsurvivable type of cancer. Thomas was rushed to surgery within hours to remove a 4 by 6 centimeter tumor from his cerebellum.

After surgery, we were faced with the decision of follow-up therapy. We discovered in short order that the standard follow-up therapies, radiation and chemotherapy, both had severe and irreversible side effects. These included the possibility that he would become blind, deaf, and sterile; that Thomas would develop hormonal deficiencies that would have stunted growth; that he would have had an immediate and progressive loss of IQ; and that he would develop secondary cancers as a result of the treatment itself.

We immediately began our search for a safer, nontoxic means of treating our son. We found a treatment that showed a great promise for treating medulloblastoma only to discover that our son would be denied access to the treatment by the FDA.

The doctor was not allowed to treat my son because the FDA did not approve his access to the treatment. Yet the FDA has never approved radiation and chemotherapy for treating pediatric cancers. In fact, if you read the manufacturer's information that the drug companies put in the box, they state, "Safety and effectiveness in pediatric patients has not been established."

This sentence, in and of itself, should cause concern. The FDA has no problem forcing this therapy on my son and thousands of others, even though the safety and efficacy has not been established in children. In fact, if you are the parent of a terminally ill child, your child can be taken away from you for experimentation and, as parents, if you do not cooperate with this madness, you can be thrown into jail for being bad parents.

Based on your experience, Mr. Chairman, what actions must I take today to get you and your committee to take the required actions to save the Thomas Navarros of tomorrow? During the course of this last year, my family has lost everything—our home, our business, even our State of residency, which although it is hot, it is a dry heat. It has been because of the kindness and generosity of others, especially the support of Citizens for Health, that Thomas has been able to receive medical care.

H.R. 3677 introduced by Congressman Dan Burton now has 43 cosponsors, and I implore to you take this issue up and get H.R. 3677 passed into law.

Thomas is very hard to recognize now as a result of conventional therapy. And I would like to encourage Mr. Waxman and others that would stand in opposition to this bill to come see him, what he looked like before and what he looks like now.

Thomas's fight for his life now includes fighting against the very treatment that he has been forced to take. And I can only tell you it has been a very long and hard year.

Thank you for letting me speak.

[The prepared statement of James Navarro follows:]

PREPARED STATEMENT OF JAMES NAVARRO

Good morning Mr. Chairman, my name is Jim Navarro. I am the father of 5 year old, Thomas Navarro, for whom this Bill is named. I have been asked to speak of the benefits this Bill would present. I would first like to go on record saying that my son's health has not stood still for the slow wheels of Government to move, and thus this Bill may not help my son. It is too late to bring hope to our family. Hope that the FDA would stand down and allow my son access to our first choice in treatment. We were forced to begin the FDA's preferred treatment this summer. This Bill will, however; help thousands of others.

This Bill was conceived as a result of the FDA's unwillingness to allow Thomas access to a treatment which had a higher rate of success than the treatment offered through conventional means. This Bill will however bring hope to others. Others, who like us, have been denied access to treatments that show promise and give a chance of survival. Treatments which are as good or greater than those treatments currently available for treating pediatric cancers.

We were faced with a decision almost one year ago, which changed our lives forever. When our son, Thomas, was diagnosed with Medulloblastoma, Thomas was rushed to surgery within hours to remove a 4 X 6-cm tumor on his cerebellum. After the surgery we were faced with the decision of follow up therapy. We discovered in short order that the standard follow up therapies, radiation and chemotherapy, both had severe and irreversible side effects. These side effects included the possibility that he would become blind, deaf, and sterile. That Thomas would develop hormonal deficiencies would have stunted growth, that he would have an immediate and progressive loss of IQ. And that he could develop secondary cancers as a result of the treatment.

We immediately began our search for a safer, non-toxic means for treating our son. We found a treatment that showed great promise for treating Medulloblastoma. Only to discover that our son would be denied access to the treatment by the FDA. The doctor was not allowed to treat my son because the FDA did not approve his access to the treatment. Yet, the FDA has never approved radiation and chemotherapy for treating pediatric cancers. In fact, if you read the manufacture's information that the drug companies put in the boxes, they state, "safety and effectiveness in pediatric patients have not been established." This sentence in and of itself should cause concern. The FDA has no problem forcing this therapy on my son and thousands of others—even though the safety and efficacy has not been established in children. In fact, if you are the parent of a terminally ill child, your child can be taken away from you for experimentation. And as parents, if you do not cooperate with this madness, you can be thrown in jail for being "bad parents."

Based on your own experience Mr. Chairman, what actions must I take today to get you and your committee to take the required actions to save the Thomas Navarros of tomorrow?

During the course of the last year, my family has lost everything—our home and business in Arizona. It has been because of the kindness and generosity of others, especially the support of Citizen's For Health, that Thomas has been able to receive medical care. HR 3677 introduced by Congressman Dan Burton, now has 43 cosponsors. I implore you take this issue up and get HR 3677 passed into law.

I would be pleased to entertain any questions from the Committee.

Mr. BILIRAKIS. Thank you very much, Mr. Navarro. I do—well, what can one say? We want to be able to accomplish something here. We want to be able to pass Dan's bill, or essentially Dan's bill, but it has got to be done on a bipartisan basis. That is your reason for imploring Mr. Waxman, who frankly has just been very much interested in health care all through the years. I know I have worked with him on this committee for many, many years. And I do not really know personally what his position is on the legislation. I guess staff here does, but we are going to do everything we possibly can.

Mr. NAVARRO. Mr. Chairman, if I might add real quick: It is interesting, when I testified last time in Chairman Burton's hearings and spoke to a number of the directors of the FDA outside in the halls, they kept trying to reiterate the great successes of conventional therapy in Thomas's case. Yet the irony is, here before me are the consent forms to the treatment Thomas is going through now, which state, "Permission to for participation of child in research."

He is not in a protocol because they do not have a protocol. They really do not know quite what they are going to do with him. It is a hit and miss, and as they would say, a crapshoot. In fact, one of the things that is sad that disturbed me, especially after hearing Dr. Pazdur testify that the rate of success was 70 and 80 percent—and this is coming out of the horse's mouth—however, with standard therapy, there is less than a 30 percent chance of curing these malignant brain tumors in young children. Furthermore, young children treated with radiation therapy for brain tumors may experience serious and irreversible, long-term side effects from the radiation.

And yet yesterday, the doctors announced to us that because Thomas has fared the toxic side effects better than the other children in the ward, they are anxious to start using high, high-dose radiation and chemotherapy five to six times greater than they have used on him so far.

And to be honest sir, he is tired of fighting the drugs. We need to have the freedom to seek out a treatment that is nontoxic and nonlethal. It is our right as Americans to have that freedom.

Mr. BILIRAKIS. Thank you, Mr. Navarro.

Mr. Brady. Mr. Brady? Obviously, the written statement that you all submitted is made a part of the record, and we would prefer that you might sort of supplement it.

STATEMENT OF ROBERT BRADY

Mr. BRADY. Thank you, Mr. Chairman. I will be quite brief and just summarize my comments.

I am Bob Brady. I am here appearing this morning on behalf of Biogen, Inc., a biotechnology company from Massachusetts. I am a partner in the law firm of Hogan & Hartson where I have been practicing food and drug law, focusing on pharmaceutical matters for 25 years, including the implementation of the Orphan Drug Act.

Let me summarize my points, and then I am just going to focus on two or three of them.

If enacted, H.R. 4242, the Orphan Drug Innovation Act would actually undercut the carefully crafted incentives of the Orphan Drug Act without providing any real benefit to patients or promoting innovation. The Orphan Drug Act has been an unparalleled success. Any changes to the act should be made only after careful analysis and consideration by fully informed Members of the Congress in the context of the entire law.

The FDA and its Office of Orphan Products Development, which has done a conscientious and successful job in implementing the law to date, should be consulted and its views taken into account. Moreover, Biogen knows of no patient advocacy groups supporting

this law nor do we know of any other organization, other than one here at the table, supporting this provision.

The Orphan Drug Act shouldn't be amended piecemeal by an amendment hastily packaged together with noncontroversial measures at the end of a legislative session. It would undermine the foundation of the Orphan Drug Act so a single company can market a product that has not been shown to be clinically superior to orphan drug products already on the market.

Let me speak one moment about the Biogen product, which is a product to treat multiple sclerosis, which was approved and is the only multiple sclerosis drug approved for two indications to treat this terrible disease. And it has been approved by the judgment of FDA that it is clinically superior for safety reasons to the prior drug approved in this marketplace. That is important, because that will be a point of discussion here during the rest of this morning's testimony.

The Orphan Drug Act is one of the most effective laws enacted by Congress with full bipartisan support in the last 20 years, especially in terms of the lives it has enhanced, the pain and suffering it has diminished, and the hope it represents to Americans with rare diseases.

I might also add parenthetically, after 25 years it has been the least controversial piece of FDA law ever enacted in terms of subsequent debate and litigation, suggesting that it was well done to begin with and remains properly implemented.

However, H.R. 4242 would undercut the overwhelming success of this act. The key incentive of the act is a 7-year period of marketing exclusivity for the first product to be approved as an orphan drug. H.R. 4242 would significantly narrow the scope of this exclusivity by limiting it to particular aspects of the orphan product subsequently approved.

Narrowing this key incentive, especially for a product which has not shown any clinical superiority, would not only hurt companies that make orphan drugs, but would also undercut Congress' intent that there be new and innovative treatments developed for millions of Americans who suffer from rare diseases.

Orphan drug policies first passed by Congress and implemented by FDA have been fair. Companies are rewarded when they produce a clinically superior drug that represents an innovation among the current marketplace.

Biogen, in fact, satisfied this standard in the law in the mid-1990's when it was found to be clinically superior to the existing multiple sclerosis product. Serono Laboratories is testifying here today on behalf of this bill. They manufacture a drug for multiple sclerosis that is the same as Biogen's multiple sclerosis product. Serono would like to get their drug into the American market, but they are blocked by the market exclusivity of Biogen's product, which does not expire until May of 2003.

The Orphan Drug Act and the FDA Act implementing regulations currently provide a way for Serono's product to get to market precisely the same way that Biogen's product got to market in 1996, which is to prove clinical superiority to the two existing products that are already available to multiple sclerosis patients today.

This is not a situation where there are not products available to patients. There are two Interferon products already approved by FDA in this area. Serono or any other company should not be held to a lesser standard than the products that are already on the market.

Thank you very much, Mr. Chairman, for allowing me this brief statement, and I am prepared to answer any questions you may have.

[The prepared statement of Robert Brady follows:]

PREPARED STATEMENT OF ROBERT P. BRADY ON BEHALF OF BIOGEN, INC.

I am Robert P. Brady, and I appear here this morning on behalf of Biogen, Inc. (Biogen). I am a partner in the law firm of Hogan & Hartson L.L.P., in Washington, D.C. I have practiced law for 25 years, and spend almost all my time on matters involving pharmaceutical and biotechnology laws including the Orphan Drug Act. I would like to thank you for the invitation to Biogen to testify before this Committee.

At the outset I would like to summarize the key points of my testimony. If enacted H.R. 4242, the "Orphan Drug Innovation Act," would actually undercut the carefully crafted incentives of the Orphan Drug Act without providing any real benefit to patients or promoting innovation. The Orphan Drug Act has been an unparalleled success. Any changes to the Act should only be made after careful analysis and consideration by fully informed members of Congress in the context of the whole Orphan Drug Act. The FDA office of Orphan Products Development, which has done such a conscientious and successful job in implementing the Orphan Drug Act, should be consulted and its views taken into account. Moreover, Biogen knows of no patient advocacy groups supporting H.R. 4242, including the National Organization of Rare Disorders (NORD) which is the chief consumer advocacy organization for orphan drug research and development and was instrumental in the development of the Act. The Orphan Drug Act should not be amended piece meal, by an amendment hastily packaged together with non-controversial measures at the end of a legislative session. It would undermine the foundation of the Orphan Drug Act, so a single company can market a product that has not been shown to be clinically superior to orphan drug products already on the market.

Biogen is a biotechnology company based in Cambridge, MA and manufacturer of a product for the treatment of relapsing forms of remitting multiple sclerosis (MS) that was approved in 1996. Biogen's product (Avonex®) was approved as an orphan drug and thereby received a grant of seven years of marketing exclusivity. Two important medical facts about Avonex® must be kept in mind. It is the only MS drug approved for both reducing the number of exacerbations and slowing disease progression. Also, the FDA concluded that it was clinically superior to the existing MS product due to greater safety. As a result patients have benefited greatly from this approval.

Biogen is strongly opposed to H.R. 4242 for the following reasons:

The Orphan Drug Act is one of the most effective laws enacted by Congress with full bipartisan support in the last twenty years, especially in terms of the lives it has enhanced, the pain and suffering it has diminished, and the hope it represents to Americans with rare diseases. The Orphan Drug Act has been an unqualified success. In particular, it spurred the development of breakthrough drugs for Multiple Sclerosis, Cystic Fibrosis, Hemophilia, Leukemia, as well as over 100 other rare diseases. During the ten years before the law, only ten drugs were approved by the Food and Drug Administration (FDA) for the treatment of rare diseases. Since the law was enacted, however, about 200 orphan drugs have been approved and about 1,000 are in the pipeline. Clearly, any modification of the Act must be the end result of a deliberative process that increases incentives to develop breakthrough treatments and, most importantly, benefits patients.

This is not the case with H.R. 4242—it would undercut the overwhelming success of the Orphan Drug Act with no real benefit to patients. The key incentive of the Act is a seven-year period of marketing exclusivity for the first product to be approved as an orphan drug. H.R. 4242 would significantly narrow the scope of this exclusivity incentive by limiting it to particular aspects of the orphan product. Narrowing this key incentive would not only hurt companies that make orphan drugs but would also undercut Congress's intent that there be new and innovative treatments developed for the 20 million Americans who suffer from rare diseases.

The FDA has skillfully implemented the Congressional intent of the Orphan Drug Act in a manner that balances the seven year marketing exclusivity incentive with

the need to foster the public health goals. One way in which FDA has balanced this issue is through the development of a regulation defining scientific/medical criteria under which an orphan drug which is the same as an orphan drug already approved for marketing can be determined to be "clinically superior" and, therefore, allowed to come to market in spite of any remaining marketing exclusivity granted to the original approved product. (See 21 C.F.R. §316). FDA, the scientific and medical expert in this area, has defined three such criteria to determine clinical superiority. These criteria were thoughtfully and deliberately developed through notice and comment rulemaking by the FDA. All interested parties had an opportunity to present their views. Ultimately, the FDA crafted a well reasoned definition of clinical superiority.

Critically important since the finalization of this rule almost a decade ago, FDA has carefully exercised its scientific and medical judgment in implementing this rule in a manner that is truly in the best interests of patients. When another orphan drug truly is clinically superior, FDA has allowed it to go to market so that particular patients will benefit. It has done so sparingly, however, because the FDA has correctly concluded, based on its extensive experience, that, absent a real showing of clinical superiority, preserving the seven year marketing exclusivity incentive is vitally important to the development of new orphan drugs and that will help even more patients suffering from orphan diseases.

These regulations are sound and fair. Companies are rewarded when they produce a clinically superior drug that represents an innovation above the current marketplace. Biogen satisfied these regulations when the FDA found that its product Avonex was "clinically superior" to another existing beta interferon product in 1996.

Serono Laboratories (Serono) is testifying on behalf of H.R. 4242 today. They manufacture a drug for multiple sclerosis that is the same as Biogen's MS drug. Serono would like to get their drug onto the American market, but they are blocked by the market exclusivity of Biogen's multiple sclerosis product, which does not expire until May 17, 2003. The Orphan Drug Act and the FDA implementing regulations currently provide a way for Serono's product to get to market: a showing of "clinical superiority" based on appropriate scientific data.

Serono, or any other company, should not be held to a lesser standard than its competitors in the marketplace. To date Serono has not demonstrated in head to head comparative trials that its product is safer or more effective than the other beta interferon products on the market for relapsing remitting multiple sclerosis. In 1999, the FDA found, based on data submitted to the FDA by Serono, that Serono's product was not clinically superior to the other similar multiple sclerosis products on the market. Therefore, it is barred from the U.S. market until the Biogen marketing exclusivity expires in May 2003. Because Serono does not represent an innovation, patients are not being denied a new or improved therapy. Serono is seeking to change these requirements because Serono has not been able to satisfy them.

Serono's situation highlights one of the key problems with H.R. 4242. Under the bill, Biogen's market exclusivity for its multiple sclerosis drug would be limited to blocking from the market only those products that cause fewer injection site reactions and less skin necrosis. However, a product which is *less safe* than Biogen's by causing more site reactions and skin necrosis—such as Serono's product—would be, under this bill, eligible for approval by the FDA. Biogen does not understand how it benefits patients to allow a drug on to the market during the exclusivity period that is neither safer nor more effective.

The Orphan Drug Act's market exclusivity is not a barrier to approval of a subsequent product that is not the same drug. A subsequent drug for the same indication may be found to be not the same drug if it is either chemically different or clinically superior. Serono's Rebif product meets the statutory and regulatory standards for "same drug" because chemically it is the same drug for the same disease as both Avonex and Betaseron. Because Rebif chemically is the same drug as Avonex, in order for Serono to receive marketing approval prior to 2003, Serono must demonstrate that it is clinically superior to Avonex. The FDA's clinically superior criteria protects the drug development incentive, while permitting the introduction of better products to treat serious illness.

Aside from the serious policy concerns with H.R. 4242, another fundamental flaw is that it is, in part, unconstitutional. As presently introduced, the bill would apply to any drug designated on or after January 1, 1990. By going back and retroactively narrowing the scope of the market exclusivity, this would constitute an unconstitutional taking under the Fifth Amendment. This legislation would not only effect the property rights of Biogen but property rights of many other companies with orphan drug designations that have made significant economic investments based on an expectation of market exclusivity. Biogen has attached a legal opinion on the unconstitutionality of the bill that was previously sent to the Committee.

For Congress to make a change to a law as successful and important to the health of the American people, as the Orphan Drug Act, one would expect that there would be strong support from the biotechnology and pharmaceutical industries and patient advocacy groups. Biogen knows of no outside parties that favor the H.R. 4242. There are no patient advocacy groups supporting this bill. The National Organization of Rare Disorders (NORD), which is the chief consumer advocacy organization for orphan drug research and development and was instrumental in the development of the law, is opposed to the bill. The views of NORD and other patient groups should not be ignored.

The stated purpose of this hearing today is to consider legislation that would secure the health of the American people. The Orphan Drug Act has already fostered the development of numerous breakthrough treatments for rare disorders and helped countless persons. H.R. 4242 will threaten this continued development and risk the security of the health of the American people with rare disorders.

Mr. BILIRAKIS. Thank you, Mr. Brady.

Ms. Meyers, please proceed, ma'am.

STATEMENT OF ABBEY MEYERS

Ms. MEYERS. Thank you, Mr. Chairman.

For those of you who do not know us, the National Organization for Rare Disorders is the consumer organization that advocated for passage of the Orphan Drug Act, and we continue to monitor its implementation.

We do not support H.R. 4242. And let me say at the outset, we have no relationship with Biogen. Biogen has never donated to NORD. This is totally independent.

Most orphan drugs have only one sponsor, and that is very important to understand, because this situation comes up very rarely when more than one sponsor is interested in the same drug. And so we caution you not to change the Orphan Drug Act in any way based on something that happens so rarely.

You can get the same drug, orphan drug, on the market to compete against the innovator drug. You can do that in several ways. You can get an orphan drug approved for a different disease.

For example, if beta Interferon was approved for cancer or something else, they could get it on the market and it could compete in the marketplace. Or you could prove that it is chemically or structurally different than the first drug to get on the market. Or you can show that it has clinical superiority.

Clinical superiority means that you have to prove that it is safer or more effective or a major contribution to patient care. In the case of Avonex and Betaseron, for example, Avonex showed that you need less injections every week, it had fewer side effects and did not cause one particular side effect. And so it was a major contribution to patient care and you needed only one injection a week.

So the current law protects the major incentive of the Orphan Drug Act, which is 7 years of exclusive marketing rights; and it is only through regulations that the current definitions of "same" and "different" was created. And I want to tell you that the Orphan Drug Act passed in 1983, but those regulations weren't written and published until 1992. So we waited many years and there was a lot of public input on the development of those regulations.

The Thornberry amendment, we feel, would destroy the backbone of the law because it would undermine the major incentive of the Orphan Drug Act. And also be aware that the Orphan Drug Act's success has been replicated all over the world. The European Union

just passed an orphan drug law; Japan has one, Singapore, every country in the world admires what we have been able to do here. So we need to keep the incentive in place that would spur other manufacturers to develop clinically superior orphan drugs.

In the case of multiple sclerosis, for example, people have very poor muscular control. Giving themselves an injection is climbing Mount Everest every day. And then they lose their eyesight, so they can't see to fill up their syringe. It is a major improvement to patient care when you only need one shot a week and a nurse can come to your house to do it.

So what do we see in this situation here with this argument over beta Interferon? If Serono—and we have the greatest respect for Serono, but if Serono believes that its drug is either safer or more effective or that it is clinically superior, or even if they want to say that their drug is the same as the original orphan drug so it would be able to get on the market today if it could prove it is the same as Betaseron, they should take their proof to the courts. They should not be hiring lobbyists to come down here and ask you to change the law. It is wrong for company after company, year after year to come to you and ask for an amendment to the Orphan Drug Act. It works; and if it ain't broke, don't fix it.

I will be glad to answer any of your questions that you may have about the law. And we say again, we do not support this amendment.

[The prepared statement of Abbey Meyers follows:]

PREPARED STATEMENT OF ABBEY MEYERS, PRESIDENT, NATIONAL ORGANIZATION FOR RARE DISORDERS

Mr. Chairman and members of the Committee, the National Organization for Rare Disorders (NORD) is the consumer organization that worked for passage of the Orphan Drug Act (ODA) of 1983, and we continue to closely monitor its implementation today. NORD represents approximately 25 million Americans with more than 6,000 rare "orphan diseases", and we are very pleased to be here today. Thank you.

As you know, the Orphan Drug Act is one of the most successful pieces of health legislation ever enacted by Congress. Today, approximately 1,000 orphan drugs have been designated by the FDA, and over 200 of them have been approved for marketing in the United States. Recognizing the public health impact of the American law, other nations have implemented orphan drug statutes including Japan, Singapore, Australia and the entire European Union.

It is extremely important that Congress not undermine the intent of the law, which is to encourage the commercial development of treatments for small populations of patients. We do not support H.R. 4242, the Orphan Drug Innovation Act, for many reasons, and we urge the committee not to approve the legislation for further consideration by Congress. Let me explain why we do not support H.R. 4242.

Early in the evolution of the American Orphan Drug Act, it became necessary to define the words "same" and "different". In other words, as defined by FDAs carefully crafted regulations, if a manufacturer of a similar orphan drug can prove that their drug is chemically different or clinically superior, even though it contains the same active ingredients as the original orphan drug, the FDA will approve it for marketing.

There are several ways to prove that a drug is "clinically superior": either by providing FDA with scientific data proving that it is either safer or more effective, or that it represents a "major contribution to patient care". The latter is usually an obvious improvement, such as developing an oral version of an injectable drug—so that patients no longer have to suffer painful injections—or developing a long-acting version of a drug that must otherwise be taken several times each day, for example. Thus, the orphan drug regulation defining "same" and "different" not only promotes, but encourages development of new improved versions of marketed orphan drugs while PRESERVING the chief incentive of the ODA.

Since most orphan drugs have no competition because companies are generally not interested in investing the huge sums necessary for research and development

of a drug that will have a very small market, the ODA offers an important incentive to encourage orphan drug innovation.

Companies can receive seven years of exclusive marketing rights for both the innovator drug and the clinically superior follow-on drug.

Mr. Chairman, from time to time there are orphan drug "races" when more than one company is developing the same orphan drug for the same disease, and the law purposely creates a winner-take-all contest. This is the very core of the success of the ODA because it prevents competition for seven years, and ensures that a manufacturer of an FDA-approved orphan drug will recoup its investment and make a profit. But losers of the race sometimes ask Congress to change the law because they want an exception for their drug. Thankfully Congress has been wise enough not to allow this, knowing that tinkering with the Act could destroy it.

In this case, Congressman Thornberry's bill aims to redefine FDA's definition of "same" and "different", and to codify it into law, based on the mistaken belief that people with rare diseases do not already have access to clinically superior orphan drugs. However, H.R. 4242 will NOT enhance patient choice because current regulations not only permit, but encourage competition when a therapeutic advantage can be scientifically proven.

We believe that H.R. 4242 would disincentivize companies to develop clinically superior orphan drugs and biologics, and it would allow companies to seek approval for clinically inferior products. Moreover, H.R. 4242 would reduce the exclusivity of orphan drugs and biologics that have demonstrated they are clinically superior, because it would limit exclusivity to the innovation that enabled a clinically superior product to reach the market.

There are no benefits to patients if H.R. 4242 becomes law. There are only benefits to companies that want to break the innovators exclusivity, but that exclusivity is the very backbone of the Orphan Drug Act which has since 1983 saved the lives of millions, and improved the quality of life for countless others.

The current regulations, which are based on sound scientific knowledge and common sense, were written to promote innovation and to allow consumers access to clinically superior orphan drugs. They are fair to consumers and fair to companies. The ODA is good public health policy and continues to be one of the most successful pieces of health legislation ever written.

We are profoundly grateful to Congress for enacting the Orphan Drug Act, and for preserving its integrity since 1983. If you write the Thornberry bill into stone, it will require an act of Congress to change it when new medical technologies emerge in the future. If you leave the orphan drug regulations alone, the FDA can easily fine tune the rules, if and when that becomes necessary.

Mr. Chairman and members of the Committee, "if it ain't broke, don't fix it." We urge you NOT to enact H.R.4242.

Mr. BILIRAKIS. Thank you, Ms. Meyers.

Mr. Lang.

STATEMENT OF THOMAS A. LANG

Mr. LANG. Good morning. My name is Tom Lang. I am Senior Vice President for Strategic Product Development at Serono, Inc. I want to thank the committee for the opportunity to testify on the issue of orphan drug evergreening, which is addressed by H.R. 4242.

Serono believes this issue needs to be addressed irrespective of the impact on our products. FDA's current evergreening policy affects all drugs governed by the Orphan Drug Act. We fully support the remedy posed by H.R. 4242, whether or not it would apply to any of our products.

Furthermore, Serono believes orphan drug evergreening is not a single-product issue.

Serono is a strong supporter of the Orphan Drug Act. However, we have recently encouraged an anomalous and confusing interpretation of the FDA orphan drug regulations which results in orphan drug exclusivity evergreening. "evergreening" refers to FDA's granting of a new 7-year orphan drug exclusivity period for the entire drug substance upon the approval of a clinically superior

version of the same drug, rather than protecting only the innovative feature exhibited by the second drug.

The results are to close the market to competition beyond the initial 7 years of exclusivity intended by Congress. This raises troubling policy issues of fairness, impediments to price competition that would benefit consumers, and delays in availability of alternative therapies for patients.

Mr. Chairman, Congress needs to decide exactly what the scope of exclusivity should be for improved versions of originator orphan drugs. We note that other areas of food and drug law limit the scope of exclusivity for new versions of previously approved products in a manner consistent with H.R. 4242. Like the Orphan Drug Act, the Waxman-Hatch Act seeks to create incentives for continued research on improved drugs and product improvements. The Waxman-Hatch Act, as one would expect, rewards only innovative features with exclusivity, rather than shielding the entire drug substance from competition when its original exclusivity period has run. This serves as evidence of Congress' intent and provides a basis for supporting the principle in H.R. 4242.

FDA's handling of one particular product has resulted in several very strained policy positions on the part of FDA. In a letter to Serono, dated November 1999, FDA indicated that while it would not allow an NDA or a BLA product to be marketed in competition with the original drug, it would allow a generic version of the original product to come on the market if it were eligible for an abbreviated new application.

Mr. Chairman, there is no rationale whatsoever for preventing competition from products that are supported by full NDAs and BLAs. Subsequently, Serono became aware of an instance where FDA has taken what appears to be a different position than that previously described, a position which actually is consistent with H.R. 4242, in a letter to Genentech.

Serono believes orphan drug exclusivity evergreening can be resolved by FDA or Congress by simply limiting the second clinically superior drug's scope of orphan drug exclusivity to the superior characteristic that distinguished it as clinically superior. This solution would probably reward the improvement found in the clinically superior drug while still allowing competition with the expired drug as intended by the law.

This would be consistent with other exclusivity-related legislative initiatives, such as the Waxman-Hatch amendments and patent law as well.

Limiting the scope of exclusivity of a clinically superior orphan drug to its clinically superior feature still leaves the drug sponsor with adequate incentives. A clinically superior drug would gain three significant rewards as follows: .

First, it would achieve the benefit of being allowed on the market immediately despite the originator drug's exclusivity; Second, it would obtain 7 years exclusivity for the improved feature; and Third, the company would be able to market its product as a clinically superior product.

These are substantial awards and incentives. These incentives make it unnecessary to keep the market closed to other products

wishing to compete with previous versions whose exclusivity have expired.

In summary, the current evergreening policy actually inhibits innovation, deters competition, and creates an anomalous windfall extension of drug exclusivity.

We have attempted to work with the FDA to resolve this issue for 2 years. Nevertheless, in Serono's opinion, FDA continues to administer the exclusivity principle in an inconsistent and unclear manner. The evergreening policy is now riddled with ad hoc exceptions not found anywhere in the statute or in the regulations. We, therefore, believe that clarifying legislation is warranted.

Again, I would like to thank the committee for the opportunity to testify on this important matter affecting the incentive to develop improved drugs for rare diseases. We appreciate the committee's attention and consideration, and I would like to thank Dr. Ganske for his earlier comments.

[The prepared statement of Thomas A. Lang follows:]

PREPARED STATEMENT OF THOMAS A. LANG, SENIOR VICE PRESIDENT, STRATEGIC PRODUCT DEVELOPMENT, SERONO, INC.

INTRODUCTION.

Good morning, my name is Tom Lang. I am Senior Vice President for Strategic Product Development at Serono, Inc. I would like to thank the Chairman, and other members of the Committee, for the opportunity to testify on the issue of orphan drug exclusivity "evergreening," which is addressed by H.R. 4242. At this time, I want to make it clear to the Committee that Serono believes this issue needs to be addressed irrespective of the impact on our products. FDA's current evergreening policy affects all drugs governed by the Orphan Drug Act (ODA) and represents a policy issue that demands your attention. We fully support the remedy posed by H.R. 4242; however, we would be equally supportive of an administrative remedy accomplishing the same goal.

As a global leader in biotechnology with a number of drugs and biologic products already approved in the U.S. and many more in our research pipeline, Serono is a strong supporter of the Orphan Drug Act. We recognize the need to provide strong incentives to develop drugs for rare diseases, and indeed, many of our drugs have orphan drug designations as well as orphan drug exclusivity. However, we have recently encountered a problem with FDA's anomalous and confusing interpretation of the Orphan Drug regulations, which results in orphan drug exclusivity "evergreening." In this context, "evergreening" refers to FDA's granting of a new seven year orphan drug exclusivity period for the entire drug substance upon the approval of a second, clinically superior, version of the same drug, rather than protecting only the innovation exhibited by the second drug. This results in closing the market to competition beyond the initial seven years of exclusivity intended by Congress.

This is an unwarranted extension of orphan drug exclusivity. It presents troubling policy issues of fairness, impediments to price competition that would benefit consumers, and the delay in availability of alternative therapies for patients.

BACKGROUND.

The phenomenon of orphan drug exclusivity "evergreening" is a result of FDA's interpretation of its regulations giving effect to the ODA, and not a result contemplated or intended by Congress. The ODA itself created incentives for drug companies to develop therapies for rare diseases by awarding a period of seven years of market exclusivity to a product approved for an orphan indication. During these seven years, FDA may not approve other applications which are for the "same drug" and the same disease or condition. Congress intended that after this period of exclusivity, the public would benefit from increased treatment options as well as price competition among various products in these areas. The ODA overall has been a significant success in driving research for rare diseases.

However, the statute is silent as to improved versions of previously approved orphan drugs. In the regulations adopted by FDA to implement the ODA, the agency created a mechanism by which a second product could also be approved during the

period of market exclusivity awarded to the first drug. Such exceptions are made where a second drug is deemed to be clinically superior to the first orphan drug. FDA's intention in creating this mechanism was to maintain incentives for companies to continue research on orphan drugs, and to reward additional advancements by allowing them earlier access to an otherwise closed market. While this objective is laudable, FDA has recently chosen to implement it in a very problematic fashion.

FDA'S EXCLUSIVITY POLICY.

Recently, FDA has adopted a policy position related to the scope of a clinically superior orphan drug's exclusivity that actually undermines the incentives for companies to continue to innovate for additional improvements in these areas. As noted earlier, FDA's policy also raises questions of fairness, alternate product availability, and patient and physician choice of therapy.

Now, after approval of an original orphan drug, whenever a subsequent orphan drug with a clinically superior improvement has also been approved and awarded exclusivity, FDA totally restarts the seven-year exclusivity clock for the drug as a whole. In this way, the improved drug shields the original drug from competition, even after the original drug's exclusivity period is over. In these instances, companies that have developed new competing versions of the same drug to treat the disease in anticipation of the expiration of the original seven-year exclusivity are unfairly denied access to the market for an additional seven-year period. Under FDA's current policy, this total period of exclusivity barring the entry into the market of competing product versions could theoretically be as long as fourteen years if two drugs were approved; as long as twenty-one years if three drugs were approved, and so on. This possible extension, or "evergreening" of the original drug's exclusivity period by restarting the clock for the entire drug substance when a second or third clinically superior version is approved is the problem sought to be addressed by the Thornberry Bill (H.R. 4242).

ORPHAN DRUG EVERGREENING IS NOT A SINGLE PRODUCT ISSUE.

FDA has designated at least five drugs as orphans, based solely on their demonstration of superiority over a previous version.

- Avonex® (recombinant beta interferon la for relapsing remitting multiple sclerosis), exclusivity based on clinical superiority to Betaseron.
- Sandostatin LAR® Depot (generic name octreotide for several orphan indications, primarily transplant rejection)—long acting formulation, exclusivity based on superiority in dosing to original drug.
- Nutropin Depot® (recombinant human growth hormone for pediatric growth hormone deficiency) dosing superiority, long acting formulation.
- Benefix™ (Coagulation Factor IX for hemophilia) - Recombinant version judged safer than two previous versions.
- Prolastin® (Alpha 1 proteinase inhibitor for emphysema), long acting formulation superior in dosing convenience to original orphan drug.

All five were considered to have presented a safety or dosing improvement over the original version of the drug. The active chemical entity in all five cases is the same as the original drug. The older versions were all approved as safe and effective products and are still being marketed. Thus, a new competitor in these other disease areas would also be expected to face an evergreening problem, based on FDA's policy.

OTHER AREAS OF FOOD AND DRUG LAW LIMIT THE SCOPE OF EXCLUSIVITY FOR NEW VERSIONS OF PREVIOUSLY APPROVED PRODUCTS.

As with the Orphan Drug Act, the Waxman-Hatch Act seeks to create incentives for continued research on approved drugs and product improvements. The Waxman-Hatch Act, as one would expect, rewards only the innovative feature with exclusivity, rather than shielding the drug substance from generic competition when its original exclusivity period has run. This serves as evidence of Congress' intent, and provides a basis for supporting the principle in H.R. 4242.

FDA'S POSITION OF ONLY ALLOWING ABBREVIATED APPLICATIONS TO COMPETE WITH AN EXPIRED ORPHAN LACKS A RATIONALE.

FDA's handling of our product has resulted in several very strained policy positions on the part of the agency. For example, in a letter to Serono dated November 8, 1999 (copy attached), FDA indicated that while it would not allow our product to be marketed in competition with the original drug approved for this orphan drug

indication, it would approve a generic version of the original product to come on the market if it were eligible for an abbreviated new drug application (ANDA.)

In Serono's opinion, this position indicates that FDA in fact agrees in principle that the exclusivity that was awarded to the second clinically superior drug should not prevent competition with the original product whose exclusivity has lapsed. However, FDA makes an arbitrary determination that only ANDA drugs can compete, but not drugs that are supported by full new drug applications (NDAs and BLAs). There is no rationale whatsoever for preventing competition from products that are supported by full NDAs and BLAs.

FDA'S ACTION IN A SUBSEQUENT CASE IS ACTUALLY CONSISTENT WITH H.R. 4242.

Recently, Serono became aware of an instance where FDA has taken what appears to be a different position than with our product, and one which appears to be consistent with H.R. 4242. In a letter to Genentech dated October 28, 1999 (copy attached), FDA advised the company that new long acting formulation of recombinant growth hormone (Nutropin Depot) has been designated as an orphan, but that the orphan designation "applies only to the long acting formulation," rather than to the entire drug substance. This means that the Nutropin Depot improved formulation, once approved, would achieve orphan protection for seven years, but its exclusivity only would cover the improvement, and manufacturers wishing to introduce additional versions of the conventional dosage form would not be blocked. Thus, in this instance, FDA's position appears to be totally consistent with H.R. 4242.

SOLUTION TO "EVERGREENING" PROBLEM.

Fortunately, the "evergreening" problem is one that has an extremely simple solution. Orphan drug exclusivity evergreening can be resolved by FDA or Congress by simply limiting the second, "clinically superior" drug's scope of orphan drug exclusivity to the superior innovation, feature, or characteristic that distinguished it as clinically superior. This solution would properly reward the innovation found in the clinically superior drug, while still allowing competition with an expired original drug, as intended by the law. Again, FDA could remedy this problem itself, without legislation, by simply modifying its current policy as to the scope of exclusivity associated with a "clinically superior" orphan. This would be consistent with other exclusivity-related legislative initiatives, such as the Waxman-Hatch Amendments, and patent law as well.

THE SOLUTION PROPOSED IN H.R. 4242 WOULD RETAIN INCENTIVES FOR INNOVATION IN ORPHAN DRUG RESEARCH.

Limiting the scope of exclusivity of a clinically superior orphan drug to its clinically superior feature still leaves the drug sponsor with an adequate incentive. A clinically superior drug would gain three significant rewards. First, it achieves the benefit of being allowed onto the market immediately despite the originator drug's exclusivity. Second, it obtains seven years' exclusivity for the improved feature. Third, it will be able to market its product as clinically superior. These are substantial rewards and incentives. These substantial incentives make it unnecessary to keep the market closed to other products wishing to compete with previous versions whose exclusivity may have expired.

CONCLUSION

In summary, the current evergreening policy unnecessarily denies patients and physicians alternative therapeutic options. In our view, given the way it is being administered, it actually inhibits innovation and deters competition, and creates anomalous windfall extensions of drug exclusivity. We have attempted to work with FDA to resolve this issue for two years. Nonetheless, in Serono's opinion FDA continues to administer the exclusivity principle in an inconsistent and unclear manner. The evergreen policy is now riddled with ad hoc exceptions not found anywhere in the statute or in the regulations. This has caused significant confusion for industry. We therefore believe that clarifying legislation is warranted to avoid policy that we believe was never intended by Congress. That is why we support H.R. 4242.

Again, I would like to thank the Committee for the opportunity to testify on this important matter affecting the incentive to develop improved drugs for rare diseases. We appreciate the Committee's attention and consideration.

Mr. BILIRAKIS. Ms. Bennett, please.

STATEMENT OF CATHERINE P. BENNETT

Ms. BENNETT. Thank you, Mr. Chairman and members of the subcommittee. I appreciate this opportunity to testify on an issue of great personal importance to me, cancer awareness treatment and research.

I am here representing the Cancer Research Foundation of America as chairman of its board of directors. We are a national nonprofit health organization whose mission is cancer prevention through scientific research and education.

Since its founding in 1985, the Foundation has funded research by more than 200 scientists at more than 100 leading universities and medical centers. And it is one of the only 10 non-Federal agencies whose grant review process is approved by the National Institutes of Health.

Within the last year, CRFA has increased its focus on childhood cancers with the establishment of Hope Street Kids, a foundation created under the umbrella of CRFA following the loss of Caroline Pryce Walker. The mission of Hope Street Kids is to eliminate childhood cancer through advocacy education and cutting-edge research and to help sustain and support children with cancer and their families during and after treatment.

Unfortunately, most us have had a personal experience with cancer. We have seen it attack a family member, a friend, a coworker, or we have been diagnosed ourselves. I was diagnosed with breast cancer in 1993. It is a dreaded and pervasive disease that claims the lives of more than 500,000 Americans each year, and it is a disease that knows no racial, ethnic, economic or gender boundaries. Perhaps what is even more disturbing is that cancer also does not discriminate based on age. Many of us think of it as a disease of the elderly or middle aged, but we must also recognize that cancer is the No. 1 cause of death by disease for children.

Each year, more than 12,000 children are diagnosed with cancer and some 2,300 children will die from the disease. That is about 100 classrooms filled with children who won't start school next September. September is significant in that it is recognized as National Childhood Cancer Awareness Month.

So it is appropriate that the committee has House Resolution 576 sponsored by Congresswoman Deborah Pryce on its agenda.

I am pleased to testify in support of in resolution which seeks to raise awareness about the realities of childhood cancer and make suggestions or recommendation about where Congress could help ensure that more children live to start a new school year. The statistics in the resolution demonstrate the challenges we face. The incidence of cancer among children is rising by 1 percent each year. One in every 330 Americans develops cancer before age 20. It constitutes about 8 percent of deaths between the ages of 1 and 19. And as I mentioned, it is the leading cause of death by disease in children.

It is clear to me that we cannot dismiss this disease as rare or ignore the substantial loss of life for which childhood cancer is responsible. In my mind, even one child lost to cancer is unacceptable. The good news is that progress has been made. Four years ago a diagnosis of childhood cancer was a death sentence. Today, almost 70 percent of children diagnosed will survive. Nonetheless,

that means 30 percent do, in fact, succumb. The success rate can be attributed in part through research through clinical trials. They have become the standard of care for pediatric oncology patients with approximately 70 percent of the children who are diagnosed participating. This makes sense to build on these efforts by making sure that opportunities for childhood cancer research are funded and that we attract the best and brightest to pediatric oncology and that we make sure that as many children as possible have access to the centers of excellence and clinical trials.

The resolution suggests that Congress support such policies. Additionally, H. Res. 576 encourages support for policies that encourage the development of new drugs in biologics. As members of this committee know, the Food and Drug Administration Modernization Act provides additional incentives to encourage greater private investments and research by providing some additional 6 months of market exclusivity to sponsors of new or approved drugs if they conduct pediatric studies. Despite the good intentions of this law, the policy has not proven as effective in stimulating research or providing additional information about drugs that may prove useful in pediatric oncology. I believe it is worth reevaluating the policies reflected in that statute.

While we look to the future with hope that we will see the day when no child becomes the innocent victim of cancer, we must also face the reality that children today are suffering and are dying. We must focus our attention on improving the quality of life for these patients. The horrors of cancer are many, but it is hard to imagine anything more tortuous than a parent witnessing their child in pain. Yet many will tell you that they have been forced to stand helplessly by while their children are enduring invasive and painful treatments.

The resolution points out a recent study which revealed that 89 percent of children with cancer experienced substantial suffering in the last month of life. Why, in this day of modern medicine and technology, is this necessary or acceptable? In my view it is not. The reason for inadequate pain relief for children in cancer patients may be many, but one can be found in the lack of training for pain management received by physicians in their medical training.

We can begin to address this issue by expanding knowledge among medical personnel to help them recognize the signs of pain and treat them effectively. The resolution is supportive of such curriculum as part of medical training.

The battle against childhood cancer is being hard fought, but those that know the horrors of this disease, and many of them will be in Washington this week to do what they can to raise awareness and recruit Congress and others, whoever will listen, in fact, to their cause. I believe Mrs. Pryce's resolution is a good first step that indicates a congressional understanding of the issues at hand and provides an outline for what a successful policy aimed at defeating childhood cancer should entail. I encourage the subcommittee to lend its support to this legislation and again, appreciate the opportunity to participate today.

[The prepared statement of Catherine P. Bennett follows:]

PREPARED STATEMENT OF CATHERINE P. BENNETT, CHAIRMAN, BOARD OF DIRECTORS, CANCER RESEARCH FOUNDATION OF AMERICA

Thank you, Mr. Chairman and members of the Subcommittee. I appreciate this opportunity to testify on an issue that is of great personal importance to me—cancer awareness, treatment, and research.

I am here representing the Cancer Research Foundation of America, as Chairman of their Board of Directors. For those of you not familiar with CRFA, we are a national, non-profit health organization whose mission is the prevention of cancer through scientific research and education. Founded in 1985 by Carolyn Aldigé, the Foundation has funded research by more than 200 scientists at more than 100 leading universities and medical centers, and is one of only ten non-federal agencies whose grant review process is approved by the National Institutes of Health. And, I am pleased that within the last year, CRFA has increased its focus on childhood cancers with the establishment of Hope Street Kids, a foundation created under the umbrella of CRFA. The mission of Hope Street Kids is to eliminate childhood cancer through advocacy, education and cutting-edge research, and to help sustain and support children with cancer and their families during and after treatment

Unfortunately, most of us have had a personal experience with cancer. We have seen it attack a family member, a friend, a coworker, or we have been diagnosed ourselves. This dreaded and pervasive disease claims the lives of more than 500,000 Americans each year. And, it is a disease that knows no racial, ethnic, economic, or gender boundaries. Perhaps what is even more disturbing is that cancer also does not discriminate based on age. Many of us think of cancer as a disease of the elderly or middle-aged. But, we must also recognize that cancer is the number one cause of death by disease for children. Each year, more than 12,000 children are diagnosed with cancer and each year, some 2,300 children will die from the disease. That's about 100 classrooms filled with children, who won't start school next September.

September is also significant in that it is recognized as National Childhood Cancer Awareness Month. So it is appropriate that the Committee has house resolution _____, sponsored by Congresswoman Deborah Pryce, on its agenda. I am pleased to testify in support of this resolution, which seeks to raise awareness about the realities of childhood cancer and make suggestions about where Congress can help ensure that more children live to start a new school year.

The statistics in the resolution demonstrate the challenge we face:

- The incidence of cancer among children is rising by one percent each year.
- One in every 330 Americans develops cancer before age 20.
- Cancer constitutes about 8% of deaths between ages 1 and 19.
- And, as I mentioned earlier, it is the leading cause of death by disease in children.
- It is clear to me that we cannot dismiss this disease as "rare" or ignore the substantial loss of life for which childhood cancer is responsible. In my mind, even one child lost to cancer is unacceptable.
- The good news is that progress has been made. Forty years ago, a diagnosis of childhood cancer was a death sentence, but today almost 70 percent of children diagnosed with the disease will survive. This success rate can be attributed to research through clinical trials. In fact, clinical trials have become the standard of care for pediatric oncology patients, and about 60 percent of children that are diagnosed with cancer participate. That compares with only 3% of adult cancer patients and 1.5 % of Medicare patients.

It makes sense to build on these efforts by making sure that opportunities for childhood cancer research are funded, that we attract the best and brightest scientists to pediatric oncology, and that as many children as possible participate in and benefit from the discoveries made through clinical trials. H. Res. _____ suggests that Congress support policies consistent with these goals.

Additionally, H.Res. _____ encourages support for policies that encourage the development of new drugs and biologics. As the Members of this Committee know, the Food and Drug Administration Modernization Act of 1997 provided an incentive to encourage greater private investment in research on the use of drugs to treat pediatric diseases. Specifically, the Act provides an additional six months of market exclusivity to sponsors of new or approved drugs if they conduct pediatric studies that may produce benefits for children. Despite the good intentions of this law, the policy has not proven effective in stimulating research or providing additional information about drugs that may prove useful in treating pediatric cancer. It is worth re-evaluating this policy and its implementation by the FDA so that we can ensure that children are not left out of the tremendous advances in the treatment of disease that new drugs and biologics can provide.

While we look to the future with hope that we will see the day when no child becomes the innocent victim of cancer, we must face the reality that children today

are suffering and dying. We must also focus our attention on improving the quality of care and of life for these patients. The horrors of cancer are many, but it is hard to imagine anything more torturous for a parent than witnessing their child in pain. Yet, many parents will tell you that they have been forced to stand by helplessly while their child endured invasive and painful treatments. As H.Res. _____ points out, a recent study revealed that 89 percent of children with cancer experienced substantial suffering in the last month of life. Why, in this day of modern medicine and technology, is this necessary or acceptable? In my view, it is not. The reasons for inadequate pain relief for children and cancer patients may be many, but one can be found in the lack of training for pain management received by physicians in their medical training. We can begin to address this issue by expanding knowledge among medical personnel to help them recognize the signs of pain and treat them effectively. H.Res. _____ is supportive of such curriculum as part of medical training.

The battle against childhood cancer is being hard fought by those that know the horrors of this disease, and many of them will be in Washington this week to do what they can to raise awareness and recruit Congress and others—whoever will listen—to their cause. I believe H.Res. _____ is a good first step that indicates a congressional understanding of the issues at hand and provides an outline for what a successful policy aimed at defeating childhood cancer should entail. I encourage this subcommittee to lend its support to this legislation.

Again, I appreciate the opportunity to participate in today's hearing and to speak to this issue during Childhood Cancer Awareness Month.

Thank you, Mr. Chairman.

Mr. BURR [presiding]. Thank you, Cathy, and welcome. The Chair would take this opportunity to recognize himself, as soon as he gets his thoughts. And we apologize that there are members trying to get back. And it is the intent of the committee to continue with the hearing rather than take a break for lunch because of the afternoon schedule. Here we think it is not only more beneficial to us, but also to you to go ahead and allow those members to make it back to ask questions.

Ms. Meyers, let me ask you some specific questions. Things have changed significantly since we originally put together the orphan drug legislation, haven't they?

Ms. MEYERS. Yes.

Mr. BURR. Can you be a visionary for us just a minute and look out once the human genome project is complete, once we have mapped the genetic outlay of the human structure, how many of what we classify as rare diseases today do you think that researchers will be out there trying to find the key to the cure for in the future?

Ms. MEYERS. Well, it is very complicated because it is not just a matter of everybody, for example, with muscular dystrophy having the same genetic defect. There are many different genetic defects that may result in Duchenne's muscular dystrophy. And down the road in about 20 years, the way I foresee it, the way the scientists do, is that they will be able to personalize drugs for the particular genetic defect that has occurred in individuals. So we will have custom-made bio technology drugs to address the specific defect in that gene.

Mr. BURR. Which means the population, that because they are going to be subsets of disease, the population that they are going to target is going to be tremendously small.

Ms. MEYERS. Minuscule.

Mr. BURR. So is it safe for the members of this committee to assume that a large share of the pharmaceutical applications that will go in are going to be under the orphan drug legislation, because the population is defined at 200,000 people, if I remember

correctly, we will clearly be chasing a multitude of things under that population.

Ms. MEYERS. It will be a growing number of treatments for the small populations, most of which will come from biotechnology.

Mr. BURR. Is there any reason that we as a committee and as an institution should, in any way, shape or form, look out at that 200,000 person number, knowing the changes that are going to take place through the genetic mapping, and at least debate or possibly change that number to be more reflective of where we think exclusivity should be in the future? I am not talking about the debate that we are at at this table, I am trying to think out a number of years.

Ms. MEYERS. Well, looking back over the 17-year history of the Orphan Drug Act, the problems that have arisen have not arisen around the size of the population. The problems that have arisen are pricing problems. And even drugs for very tiny numbers of people, if you are going to charge $100- or $200,000 a year for that treatment, you are going to make a lot of profit. And so, if there are any changes to the Orphan Drug Act and one of them was introduced and actually passed the House and Senate by Mr. Waxman in 1990, and it was vetoed by President Bush and that was aimed at shortening the period of exclusivity for blockbuster drugs. So I would not lower the size of the population because 200,000 is not a huge number and believe me, it is even hard to find companies that are willing to make drugs for 3- or 400,000 Americans.

Mr. BURR. In today's research environment?

Ms. MEYERS. Yes.

Mr. BURR. Ten years from now, in tomorrow's research environment where you have got a map that leads to you a point that it took you 5 years now to hopefully do research to find, my question was not should we, it was should we at least have a debate on it? Should we bring in individuals out of biotechnology and pharmacological research to discuss what do you see down the road? Are you going to be chasing diseases because of the information you have that there is a population of 5,000 and 7,000 and 12,000, which means that the majority of the stuff that we do will be classified as under the Orphan Drug.

Ms. MEYERS. It is true, but, you know, the bigger these companies are getting with their mergers and their acquisitions, I mean, they are interested in Viagra, they are not even going to be looking at these types of diseases. The latest one is something about removing facial hair. I mean these kinds of markets are so huge, the big companies don't want to look at a drug with an estimated sales under a billion a year.

Mr. BURR. Clearly you make a point that is probably an accurate one today, if through these advances it is much easier for them to design that drug of the future, as you said, a custom-designed drug, it may be a whole different situation.

Ms. MEYERS. I think it will be, yes.

Mr. BURR. Did you ever envision under the Orphan Drug law that—let me ask it a different way: Do you think it is right under the Orphan Drug law that a company could have an approval, could have their exclusivity, at some point during that period of exclusivity they made an enhancement to the product, they reapplied,

and were approved for whatever reason at FDA and got a new year—7-year exclusivity?

Ms. MEYERS. Yes.

Mr. BURR. Did you envision when the Orphan Drug law came about, that that was something that would happen?

Ms. MEYERS. First of all biotechnology was in its infancy. We couldn't imagine what would happen with biotechnology. But we saw early on in 1985, Genentech got approval for human growth hormone, and a few months later Eli Lilly came on with a different version of human growth hormone. And it created exactly this situation. FDA approved Eli Lilly's second version of human growth hormone saying it was economically or structurally different.

Mr. BURR. Two different companies.

Ms. MEYERS. Two different companies.

Mr. BURR. Should the same company have the ability to reapply for whatever changes, get a new 7-year exclusivity agreement?

Ms. MEYERS. Yes. And that also happened with Genzyme's drug for genetic disease for Gaucher's disease where they did improve it. It had been made out of a natural blood substance or something, and then they made a biotechnology version and they got another 7 years. Yes, they should, because the main incentive is to develop a better drug. And it worked.

Mr. BURR. Do you see any problem with the fact that the company who has the current exclusivity certainly has a tremendous advantage because they have the data? That is not—that is not data that is shared within the community of researchers that are out there. And if, in fact, nobody wants to invest the money to create that data base to chase that small population drug, you really do have an inherent ability of one company to continue to restart the clock. I am not saying that it happens today. I think that to some degree, in health care we have to start getting visionary in this institution.

We do a poor job at crisis management, but that seems to be the only thing that we try to address now is the crisis management of today's problem. And I think that we have got to focus out on the future and ask ourself what do we need to do in preparation for the changes. I would only suggest to you that I see a potential problem there as a Member of Congress. I see the ability for one company to continue to restart the clock almost like FDA used to do in their application process when they changed investigators and when they wanted to slow down the process, they asked for a new piece of information and the new 180 days started. And that became more the norm than the exception. But it is a question that I raise.

Ms. MEYERS. I agree with you. It could be a potential problem, but the fact is when the exclusivity on the first drug expires, any other company can get on the market and make that first drug. Like a generic drug, except for one thing. Congress has never passed a law that allows the FDA to approve generic biologics. And so they have to do all of the research, all of the clinical research and prove all the safety and effectiveness of a brand new drug, and then they are allowed on the market to compete with the drugs whose exclusivity has expired. That is what could happen here. Betaseron, the first beta interferon, their exclusivity has expired.

If any company can prove that their beta interferon is the same as Betaseron, they would get on the market.

Mr. BURR. We have clearly got some work that we know we need to do.

I want to turn to Mr. Navarro. Mr. Navarro, I don't want you to think in any way, shape or form that members of this committee and Members of Congress haven't struggled not just this year, but for a number of years to try to find the right balance of the goals standard of the FDA, their process, and the innovative treatments that Dr. Brezinski and others have in the marketplace today, and certainly I have been involved for 4 years in Dr. Brezinski's treatments. And hopefully we have—this committee has contributed greatly to the process forward of the current clinical trials that he has, the expansion of those trials as a liaison between FDA and Dr. Brezinski on the data that was needed for us to get expansions. But I don't want to address Dr. Brezinski's treatment specifically, because one thing I want you to understand is that Members of Congress are not here to practice medicine. But we are here to try to address the structure that is needed for everybody to receive the quality of care that they deserve. In doing that, I have found it to be very difficult. Because quite honestly, many of the patients that visit me with the personal stories of their fight don't come back the next year. That makes a very, very big impact on every Member of Congress I can assure you, as it does the families, of which many of us have affected in our families.

My hope is that we can be visionary, we can look at some of the treatments that exist out there. And that we can form a partnership between medicine and FDA and medicine and NIH and medicine and HCFA, and that we can get patients back to the forefront of the health care delivery system in this country. We spent a lot of time arguing whether it is reimbursements or whether it is doctors or whether it is hospitals or whether it is insurers, and really more time about the process than we do about the outcome. I understand you are only concerned with the outcome. That is all you should be concerned with. We have got to deal with everything else.

But let me ask you specifically as it relates to your son, is it your understanding from the health care professionals that treated your son, that there was no conventional treatment that was FDA approved, be it chemotherapy or anything else that they had suggested that was specifically FDA approved for pediatrics?

Mr. NAVARRO. You have to understand that radiation and chemotherapy, and I am going to pick just on Thomas's disease for a minute, has not been approved for the very reason that it doesn't produce successful results. I have had the opportunity in the last year to speak to more parents than I care to remember that are the parents of dead children who presented to me their medical records, the results of the chemotherapy the results of the radiation. And it became very clear very early on that this was a very, very dangerous option that I did not want to take with Thomas. In the case of chemotherapy you have to understand that chemotherapy is a cytotoxic poison and Thomas' oncologist made it very clear that we are going to basically stretch you to your limits because it is unnatural for a parent to voluntarily poison their child

in the hopes that it will create a cure. And we have had to go through this process with Thomas and watch him endure the poisoning with great frustration and anxiety realizing that there was a non toxic chemotherapy available that other children had been allowed to use and yet Thomas had been denied access to that.

That particular therapy has been with us for almost 30 years, and for the last 18 years there have been efforts made to bring it to the forefront where it can be approved but again, it has been continually blocked. And the point that I have been trying to make for the last year is if I have to choose between two unapproved therapies, which both are, why as a parents do I not have the right to go with the therapy that will do the least amount of damage to my son and then if it doesn't work, step up to a more aggressive therapy. I have spoken to parents of children that have been destroyed by radiation and chemo. And I am thinking in particular of the young man from Houston, Texas who today, at 19 years old, is deaf, dumb, blind, strapped to a wheelchair, has an arm's length list of side effects, and yet now that his parents need help in his maintenance and care, are denied access to that. Because this child, who is—picture him strapped to a chair, he can't see, speak or hear, can't move, can't function, is deemed a danger to the other patients, therefore he can't go into a group home. I am still, after almost a year, trying to figure out how he becomes dangerous if he can't operate under his own power.

And again, my frustration with the FDA is we have even applied for a compassionate use exemption. Now the doctor that we chose to go to in Houston has a protocol for medulloblastoma. He has treated with the blessings of the FDA children with medulloblastoma. But I found it odd that as more and more children came through the process well, that all of a sudden there was a new step put in place saying we can no longer allow you to treat these children until they first go through radiation and chemotherapy and fail and have recurrent measurable tumor.

If this is a pure glass of water, and my agency is in charge of making sure that water is available that is healthy to all and I allow someone to come over here and pour a substance into it and say, well, Mr. Brady, we want you to have clean water, but before you can drink this clean water, someone is going to be allowed to taint it. I think he would be reluctant to drink the water.

And in Thomas' case, how can we know if the FDA is truly and sincerely interested in progress and medical and scientific breakthroughs? How can we ever know if the treatment we wanted for him is successful, if we taint the baseline about other therapies that take, to be honest, a lifetime to recover from?

Mr. BURR. I hope you will accept my answer which is, I don't have one. I can't explain it to you. But I will assure you that this committee has not quit, the members on this committee have not quit to try to one, wade through the modernization of the Food and Drug Administration, which we completed in 1997, which people gave us no hope could be done and had passed with unanimous bipartisan support from this House and from the Senate and was signed into law by the President. We are still waiting to see the full changes as they are implemented from that legislation. It is not always a fast process. But much of that is by design in this sys-

tem. I hope you understand that we will continue to strive to make sure that we have the answer for you and for the other parents that I know will be here in the future, whether it is on this treatment or another treatment, because we will never build a system that is perfect. But we will never be content with what we have. We will always strive for something better.

The unfortunate thing is I have been notified that we have a series of votes. And because I know that that will throw further the end of the turmoil of members' schedules this afternoon because of the knowledge of their schedules, I am going to take this opportunity to apologize to all of you, because I know that we will have a lack of participation if we take 45 minutes off and try to reconvene.

I am going to leave the record open for written questions to come to each of you from any members of the subcommittee. And I hope you will respond to those written questions with answers for the purposes of the record. Let me, once again, on behalf of the chairman, thank you for your participation in this hearing. This hearing is now adjourned.

[Whereupon, at 12:45 p.m., the subcommittee was adjourned.]

[Additional material submitted for the record follows:]

ADDITIONAL TESTIMONY FOR THE RECORD OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES

The Food and Drug Administration (FDA or Agency) has serious concerns about H.R. 3677, Thomas Navarro Patients Rights Act because this bill will seriously weaken the Agency's ability to protect individuals who volunteer to participate in clinical trials, one of its primary statutory missions. The Agency would be precluded from protecting a segment of the population from insufficient information, misinformation and, at worst, fraud. The Federal Food, Drug and Cosmetic (FD&C) Act created a process that carefully balances the need for scientific support for new products with the overriding need to protect human subjects. H.R. 3677 upsets this balance and could lead to harm or possibly death for some patients.

Under the FD&C Act, FDA has been provided the authority to regulate the use of investigational (unapproved) drugs. As an element of this authority, FDA regulates clinical human investigation conducted by a sponsor. Under statutory and regulatory authority, sponsors wishing to use investigational, unapproved drugs in human patients must file an Investigational New Drug application (IND) with FDA. This IND is either an IND that is designed to involve a number of patients or can be filed as a single patient IND to treat one patient.

The Food and Drug Administration Modernization Act of 1997 (FDAMA) codified and expanded FDA's programs to provide access to unapproved products in section 561 of the FD&C Act. This was done after extensive review and consideration of the needs of patients. The intent was to provide access to therapies for which there was no effective, approved therapy and particularly for patients who had failed existing approved therapy. The provisions are clear in requiring the individual physician, FDA and the sponsor of the investigational drug to go through a series of steps before allowing the drug to be made available to the patient. These ultimately require a balancing of the risks and benefits of the proposed administration of the investigational drug. As part of the access program, the sponsor is still required to file either a single patient IND or an IND to treat a small number of patients.

FDA is obligated to evaluate an IND submission within 30 days and make a determination if the clinical investigation should proceed or the investigation should be put on clinical hold. The primary focus of this decision is the safety of the patients who may receive the unapproved drug. The evaluation includes a determination of the nature and level of risk to the patients who may be the subject of the clinical investigation, design of the clinical investigation, various qualifications of the investigators, the disease being investigated and other information about the drug. The same evaluation is done for submissions that may be considered single patient INDs or emergency INDs, although FDA makes the decision in a considerably shorter time period than 30 days and in the case of an emergency IND usually within 24 hours or less.

FDA has, in rare instances, placed on clinical hold a proposal to administer an investigational drug about which little was known to treat a serious or life threatening disease when there was known effective, or life saving, therapy for that condition. We did so because those subjects would have been exposed to an unreasonable and significant risk of illness or injury. This is also required under FDA regulations governing clinical holds. (Title 21, Code of Federal Regulations § 312.42). The risk in these cases was not simply the possible untoward effects of the investigational agent but also the risk of substituting a known effective therapy with something that might have no effect. Although these circumstances occur rarely and are dwarfed in numbers by those clinical trials allowed to proceed, the ramifications of being unable to put a particular investigation on hold would be dramatic.

FDA understands the seriousness of placing any investigation on clinical hold and does so only after following a careful process that includes deliberation with internal experts and, if necessary, consultation with external experts about the particulars of the disease state and potential for available therapies.

The ability to put an investigation on clinical hold is the primary mechanism FDA has to protect human subjects who are being asked to participate in a clinical investigation and asked to be part of an experiment with unapproved investigational drugs. H.R. 3677 contains several provisions that could impair the ability of FDA to put clinical investigations on hold even if a patient's safety is being compromised and could prevent FDA from taking action specifically for an individual patient who may be at a high level of risk.

Section 2 (a) of H.R. 3677 amends section 505(i)(3) of the FD&C Act by limiting the ability of FDA to impose a clinical hold on an investigation. The new provision would prohibit a clinical hold even if another therapy is determined to be safer because it is a known curative therapy. The entire basis for this prohibition on FDA is that the patient has, in effect, waived their right to informed consent. The patient, by declaring in writing that s/he is "aware of the comparable or satisfactory alternative therapy . . . aware of the risk involved in receiving the drug in the investigation, and chooses to receive the drug notwithstanding such risk and notwithstanding the comparable or satisfactory alternative therapy" could prevent the imposition of a clinical hold even for safety reasons which may be directly related to the individual patient's safety.

The bill creates a situation in which research subjects may be presented with incomplete and/or biased information by investigators who often have substantial personal, financial or professional interests at stake in the research. FDA is concerned that the consent obtained under these circumstances will not be truly informed consent because it will not be based on a thorough and objective explanation of the risks and benefits of both the unapproved investigational product and the proven treatment that is being foregone.

H.R. 3677 does not even require that the sponsor administering the unapproved investigational drug provide all the information to the patient typically contained in an informed consent. The idea that a patient could essentially sign away their rights to adequate health care to anyone who is able to convince them to do so, without oversight and without any assurance of proper information, is offensive and unethical. Even absent mal-intent, the most well intentioned investigator is unlikely to have access to all that is known about an unapproved investigational drug very early in its development.

Furthermore, since FDA has been provided the authority to oversee the use of unapproved investigational drugs, the Agency is the one central location that collects data on those unapproved investigational drugs. FDA is often the only party in possession of information from different sponsors that could impact the decision as to whether an unapproved drug should be used in a clinical investigation. There is no means of ensuring that the patient actually knows all of the risks involved. Reliance on the sponsor of the investigational drug to provide all the known risks is misplaced since that particular sponsor may not have access to all of the information known about a drug. Thus, through no fault of the sponsor, complete information on risk may not be provided to the patient considering the use of the unapproved investigational drug.

The importance of clinical hold as an Agency tool to help ensure the protection of human subjects in clinical trials is illustrated by the recent example of the Jesse Gelsinger case. At age 18, Mr. Gelsinger volunteered to participate in a clinical trial of a gene therapy product and died shortly after the administration of the product. The investigator who recruited Mr. Gelsinger to the trial did not follow the terms of his protocol and did not reveal important safety information during the informed consent process, so that Mr. Gelsinger's consent was not fully informed. When FDA learned of this subject's death, the Agency put this trial on clinical hold so that no other patients would be subjected to the dangers inherent in this trial.

Under H.R. 3677, FDA would have no ability to protect subjects even if the Agency had information that practitioners were using dishonest means to coerce patients into participating in trials in lieu of taking proven therapy. If H.R. 3677 is enacted and such ethically suspect practices are allowed to proliferate, it also could seriously undermine the public's confidence in the process of conducting biomedical research in this country with dangerous consequences to the public health.

There are other technical drafting problems with H.R. 3677 which are not included in this submission. Even if technical changes were made, however, FDA would still have concerns with the impact of the proposed legislation.

FDA has a long, and successful, history of expediting access to investigational agents for those who patients with serious and life threatening illnesses who have no satisfactory therapy available to them. We also have a long and successful history of protecting patients who are most vulnerable, including those with life threatening illnesses who are desperately seeking help and hope.

LUPUS FOUNDATION OF AMERICA
November 9, 2000

The Honorable MICHAEL BILIRAKIS
Chairman, Subcommittee on Health & Environment
U.S. House of Representatives
Committee on Commerce
2125 Rayburn House Office Building
Washington, DC 20515

DEAR MR. CHAIRMAN: In response to your letter of November 2, 2000, I am pleased to submit the attached answers to the questions prepared by members of the Subcommittee on Health & Environment. Please contact me if I can provide additional information.

It was a pleasure to appear before your Subcommittee on behalf of the 1.4 million Americans with lupus. I want to express my sincere gratitude to you and the Members and staff of the Subcommittee for your support of the Lupus Research & Care Amendments of 2000 Act.

Sincerely,

TOMIKO FRASER
National Spokesperson

ANSWERS TO QUESTIONS SUBMITTED BY SUBCOMMITTEE MEMBERS.

Question 1. Why does lupus seem to affect women of color more often than Caucasian women?

Response. This is the subject of a research project currently underway by NIH. (Lupus in Minorities Study, or LUMINA) We believe lupus has a genetic basis and it appears that the genes suspected of causing lupus might be more prevalent among women of color.

Question 2. Are manifestations of lupus more serious among African-Americans than among Caucasians?

Response. African Americans have more kidney involvement than Caucasians. Researchers may have located a gene believed to cause kidney disease in African American lupus patients.

Question 3. Can lupus be prevented, or the health impact minimized in any way?

Response. Unfortunately, you can't prevent lupus. However, you can take steps to minimize health effects of lupus, such as adopting a healthy lifestyle, such as avoiding stress, getting plenty of rest, eating well, light exercise, and following your doctor's advice. Diagnosing lupus early, and seeing a doctor regularly can minimize damage to vital organs. The earlier lupus is diagnosed and treated, the more likelihood of preventing the need for more expensive treatment.

Question 4. Do we know why lupus strikes mostly young women?

Response. The exact cause of lupus is unknown, but researchers believe lupus has a genetic basis. Hormonal influences may explain why lupus affects mostly women in their childbearing years. But we don't know if there is something about women that makes them more vulnerable to developing lupus, or if there is something about men that protects them from lupus.

Question 5. Why is lupus so expensive to treat?

Response. Lupus requires constant medical attention by a number of specialists, requiring many tests to monitor the status of the immune system. Because the disease usually presents multiple symptoms, people with lupus must take many medications. It is common for people with lupus to take over a dozen medications. In addition, monitoring lupus activity requires many expensive tests to determine the

functioning of the immune system and many vital organs, such as the kidneys, lungs, heart, and brain.

Question 6. What impact does lupus have on the work force or corporate community?

Response. One in five people with lupus is disabled. Many victims of lupus must cut back their work hours, or change jobs to reduce stress. This results in lost productivity for corporations, and costs millions of dollars. In addition, disability costs rise to cover people with lupus.

Question 7. What is The financial impact of lupus on the rest of the family?

Response. It's difficult to measure, but it has to be significant. On average lupus costs $6,000 to $10,000 annually to treat, but some victims incur costs of several thousand dollars a month. This level of expense can have an enormous impact on the family budget.

Question 8. Does the environment play a role in causing lupus?

Response. Yes, while lupus has a genetic basis, we know that certain environmental factors trigger disease activity, including UV light, infections, certain chemicals and drugs, and stress. There is much interest in this area of research, particularly in regard with the role breast implants may have in causing an autoimmune reaction.

Question 9. Are we seeing more cases of lupus today than in the past?

Response. It's hard to determine the exact number of lupus cases. We don't know if lupus is on the rise, but doctors are getting better at diagnosing the disease, which may be the reason we are seeing more cases of the disease. However, some researchers do believe that lupus is increasing among young women.

Question 10. Can lupus be treated with less expensive herbal or complementary therapies?

Response. There is considerable interest in this area. Some therapies, when used in combination with a doctor's care, can help reduce symptoms, but they are no substitute for traditional medicine. Lupus is a dangerous disease that needs constant monitoring by a trained doctor. The FDA has given fast track designation to a new therapy for lupus using the hormone, DHEA.

Question 11. Are there new treatments in the pipeline?

Response. Yes, there are several therapies undergoing clinical trials that will address various manifestations of lupus, but the disease is so complicated, no magic pill will ever cure lupus. It will take much more research. Some therapies include biologics that can block the immune system from producing autoantibodies.

Question 12. What is the outlook for a cure for lupus?

Response. While there has been progress, a cure is not on the horizon. We are getting better at treating symptoms of the diseases and patients are living longer, but there is no cure for the foreseeable future.

RESPONSE OF JAMES NAVARRO TO QUESTIONS OF THE SUBCOMMITTEE ON HEALTH AND ENVIRONMENT

Question 1. Mr. Navarro, in your opinion, who should decide the course of medical treatment for your son: you, or the FDA?

Response. This answer requires very little thought. The Food and Drug Administration (FDA) is an agency made up of many different people from many schools of thought. These people many times as we have discovered, get caught up in defending a position, or a particular discipline of medicine and often forget the "PATIENT'S RIGHT TO CHOOSE". Often, the patient is ignored entirely. We as parents of a terminally ill child, have only one agenda, and that is to see our son survive, with dignity and quality of life. Agencies and doctors are often driven by egos and money, as we have tragically experienced during our journey with Thomas. Nobody and I mean nobody, will ever have his best interest at heart, more so than his mother, Donna, and I do.

Question 2. My understanding is that the FDA denied Thomas access to a clinical trial because he had not first gone through and failed chemotherapy and radiation. Why did you decide to forgo this treatment?

Response. Before I can answer this question, we must first clarify a very important fact which is quite often ignored, that fact is that, "RADIATION AND CHEMOTHERAPY HAVE EVER BEEN APPROVED BY THE FDA FOR USE IN TREATING PEDIATRIC CANCERS", it has merely become the unopposed standard of care for treatment, because anyone who stands in opposition to its use is either crushed as far as career advancement goes, or is dismissed as a charlatan as history has bore out. Chemotherapy alone represents a $107,000,000,000.00 ($107 Billion) a

year industry. Our history unfortunately has always born out that profit always comes before people.

It is important to remember that "STANDARDS OF CARE" does not mean that a treatment has been thoroughly tested and adequate evidence reviewed by the FDA or other Federal Agency to assure safety and efficacy. A "STANDARD OF CARE" is not and should not be an endorsement by a Federal agency that has never evaluated the data. "STANDARDS OF CARE" are protocols that doctors in cancer research centers have developed according to their own research as the best treatment option according to their perspective in how to treat cancer.

Now, to be more specific, our reasons for not wanting to use these "STANDARDS OF CARE", on our son were much simpler. The simple fact is these treatments are extremely dangerous to use, and more often than not, end in permanently damaging or even killing the patient. Quite simply, if it is all a "crap shoot", we as parents are compelled to start with a treatment which will do the least amount of harm first. The following is a list of just some of what Thomas would suffer as a result of being treated by Radiation and Chemotherapy: FATIGUE, NAUSEA, VOMITING, ABDOMINAL CRAMPING, HAIR LOSS, LOSS OF IQ, LOSS OF HEARING, LOSS OF MEMORY, FLUID IN THE MIDDLE EAR, HYPOTHYROIDISM, SPINAL GROWTH DEFICIT, HYPOPITUITARISM, SECONDARY TUMORS, LOW LEVEL HORMONES (For the rest of his life), RADIATION NECROSIS, KIDNEY NECROSIS, AND DEATH FROM EITHER RADIATION POISIONNG OR CYTOTOXIC POISIONING. These are just some of the possibilities we faced with Thomas. You must also understand that every child we have met during Thomas's journey that was treated using the "STANDARD OF CARE", is now dead, the most recent we buried just two weeks ago. The choice we made was not a difficult one. We chose life. We knew through careful research that there were other possibilities for Thomas, we never thought our government would stand against us in making those choices.

Question 3. According to the administration's written testimony, the intent of current law is to protect "our most valuable citizens, those who are desperately ill" and that the FDA believes this bill would undermine FDA's ability to help assure reasonable safety and effectiveness of subjects in clinical trails and informed consent for patients given access to experimental therapies." In that Administration statement, with what do you agree or disagree?

Response. The opening statement of this question reminds me of the old axiom; "THE ROAD TO HELL IS PAVED WITH GOOD INTENTIONS." First, all citizens of this great country should be considered valuable, not just the sick, and in keeping with that thought, it is we the people who should be allowed to decide what is best for us. Second of all, the Agency's roll is to monitor safety and effectiveness, not to sit in judgment, deciding who can and can't introduce new promising therapies: as is the case with the treatment we choose for Thomas. For almost twenty years, the FDA has stood as a roadblock to progress, instead of helping to advance a therapy which shows great promise in treating the specific cancer that Thomas suffers from. Third, as far as informed consent goes, this is a process that we personally have seen abused and the FDA and HHS does nothing to correct it. There needs to be better accountability at the FDA and amongst the Doctors. Until or unless that happens, no expanded authority in the decision making process should be considered. The role of both the doctor and the FDA should be to assist us in making decisions by providing us with all of our treatment options and offering their best advice. It is not the role of the FDA or the doctor to take control of our lives and forcing us to submit to their will.

Question 4. H.R.3677 precludes the FDA from establishing a clinical hold on the basis that there is a comparable or satisfactory alternative therapy if the patient is 1) aware of the other therapy; 2) aware of the risk associated with the investigational drug; and 3) chooses to receive the drug. How would this bill affect you and others you may have met during the ordeal you have faced in getting your son the treatment you have decided to be best? Do you see ways in which this bill might be abused by charlatans pushing treatments that do not work?

Response. Again we see in the opening statement, the FDA, usurping a patient's right to choose. Understand that ALL CANCER THERAPIES ARE EXPERIMENTAL AT THIS TIME IN OUR SEARCH FOR THE CURE, and to deny a patient access to their personal choice of treatment based on a personal bias is IMMORAL. The bill does not open the door for charlatans to abuse the law anymore than current laws do. This bill would have allowed us access to the therapy of our choice, a therapy that would not have destroyed our son as conventional treatment would. Also understand that if we had been allowed access to it and it had not worked, we would have stepped our mode of treatment to a more aggressive treatment like chemotherapy or radiation. But to be FORCED into a treatment from the

onset is wrong. The FDA will still be allowed to put clinical trials on hold that have safety concerns. It is the role of the FDA to advance science monitoring the safety of trials involving human subjects. It is not the role of the FDA to pick one trial over another, or to stand in the way of advancing science by excluding access to a clinical trial for a "STANDARD OF CARE" that has never been through an FDA approval process for the specific condition or age group in question.

Question 5. In a news account entitled "PARENTS FIGHT TO SAVE SON", published by Wired News, the article stated that "When the Navarro's decided they wanted their son to be treated by Burzynski, the FDA denied them permission, ruling that the treatment could only be used as a last resort. FDA officials threatened to take Thomas into protective custody if the Navarro's denied him traditional treatment." Do you have any documentation you can provide the Committee that the FDA, or any other government agency, was going to place your son in protective custody?

Response. First of all, I would like to state for the record that I was unaware of this article until I read of it in your questions from the subcommittee. With that said, I found a copy of the article and read it. Now in answer to your question:

It is true that the FDA denied Thomas access to treatment at the Burzynski Clinic, citing that there was no scientific, ethical, or moral basis for allowing Thomas access to treatment when an existing "STANDARD OF CARE" was already available. It didn't matter to them that the "STANDARD OF CARE" had such devastating and deadly results. It didn't matter to them that in the "STANDARD OF CARE" two of the three recommended chemotherapy drugs stated on the package insert, "this product not proven safe or effective in the pediatric population." It was their way of doing business, and to that end their word was final.

In following their logic for a moment, if you have used the most damaging and deadly treatment first, what is left of the patient to treat if the patient has been rendered permanently damaged, or worse, if the patient has died? At this point, treatments that would offer as great or greater a hope have been rendered useless by the FDA's decision making process. In effect, "THEY HAVE THROWN THE BABY OUT, WITH THE BATH WATER".

It is incorrect that the FDA threatened to take Thomas into protective custody. In actuality, When my wife and I made the decision not to subject Thomas to the standard of care, Thomas's oncologist back in Arizona swore out a complaint, alleging CHILD ABUSE, CHILD ENDANGERMENT, AND MEDICAL NEGLECT for refusing a treatment which had discovered would leave our son retarded, deaf, sterile, blind, with stunted growth, and even dead. WHAT IS WRONG WITH THIS PICTURE? It is our undaunted opinion, that the current "STANDARD OF CARE" is LEGALIZED CHILD ABUSE. What loving parent would knowingly and willing subject their child to this type of torture with no guarantee of success, knowing that there were other treatments available, that didn't do this type of damage that hadn't been tried first.

Question 6. Critics at the FDA state that by pursuing alternative therapies that are "not FDA approved", you are placing your "son at greater risk of death" than if he first pursued FDA approved therapies that include radiation and chemotherapy, that may render your son to be retarded. How would you respond to your critics at the agency?

Response. First, I would like to remind my critics at the FDA of an oath they took many years ago. And I quote, "FIRST, DO NO HARM", it is the beginning of the Hippocratic Oath. With that said, let me start by saying, I agree, unapproved therapies can present risks. Some are great and some are small. The risk is no greater than the risks taken by using Radiation and Chemotherapy, which again I will remind you are, " NOT FDA APPROVED FOR TREATING PEDIATRIC CANCERS". They are standard treatments used, which "IMPLIES APPROVAL", it does not mean that have been approved going through the "NORMAL APPROVAL PROCESS". LET US NOT CONFUSE THE TWO! If under any other means, if I were to go out with forethought and blind my son, or deafen my son or by some means, cause him to become retarded I would be arrested, tried, and thrown into jail, and rightfully so, but it is done everyday in the treating of childhood cancer with NO ACCOUNTABILITY . And not allowing my son to be subjected to these medieval treatments, makes me a bad parent in the eyes of the "STANDARD OF CARE COMMUNITY". There is nothing in my life that I love greater than my children, and they will be no doctor's "LAB RAT", not while I breath.

I hope this has clarified any questions you might have. Please feel free to contact me if you have any further questions.

NATIONAL ORGANIZATION FOR RARE DISORDERS, INC.
November 15, 2000

The Honorable MICHAEL BILIRAKIS
Chairman
Subcommittee on Health and the Environment
US House of Representatives
2369 Rayburn House Office Bldg.
Washington, DC 20515

DEAR CHAIRMAN BILIRAKIS: Thank you for your letter of November 2, containing additional questions from the September 13, 2000 hearing on H.R. 4242, the *Orphan Drug Innovation Act.* My answers to the questions follow:

Question 1. Do you believe that shielding the original orphan drug from competition for longer than 7 years is good policy?

Response. No. The *Orphan Drug Act of 1993* provides seven years of exclusive marketing rights to the sponsor of an orphan drug, and no manufacturer should have more than seven years without competition. However, there are many orphan drugs that have had no competition after seven years on the market simply because no other companies have made an effort to compete after the innovator's exclusivity expired.

On the other hand, the European Union enacted the *Orphan Medical Products Regulation* in December 1999, providing ten years of exclusivity to orphan drug manufacturers. Since this is a new law, we do not yet know how successful it will be in comparison to the U.S. law. In other words, is ten years of exclusivity a better incentive than seven years? Will more companies develop orphan drugs in Europe than the United States because American incentives are not as strong? We believe it is premature for Congress to consider revising (either contracting or expanding) orphan drug exclusivity in the United States at this time.

Question 2. Do you believe that this policy needs clarification?

Response. Under very limited circumstances the FDA may allow the manufacturer of a "similar" orphan drug to reach the American market before an innovator's orphan drug exclusivity expires IF it can prove that the follow-on drug is "different" from the original orphan drug. A manufacturer must prove that its drug is chemically or structurally different from the first orphan drug, or that it is superior because it is more effective or safer, or represents a "major contribution to patient care." FDA's regulations defining these requirements were established in 1992. We believe the regulations have worked very well for many years, and they do not need to be revised at the current time.

Please note that the orphan drug regulations were printed nine years after the *Orphan Drug Act* became law, they went through extensive public comment periods, and they have been time tested since 1992. Mr. Chairman we believe these regulations effectively carry out the spirit and intent of the law, and they should NOT be written into law because minor changes would subsequently require an act of Congress. Regulations are easier to change when the need arises, and the public is encouraged to comment and provide input into revised regulations.

Question 3. On February 7, 2000, you sent a letter to FDA Commissioner Henney stating, "As you probably know, we have been concerned about the blockage of a new version of beta interferon form multiple sclerosis. FDA seems to believe that the product is the same as both Avonex and Betaseron, even though those two products have already been determined by both FDA and a federal court to be 'different.' This puts Serono in a no-win situation, even with its full BLA and having been initially determined to be 'the same' as Betaseron under the Orphan Drug Act." Why did you write that the FDA implementation of the Orphan Drug Act puts Serono in a no-win situation?

Response. If you read my entire letter of February 7, 2000 to FDA Commissioner Henney, you will clearly see that the question I raised involved FDA's refusal at the beginning of this year, to decide whether Avonex was the "same" as Betaseron or the "same" as Avonex, but I asserted it could *not* be the same as BOTH. The letter was an effort to force the agency to decide which ONE of those two drugs Rebif is the same as.

Let me explain. At the beginning of this year, FDA determined that Rebif is the same as the *two* competing versions of the multiple sclerosis treatments, Betaseron and Avonex. Betaseron was the first version of beta interferon to reach the market, but FDA subsequently decided that Avonex was a "clinically superior" orphan drug, and therefore should be made available to multiple sclerosis patients before Betaseron's exclusivity expired. The manufacturer of Betaseron went to court to stop Avonex from reaching the market, claiming that its orphan drug exclusivity would be violated. The court decided that FDA's decision was correct and that Avonex is

a "different" drug because it was "clearly superior," and thus could be approved by the agency despite Betaseron's exclusivity.

Late last year, FDA told Serono that it could not approve its multiple sclerosis treatment, Rebif, because it was the "same" as *both* Betaseron and Avonex. I wrote to Commissioner Henney in February explaining that FDA cannot claim Rebif is the "same" as *both* of these drugs because the FDA had already determined, and a federal court had agreed, that Betaseron and Avonex are not the same drug. Serono was in a no-win situation because the company would have to prove that Rebif was "different" than **two different** drugs, not one. I urged the Commissioner to determine which of those two Multiple Sclerosis treatments Rebif was the "same" as. I did not urge the Commissioner to cast a vote toward one drug or the other; we simply wanted a decision to be made. Later this year FDA did make the decision that NORD was asking the FDA to make, and the agency decided that Rebif is the "same" as Avonex. Apparently Serono disagrees with that decision.

Note. The answer to the following three questions is written below:

Question 4. Can you reconcile your written testimony today with your February 7 letter to FDA Commissioner Henney where you state, in reference to 7-year market exclusivity enjoyed by Biogen, "However, after seven years expire, competitors should be allowed on the market without undue delay, and the beta interferon scenario, as a precedent, very troubling."

Question 5. Would you consider your February 7, 2000 letter to FDA Commissioner Henney to be at variance with your testimony today?

Question 6. What caused you to change your mind?

Response. My testimony on September 13 conforms to the statements made in the February 7 letter to Commissioner Henney. The beta interferon scenario was very troubling because there was no way that Rebif could be the "same" as *both* Avonex and Betaseron! It could only be the same as ONE of those drugs.

I believe that FDA was wrong for not making a decision on this matter much sooner, and for keeping their decision confidential when it was made. Unfortunately, FDA is required under law to keep all information confidential unless a drug sponsor agrees to make it public. It was only after Serono gave written permission to FDA to talk to me about Rebif that I was told the agency's scientific analysis concluded that Rebif is the "same" as Avonex, and not the same as Betaseron. This means FDA cannot approve Rebif for sale in the United States until the exclusivity of Avonex expires. If Serono disagrees with this decision, the onus is on the company to scientifically prove their drug is not chemically the "same" as Avonex, or to prove their drug is "clinically superior" to Avonex. I understand that Serono is conducting clinical trials now in an effort to prove clinical authority.

Question 7. The testimony of your organization was requested by Biogen, the company that has been trying to thwart Serono's legislative activities in this area. Have you had any contacts with Biogen or its agents on this matter?

Response. I have had no contact with Biogen on this or any matter. I am not surprised that Biogen recommended that we testify at the hearing because we are usually invited to testify at all hearings concerning the *Orphan Drug Act*. In fact, I was quite surprised when I learned there would be a hearing about orphan drugs, and we were not invited to testify. I finally received a telephone request from your staff a few days before the hearing and was delighted to change my plans and go to Washington, DC. I had no idea that Biogen made this recommendation, and let me assure you NORD is not conspiring with anyone to keep Serono off the market.

Since Biogen had no way to know what I would say in NORD's testimony, it was certainly considerate of them to suggest that NORD be included. However, people in Washington generally know that NORD is always fair and unbiased, it is the quintessential patient advocacy organization, it does *not* favor one drug over another, one company over another, and NORD can always be relied on to defend the *Orphan Drug Act* and its regulations.

Question 8. Do you believe that co-marketing during the original orphan's exclusivity period, protection for that innovation, and the opportunity to market that advantage are enough of an incentive to foster research and development investment to improve orphan drugs? If not why not?

Response. This is a very complicated question, but the basic answer is: Exclusivity is the *most important* incentive of the *Orphan Drug Act,* and any weakening of exclusive marketing rights would greatly undermine development of future treatments for rare diseases. If you allow orphan drug exclusivity to be violated because a manufacturer makes a minor change to a drug that has no substantial benefit to patients, then you will have diluted the ODA's chief incentive, and fatally weakened the law.

Mr. Chairman, when a pharmaceutical company decides which drugs to invest in, they prefer to focus R&D on the least risky products. This is why so many drug

companies invest billions of dollars in research and development of "**me-too**" drugs, compounds that are very similar and vary only slightly from other marketed drugs that are very successful and profitable. They practically copy the original compound and make some minor chemical or structural changes so that they do not violate the innovator's patent, and then they get the drug on the market to compete with the original drug. Historically this is why we have so many beta blockers on the market for hypertension, so many anti-inflammatories for arthritis, and soon there will be many drugs for erectile dysfunction.

This is the way the marketplace works so well for drugs that are used by large numbers of people. But orphan drugs affect few people, manufacturers know there is a limited potential market to buy their drug, and they want assurance that a competitor will not take part of their market away. The industry did not manufacture orphan drugs before the *Orphan Drug Act* was enacted (e.g., only ten orphan drugs were brought to market in the 10 years before the *Orphan Drug Act* became law); but since 1983, over 200 orphan drugs have reached the American market.

These companies will tell you they would not have invested in development of their orphan drug if they were not guaranteed seven years of exclusivity.

In the very few instances when FDA has approved a "similar" orphan drug before the exclusivity of the first drug expired, it has only occurred when manufacturers AGREED to SHARE exclusivity, or the follow-on company PROVED SCIENTIFICALLY that their drug is clinically superior.

In the case of the three versions of beta interferon the first version (Betaseron) caused a very serious injection site reaction necessitating surgery. The second version (Avonex) does not cause this very serious adverse reaction, so it was allowed on the market. This is a safety advantage, and it would have been unjust to prevent Avonex from reaching Multiple sclerosis patients. Rebif on the other hand has *not yet* proven that it is clinically superior to Avonex, FDA has determined that Rebif is scientifically the "same" as Avonex, but it also causes the same serious injection site reactions as Betaseron.

The onus is now on Serono to prove that their drug is clinically superior to Avonex. The company is conducting a clinical trial right now, comparing Avonex to Rebif. We believe that the scientists at FDA will then be able to determine whether Rebif is clinically superior to Avonex. Thus Congress should await the results of that trial and allow FDA to make that determination. We believe that tinkering with the law now, and diluting the exclusivity incentive of the *Orphan Drug Act,* will weaken the law and remove any incentive for manufacturers to develop clinically superior orphan drugs that patients need.

Question 9. Do you believe FDA's policy should distinguish between drugs that are clinically superior based on improved safety or efficacy from those based on being a major contribution to patient care?

Response. We believe FDA's current regulations defining clinical superiority are right on target, and they should be left as they are. If and when FDA decides to change the regulations, the agency is required to publish the proposed revisions in the *Federal Register,* and patients will then have an opportunity to express their point of view. Today the agency will only approve a competing orphan drug if it can prove that it is safer, more effective, or is a major contribution to patient care. Patients want and need these therapeutic improvements. The current regulations act as an important *incentive* to companies to develop better orphan drugs.

Question 10. Do you object to Congress providing FDA with guidance on handling clinically superior drugs, an issue not currently covered in the statute?

Response. We do not believe it is necessary or warranted for Congress to provide guidance to FDA on handling "superior" orphan drugs. Firstly, we recommend that Congress ought to leave these decisions up to the physicians and dentists at FDA. Secondly, although "clinical superiority" is not specifically mentioned in the statute, it was absolutely proper and necessary for the agency to develop this regulation because the terms "**same**" and "**different**" in the statute had to be defined in regulations.

The FDA's orphan drug regulations define the terms "same drug" and "different drug" because recombinant DNA technology made this necessary. Seventeen years ago when the law was written we were dealing solely with chemical compounds that could easily be differentiated. Today, however, many new treatments are developed through biotechnology engineering and the differences between biologics is very difficult to discern. One simply cannot define the chemical structure of a biologic and determine if it is the same or different from a "similar" biologic. Most of these products are copies of proteins or enzymes that human bodies naturally make. Moreover, Congress cannot develop a formula that fits every clinically significant difference, and which factors should be considered. For example, is a three-hour intravenous infusion clinically superior to a six-hour infusion? Does a lower price for a follow-

on orphan drug represent clinical superiority? Once you ask questions like these, you open a very big can of worms.

In conclusion Mr. Chairman, the patient community is indebted to Congress for enacting the *Orphan Drug Act* in 1983. We advise that if "it ain't broke, don't fix it," *nor* its regulations. Serono is doing the right thing now; they are conducting clinical trials to try to prove scientifically that its drug is superior to other competing drugs. This process is available to them under the current Act and its regulations. NORD's concern is not which company is right or wrong, nor, how much profit they may lose when FDA denies them early marketing approval, but whether **patients** are suffering because of lack of access. There are three good FDA approved treatments for multiple sclerosis available to American patients today, and at best any clinical superiority that Serono will claim will *not* indicate that Rebif is a cure for multiple sclerosis. If it were, FDA would approve it! Rebif may be a treatment that is superior in some ways, but inferior in others. Only science can tell us, and we await results of its clinical trials comparing it directly to Avonex.

Please do not hesitate to contact me if you have any other questions.

Very truly yours,

ABBEY S. MEYERS
President

UNIVERSITY OF VIRGINIA
DEPARTMENT OF RADIOLOGY
November 10, 2000

Congressman MICHAEL BILIRAKIS
Chair, Subcommittee on Health and Environment
U.S. House of Representatives
Rayburn House Office Building, Room 2125
Washington, DC 20515-6115

DEAR MR. BILIRAKIS: The following are my responses to the questions in your letter of November 2, concerning my testimony on HR 1795.

Question 1a. Why is an institute necessary to solve the problems associated with biomedical imaging research at the NIH?

Response. That imaging research is spread over 16 institutes and centers means that there is no single institute charged with responsibility for support of basic research to develop new imaging techniques and technologies with broad applications to the diseases and organ systems that are the focus of the existing institutes. Consequently, such research, which is critical to advances in imaging, receives little or no support from the NIH. There is also no coordination of imaging research at NIH. Major opportunities are lost, as they are not apparent in the content of the institutes' disease focus. There is duplication, as there is little coordination of imaging opportunities. Given the declining ability of both academic departments and industry to finance imaging research, an institute directed specifically at imaging, with a comprehensive plan, able to prioritize and pursue opportunities is essential.

Question 1b. Could the Bioengineering Consortium (BECON) that the NIH has established, or a coordinating committee of some type be an alternative?

Response. Such alternatives fall short of what is needed in both scope and authority. An institute has the capability of addressing the diverse needs that are essential to successfully addressing the nation's needs with respect to medical imaging, including the authority to fund grants, set a research priorities through the request for applications process, and enable research training. This level of comprehensiveness does not exist through any other mechanism.

Question 2. The National Cancer Institute has made imaging a top research priority and has put much more money into this field. Can't we solve the problem by further increasing the amount of money that NCI commits to imaging?

Response. While more NCI money certainly can increase imaging research in cancer, it does not address the need to advance imaging research more broadly in support of the nation's health. Indeed, it is this "silo" approach to imaging that is so ineffective. Imaging is applicable across a broad range of organ systems and diseases and needs, as such, to be addressed more directly.

Question 3. Other groups have come to the Congress requesting that new institutes be created. How can Congress distinguish among these proposals?

Response. The Institute of Medicine has advised Congress in a 1984 report titled Responding to Health Needs and Scientific Opportunity: The Organizational Structure of the National Institutes of Health—on when it should consider establishing a new institute. The proposed Institute for Biomedical Imaging and Bioengineering fulfills all of these criteria and is also consistent with a second IOM report, which

was written in 1998 and titled Scientific Opportunities and Public Needs: Improving Priority Setting and Public Input at NIH. Establishment of the proposed institute will advance research that will have a positive impact on the public health while, at the same time, reducing inefficiencies and duplication. Dr. Reed Dunnick discussed both IOM reports at greater length in his testimony.

Question 4. What role can new imaging technologies play in the advanced research in molecular biology and genetics that is conducted by the other institutes at the NIH?

Response. Both advances in established imaging technologies and the emergence of a host of new technologies promise spectacular contributions to our understanding of the early phases of such important disease processes as cancer and heart disease. Medical imaging is, in essence, the "noninvasive biopsy" that can provide insight into how subcellular structures are altered by disease in both their morphology and function. Imaging technologies already are being used for these purposes. Their importance in investigation, diagnosis, and treatment will grow over the near term.

Question 5. What makes the basic scientific research involved in imaging and bioengineering different from the scientific research at the disease and organ-system institutes?

Response. The most fundamental difference is in the nature of the training and expertise of the individuals involved. Medical imaging technology development requires the skills of physicians, computer scientists, physicists, mathematicians, information technology specialists, and engineers. The research is interdisciplinary and cuts across disease and organ system lines.

I appreciate the opportunity to further comment on the need for an Institute for Biomedical Imaging and Bioengineering. Please let me know if you wish me to address these or other issues further.

Sincerely,

BRUCE J. HILLMAN, *MD*

UNIVERSITY OF PENNSYLVANIA HEALTH SYSTEM

R. Nick Bryan, M.D., Ph.D.
Eugene P. Pendergrass Professor and Chairman
Department of Radiology

November 20, 2000

The Honorable Michael Bilirakis
Chairman
Subcommittee on Health and Environment
U.S. House of Representatives
2125 Rayburn House Office Building
Washington, D.C. 20515-6115

Dear Mr. Chairman:

Thank you for the opportunity to testify before the Subcommittee on Health and Environment on September 13 and especially for your support of H.R. 1795. I am pleased to respond to the follow-up questions from Subcommittee members that you sent to me.

1. As I mentioned in my September 13 testimony, in order to flourish and grow consistently at the NIH, a scientific field requires an organization with the mandate, the responsibility, the authority, and the resources to direct and drive investigation in that field. In the NIH structure, only institutes possess those attributes. While entities such as the Bioengineering Consortium (BECON) and the new Office of Bioengineering, Bio-imaging, and Bio-informatics (OB3) may be able to improve inter-institute coordination marginally, these organizations do nothing to address the fundamental problem of providing support for the basic scientific research that is necessary to develop new imaging and bioengineering techniques and technologies with wide applications to the disease processes and organ systems that are the focus of the existing institutes. The 1999 BECON symposium on imaging, for example, produced an ambitious agenda for this field, but it is highly unlikely that this research program can be accomplished under the present NIH structure. The current institutes support research that is likely to result in more effective uses of established technologies to address problems associated with specific diseases or organ systems rather than the development of new modalities.

2. The growth of the Biomedical Imaging Program (BIP) at the NCI has been a significant and positive development that is widely supported throughout the imaging community. Cancer imaging should be a high priority, but imaging is not disease- or organ-specific. It has applications far beyond cancer, and these applications are neglected when the research focus is solely on cancer or any other individual disease. Indeed, major breakthroughs in cancer detection, diagnosis, and treatment are more likely to result from basic research in the imaging sciences than from applied research focused on achieving incremental improvements in the use of existing technologies in connections with cancer.

3. I recognize that the Congress has long grappled with the problem of distinguishing among the various proposals, many of which may be meritorious, for organizational change at the NIH. The Congress was wise to seek input from the Institute of Medicine on this question, and I believe that the 1984 IOM report titled Responding to Health Needs and Scientific Opportunity: The Organizational Structure of the National Institutes of Health offers an excellent guide. The proposed National Institute of Biomedical Imaging and Bioengineering meets all the criteria for new institutes set forth by the IOM. The proposed institute is also consistent with the 1998 IOM report titled Scientific Opportunities and Public Needs: Improving Priority Setting and Public Input at NIH. In this report, the IOM recommended that the Congress should establish "new organizational entities only when other approaches have proven inadequate." In this case, the

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4. imaging community has worked with the NIH leadership for more than 20 years to locate imaging research appropriately within the NIH structure. Toward that end, the NCI replaced the NIGMS as the principal source of support for extramural imaging research in the 1980's, and the intramural Laboratory of Diagnostic Radiology Research (LDRR) was moved from the NIH Director's Office to the Clinical Center in recent years. Both changes, as well as numerous others, were accomplished after consultation between the NIH and the imaging community. Despite good intentions on both sides, however, it has become evident that disciplines such as imaging and bioengineering, which transcend the missions of the current institutes, do not fit into the existing institute structure. Finally, it should be recognized that the proposed institute is completely consistent with the rationale offered by the NIH itself when the National Center for Human Genome Research was elevated to institute status in 1997.

5. The development of advanced imaging technologies is essential for continued progress in molecular biology and genetics. As the late Dr. Leonard Holman of the Harvard University said in 1997 testimony before the Senate Subcommittee on Public Health and Safety, there are now "old" and "new" imaging sciences. The old imaging science allowed physicians to visualize anatomy noninvasively and continues to be critical for the detection and diagnosis of disease and injury. The new imaging science, on the other hand, is taking us far beyond static visualization of the anatomy. It is directed toward allowing us to visualize and quantify tissue function in living bodies. We cannot only see the brain, for example, but we can begin to see how it works. Molecular imaging permits researchers to visualize gene expression in a living body instead of a test tube, thus creating conditions for more accurate investigations and more rapid advances. In general, the imaging of the 21st century is a discipline grounded in basic science that provides the tools to answer increasingly sophisticated questions about organ systems and disease processes.

6. The basic science of imaging and bioengineering is fundamentally different from that of the existing institutes at the NIH. Imaging and engineering are highly quantitative and based on mathematics and physics, not the biological sciences that underlie most of the research in the existing disease- and organ-based institutes. Imaging and bioengineering are unique scientific fields at the NIH and they are critical to future advances in the delivery of high quality medical care. The current institutes cannot accommodate the basic sciences of imaging and bioengineering; these disciplines therefore require an identity that is independent of the existing institute structure.

Sincerely,

R. Nick Bryan, M.D., Ph.D.
Eugene P. Pendergrass Professor and Chair

RNB/adr

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Marc Wheat, Esq.
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House Committee on Commerce
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Dear Mr. Wheat:

Biogen appreciates the opportunity to provide additional comments regarding H.R. 4242 and the testimony provided at the hearing on this and other matters on September 13, 2000 before the House Commerce Subcommittee on Health and the Environment. Most importantly, Biogen strongly agrees with the National Organization for Rare Disorders (NORD) that there is simply no reason to amend the Orphan Drug Act to allow on to the market a product that has failed to demonstrate clinical superiority. We heartily agree with Ms. Abbey S. Meyers, President of NORD, that "if it ain't broke, don't fix it". At the very least, we also wish to echo the sentiments made by a number of Members of the Committee in their opening statements: no change should be made to the Orphan Drug Act without greater deliberation and input from other stakeholders.

In addition, we have comments on four specific issues that we wish to bring to the Subcommittee's attention.

FDA Letter of November 8, 1999 to Serono

In a letter to counsel for Serono of November 8, 1999, FDA seriously confuses the relationship between the Orphan Drug Act and the Waxman-Hatch generic drug laws. The lawful grant by FDA of a period of seven years of marketing exclusivity pursuant to the Orphan Drug Act blocks the approval of any other marketing application for the same drug irrespective of whether the application is a New Drug Application (NDA), Abbreviated New Drug Application (ANDA) or a Biologics License Application (BLA). To discuss the possibility of a generic drug approval as a way to avoid being blocked by a grant of orphan drug marketing exclusivity suggests a relationship between the Orphan Drug Act and the Waxman-Hatch law that simply does not exist as a matter of law.

FDA Letter of October 28, 1999 to Genentech

Serono also relies on a second FDA letter to manufacture support for H.R. 4242. On October 28, 1999, FDA issued an orphan drug designation for Genentech's somatropin product "for the long-term treatment of children who have growth failure due to a lack of adequate endogenous growth hormone secretion. Long term administration is defined as one injection per month. Please note that this designation applies only to the long acting formulation". Serono suggests that this designation supports the logic of H.R. 4242 that orphan drug marketing exclusivity may be limited to an innovation over an existing drug if it otherwise qualifies as an orphan drug. To the best of our knowledge, Genentech's somatropin long acting formulation product was never granted marketing exclusivity by FDA. Thus, this may well be irrelevant.

In addition, the exclusivity contained in the Orphan Drug Act was intended to be a broad grant of exclusivity to act as the major incentive to the development of orphan drugs. And it has worked magnificently. The three-year marketing exclusivity, referenced by Serono in its testimony, which is contained in the Waxman-Hatch law is very different. The Waxman-Hatch law contains explicit statutory authority to FDA to grant additional three-year marketing exclusivity for previously approved products. That exclusivity, if clinical studies are conducted, is limited to the basis of the new approval (for instance, a new indication or dosage form). If FDA intended, as Serono suggests, through this single letter to alter radically in a similar fashion the implementation of the exclusivity provision of the Orphan Drug Act, we believe it is wrong both as a matter of law and public policy.

Moreover, the somatropin example is not even analogous to Avonex because FDA's designation of somatropin involved a different formulation. The innovation with somatropin was the concrete, physical new formulation itself. In the case of Avonex, the innovation that made it clinically superior to Betaseron was the patient benefit -- fewer injection sites reactions and no skin necrosis.

Indeed, the danger in applying the logic of the Waxman-Hatch three-year marketing exclusivity to the Orphan Drug Act exclusivity is clearly described in my testimony before the Subcommittee as follows:

> "Serono's situation highlights one of the key problems with H.R. 4242. Under the bill, Biogen's market exclusivity for its multiple sclerosis drug would be limited to blocking from the market only those products that cause fewer injection site reactions and less skin necrosis. However, a product which is less safe that Biogen's by causing more site reactions and skin necrosis--such as Serono's product--would be, under this bill, eligible for approval by the FDA."

The Same Versus Different Drug

Under FDA regulations, Rebif is chemically the same as both Betaseron and Avonex. Serono suggests, however, that since Rebif is the same as Betaseron it is irrelevant what the relationship between Rebif and Avonex is because Avonex was found to be clinically superior (and, therefore, different from Betaseron). This argument completely destroys the independent grant of seven years of marketing exclusivity provided to Avonex and ignores the FDA's substantive regulations implementing the Orphan Drug Act on what constitutes the same drug (21 C.F.R. § 316). Orphan drug exclusivity is tied to whether products are the same or different. Drugs are the same or different in two ways. First, drugs can be *chemically* the same or chemically different. Second, they can be *clinically* the same or clinically different.

Products that are chemically the same can be clinically different from one another based on *"clinical superiority"*. A product can be clinically superior to another if it provides (1) greater safety; (2) great efficacy; or (3) a major contribution to patient care. If a product is clinically superior to an approved orphan drug product, it is deemed not to be the "same drug" as the approved product and, therefore, may be approved by FDA despite the exclusivity of the first product. Based on the present FDA regulations Rebif has a lawful way to come to market during the seven-year marketing exclusivity granted to Avonex: a demonstration that Rebif is clinically superior to Avonex. Any other interpretation of the laws and regulations illegally destroys Avonex's seven year grant of marketing exclusivity.

This regulation makes very good sense from a public policy standpoint. Patients will get the benefit of a drug that is proven to be clinically superior to a chemically similar already existing orphan drug, but will not be able to destroy the exclusivity of the earlier drug just by copying it and claiming a patient benefit. This

regulation thus serves both the need for a reliable incentive of marketing exclusivity to encourage the development of orphan drugs, and at the same time assures that a drug that is better for patients, or clinically superior, will be available to patients. H.R. 4242 would destroy the incentives and add nothing to benefit patients.

Another flaw with Serono's argument to equate Rebif as chemically the same as Betaseron but chemically different to Avonex is the individual chemical structures of Avonex, Rebif, and Betaseron. Rebif is actually more similar in chemical structure to Avonex (IFN-beta-1a) than Betaseron (IFN-beta-1b).

Retroactive Application of This Amendment

We also wish to reiterate strongly that it is unconstitutional to apply retroactively a legislative change to the market exclusivity provisions of the Orphan Drug Act. Further, as a matter of public health policy, for the sake of one company, it sends a dramatically chilling message to the pharmaceutical and biotechnology industry that the major incentive in the Orphan Drug Act cannot be relied upon.

In order to have a complete record on this issue, we respectfully request that the Congressional Research Service Report, requested by Congressman Greenwood, entitled "Interferon Drug Products For Multiple Sclerosis: Questions Concerning Exclusivity Under the Orphan Drug Act," (dated April 27,2000), and the letter from Abbey Meyers, President of the National Organization of Rare Disorders, to Holly Rocco, Legislative Assistant to Congressman Thornberry (dated April 18, 2000), be included as part of the hearing record. (Copies attached.)

In conclusion, we find that there is little support on the Commerce Committee or in Congress to undercut the most important incentive responsible for the success of the Orphan Drug Act.

Sincerely yours,

Robert P. Brady

Robert P. Brady
Counsel to
Biogen, Inc.

Attachments