PATIENTS DIED PREMATURELY in two failed clinical trials at Seattle's Fred Hutchinson Cancer Research Center — experiments in which the Center and its doctors had a financial interest. The patients and their families were never told about those connections, nor were they fully and properly informed about the risks of the experiments, an investigation by The Seattle Times has found.
The patients in these trials were ill with cancers that, left untreated, would almost certainly have killed them. But many stood a good chance of survival or at least prolonged life with traditional care. Instead, many actually died from the experiments — sooner than they would have with no treatment at all.

This series of articles published March 11-15, 2001, explores the experiments and the complex legal and ethical issues surrounding them. These issues are at the heart of a national debate under way on how medical research is conducted and regulated. Congress will take up the discussion this spring.

Patients never knew the full danger of trials they staked their lives on

By Duff Wilson and David Heath
Seattle Times staff reporters

AT A KITCHEN TABLE in a noisy apartment in the Flatbush neighborhood of Brooklyn, N.Y.:

David Blech, a 24-year-old songwriter and entrepreneur, sits with his brother and father. Like expectant parents choosing a baby name, they bark ideas for what to call their just-invented company: "DNA Techniques." "Hybridoma Service Center." "Genetic Systems."

"That's it!" Blech calls out, rising excitedly. "Genetic Systems Company!"

The Blechs will start with that name. They will use it, shares of stock and personal charm to recruit top cancer doctors to jobs and board positions. And, they dream, they will all get rich in the nascent biotechnology boom of the 1980s.

AT A KITCHEN TABLE in a quiet house in rural Heflin, Ala., five years later:

Becky Wright, a 36-year-old housewife and mother of three, sits with her husband, Pete, owner of the local drugstore. Their talk is not about dreams, but a nightmare: Becky has leukemia.

Pete has searched for the best place in the world to take his wife for treatment. His choice: the Fred Hutchinson Cancer Research Center in faraway Seattle.

They are hopeful. "The Hutch" is the pioneering institution in transplanting bone marrow - by then a proven treatment for the type of leukemia Becky Wright has - and she is the perfect candidate, with a donor sister whose marrow matches hers.

Doctors tell the Wrights that with a standard transplant, chances are good that Becky will live to see her youngest, a 5-year-old girl, grow up.

But when the couple travels to Seattle in 1985, Becky is not given a standard transplant.

Instead, she is thrust, unwittingly, into a world where the quest for cure gets tangled in the pursuit of fame and fortune. The world of David Blech.

At the urging of her Hutchinson Center doctors, Becky Wright joins an experiment in which eight manmade proteins are added to her sister's bone marrow before it is transplanted.

Some of those proteins belong to a Seattle biotech company - a company named Genetic Systems.

Some of Wright's doctors at The Hutch were among David Blech's recruits. The doctors - and The Hutch itself - had financial ties to the company Blech and his family had invented in their Flatbush flat.

Becky and Pete Wright leave the hospital after her first bone-marrow transplant, in 1985.
By the time Wright was enrolled in the clinical trial, the doctors knew it wasn't working. Transplants were being rejected at alarming rates. New cancers were appearing and old ones reappearing far more than they normally would.

All were problems directly attributable to the experimental treatment.

The doctors didn't tell the Wrights any of that.

Not about the 11 patients who had already died. Not about other, less-dangerous ways of treating her disease.

Not about their own financial interests.

Becky Wright died of causes directly attributable to this experiment, as did at least 19 other people, according to evidence in medical journals and Hutchinson Center documents.

Odds are high that some of them would otherwise have survived a standard transplant and lived full lives. Many of the others likely would have lived at least a year or two longer than they did --a year or two they would have shared with their spouses, their children, their families and friends.

What happened
A timeline of events in Protocol 126.

The story of Protocol 126, as this experiment was called, has never been told. Federal and state investigators looked into Protocol 126 for a while, then closed their investigations half-completed - leaving one investigator "saddened and alarmed" at the lack of follow-through.

During the 12-year span of the trial, several doctors at The Hutch tried to curb it. They said it was hurting rather than helping patients, and that mice or dogs rather than humans should be the test subjects. They complained that patients weren't being told about the risks, the alternatives, the researchers' financial conflicts.

As Dr. John Pesando, a member of a Hutch committee charged with protecting the rights of patients, wrote to federal officials in 1998:

"Many patients died at the Fred Hutchinson Cancer Research Center when the Institutional Review Board charged with protecting them was shamelessly used and abused by senior staff."

Hutch management "denied the existence of financial conflicts of interest, refused to halt the protocols, and refused to have protocols reviewed by independent outside examiners," Pesando wrote.

The researchers involved were Dr. E. Donnall Thomas, Hutch co-founder and clinical director and winner of the 1990 Nobel Prize in medicine; Dr. John A. Hansen, head of a tissue-typing lab and later clinical director; and Dr. Paul J. Martin, a young oncologist.

When the review board questioned the work of these doctors, Pesando said, board members were "lied to, intimidated, ignored and punished." Thomas argued in writing that it was the board's job to promote, not hinder, the research.

That's not what federal law says. By law, the board was to ensure that risks to patients in clinical trials were minimized in relation to potential benefits, and that patients fully understood those risks before consenting to participate.

More than 100 interviews and 10,000 pages of documents - including Becky Wright's consent form - reveal that neither occurred in Protocol 126.

Thomas refuses to discuss the trial or his financial holdings. The other doctors involved defend their actions, saying they were driven by science and that money issues didn't affect them.

Martin adds: "I don't think survival is the best measure of outcome in these studies."

Fifteen years after his late wife began her treatment at The Hutch, Pete Wright, who still runs the Wright Drug Co. in Heflin, was shocked to learn all he didn't know: That other Hutch doctors had tried to stop the experiment. That the doctors running the trial had financial interests in it. That there was an alternative treatment with a higher likelihood of success.

"To say it's disturbing is an understatement," Wright said.

"All these years I have told myself that she got the very best care possible and I swore that would be the case when she was diagnosed. It makes me want to buy a plane ticket to Seattle and beat the hell out of somebody."

The biotech boom begins

When young David Blech went recruiting for his fledgling company, he found a kindred soul in the upper-left corner of the country: Dr. Robert Nowinski of The Fred Hutchinson Cancer Research Center in Seattle.

Both hailed from New York. Both were brash and ambitious. And both saw potential riches in biotechnology.

The Bayh-Dole Act of 1980 had encouraged publicly financed scientists to patent their inventions, setting off a boom in biotech. Nowinski, who was 35 that year, wanted in, and Blech was holding the door open.

Blech asked Nowinski to head up Genetic Systems, and to bring some of his Hutch colleagues along. With their reputations, Blech knew they could create enough buzz around the company's stock that they would all get rich.

Genetic Systems incorporated on Nov. 13, 1980. In the next two months, Nowinski and Blech gave penny-a-share stocks to three key scientists at The Hutch:

• Don Thomas got 100,000 shares, a $3,000 annual stipend and a seat on the company's scientific advisory board.
• John Hansen got 250,000 shares and a job as the company's medical director. He would continue to work at The Hutch but promised to "devote such time as is necessary" to Genetic Systems for an $18,000 consulting fee.

• Paul Martin, Hansen's protégé and assistant, got 10,000 shares and a three-year exclusive consulting agreement with Genetic Systems.

Blech put together a prospectus touting the doctors and The Hutch. He raised $3 million in the first three months of Genetic Systems' existence, swelling the value of the doctors' stock holdings.

Thomas' presence on the prospectus was particularly important. At age 60, he had earned an international reputation.

An immunologist, Thomas had been involved in the world's first bone-marrow transplant, in New York in 1956. The patients, identical twins, had died, but the procedure had shown promise.

Marrow, a spongy tissue inside bones that produces blood cells, begins to die when cancer patients receive radiation and chemotherapy. The amount of damage to the marrow depends on the amount of cancer-killing material the patient receives. It limits how much treatment a person can survive.

Thomas and others believed that if marrow could be replaced through transplant, they could boost the cancer-killing treatment and then restore the patient's ability to produce new blood cells.

The difference between a standard treatment and Protocol 126
An allogeneic bone-marrow transplant involves a leukemia or lymphoma patient and a tissue-matched donor of bone marrow.

A bone-marrow transplant is a straightforward procedure. Marrow from a donor is infused through a catheter into a recipient's veins. If all goes well, the factory cells in the donor marrow, known as stem cells, lock in and begin forming new blood cells in the patient.

Thomas moved to Seattle in 1963. Between 1969 and 1974, he transplanted marrow into 54 patients with supposedly incurable leukemia. Most died, either from their cancer or from treatment complications such as infection. But six were cured.

In 1975, Thomas and other doctors opened the Fred Hutchinson Cancer Research Center, naming it after a former professional baseball player from Seattle who had died at age 45 from lung cancer. The Hutch specialized in cancers of the blood, and grew to perform some 450 bone-marrow transplants a year.

Worldwide, the procedure has been credited with saving more than 150,000 lives.

Meanwhile, Hutch doctors have conducted hundreds of clinical trials to advance the science. The Hutch receives more than $140 million a year in federal grants to pay for these experiments.

Controversial from the start

On Jan. 20, 1981 - two weeks after Thomas, Hansen and Martin received their founders' shares from Genetic Systems - the Human Subjects Review Committee at The Hutch met to consider a research proposal from those three doctors.

The doctors wanted to use money from the National Cancer Institute and leukemia patients from The Hutch in a new bone-marrow experiment, labeled Protocol 126.

The experiment would try to prevent an immune-system reaction known as graft-versus-host disease, or GVHD.

As many as half the recipients of marrow transplants from tissue-matched sibling donors suffered GVHD. At best, the disease was annoying, like a rash. At worst, about 5 to 10 percent of the time, it was fatal.

The researchers believed GVHD was caused by "T-cells" in the donor marrow. T-cells, so named because they mature in the thymus gland, are certain white blood cells that trigger the immune system to destroy foreign material and fight infection.

The researchers wanted to use newly manufactured drugs, known as monoclonal antibodies, to kill the T-cells. If it worked, they believed, the success rate of bone-marrow transplants would improve.

But first, they needed the approval of the Human Subjects Review Committee, which assessed the ethics of all human experiments at The Hutch. Congress had mandated that all medical research centers have such review panels.

In pushing their proposal, Hansen and Martin cited studies in which this therapy had been successful in mice. And, they said, the only known study with dogs had also been successful.

However, Dr. Rainer Storb, the Hutchinson Center's expert on GVHD, knew that at least one T-cell study on dogs had been unsuccessful, with some of the subjects dying in treatment. Although the results were not published, Storb said, they were widely known by those in the field.

Storb was not a member of the review committee, but he opposed Protocol 126. In doing so, he collided head-on with one of his fellow Hutch founders, Thomas.

Storb

"Don Thomas clearly favored this approach for whatever reasons ... " Storb said. "There was a feeling of not wanting to be left behind" other research centers.

Thomas, Hansen and Martin did not mention financial interests in Genetic Systems to Storb or the review committee. When Storb ultimately learned about those interests, he said, "It raised issues in my mind" and solidified his opposition to the trial.
First proposal is rejected

Most of the 11 members of the Human Subjects Review Committee were Hutch employees. Among them was Dr. Michael Kennedy, a specialist involved in the type of research proposed in Protocol 126.

In a recent interview, Kennedy recounted that he, too, had objected to many features of the proposed study. His objections in 1981 would presage the problems of the next dozen years.

Kennedy

The committee kept detailed minutes of its discussion. Hutch officials refused to make those minutes public, but The Seattle Times obtained them through a Freedom of Information Act request to the federal government.

The committee - whose members are identified by numbers rather than by name in these records - gave the proposal a largely negative reaction. Among their concerns:

• The lack of adequate prior research on animals. Normally, experiments of this type at The Hutch were performed extensively on mice, followed by studies of dogs before moving to humans.
"The jump from mouse to man is too great ... " said one committee member.

• Contrary to most such research, Protocol 126 proposed experimenting on the healthiest, rather than the sickest, patients. Some of them, whose leukemia was in remission, had a 60 percent chance of lifetime cancer-free survival with a standard transplant from a matched sibling donor.

• The proposed subjects for the experiment - those with siblings whose tissue type matched theirs - were the least likely to get GVHD, much less die from it.

• Some thought T-cell removal might actually prevent the bone marrow from engrafting, or taking hold in the recipient's body. Normally, graft failure is extremely rare, occurring in 1 out of every 100 marrow transplants.

Kennedy, in particular, thought T-cells were needed for new marrow to lock in and start producing healthy blood. And some thought T-cells helped prevent cancer relapse.

• The "informed-consent" form for patients minimized the risk of graft failure and made it sound as if a second transplant could be done without difficulty if the first one failed. In fact, second transplants were known to be fatal about 95 percent of the time.

• The consent form also failed to mention alternative treatments for GVHD.

Given all that, the committee voted not to approve Protocol 126. Hansen was told he could change it and reapply.

The experiment was revised to cut back the T-cell-killing power of the drugs and resubmitted. This time, the review team was headed by Dr. John Ensinck, an endocrinologist and Thomas' counterpart as head of clinical research at the University of Washington, where many Hutch doctors taught.

The committee voted on April 21 to approve the experiment. The minutes do not show why, and Ensinck couldn't recall specifically.

Ensinck, now retired, said in a recent interview: "At that point, I recall, The Hutch was doing uniquely experimental protocols at the cutting edge, so I recall we reviewed them very stringently."

Kennedy, who now has a private practice and teaches at the UW, says the committee's concerns were never addressed.

Again, committee members were not told that some of the drugs in the experiment - three of the eight antibodies ultimately used - were licensed to a company in which the researchers had a financial interest. Nor were they told that by that time, The Hutch itself had a monetary stake in the experiment.

In March, Nowinski had struck a deal with The Hutch to acquire the exclusive commercial rights to 37 specific monoclonal antibodies for 20 years. In return, Nowinski promised the center a percentage of royalties on sales of the antibodies. Simultaneously, he signed a deal with the Hutch-affiliated Pacific Northwest Research Foundation — the parent from which The Hutch was founded and, like The Hutch, headed at the time by Dr. William Hutchinson

— that would give Genetic Systems the rights to new antibodies developed by Hutch doctors in exchange for 50,000 shares of stock and at least $125,000 in research funding.

Blech proceeded to raise $3.7 million from a pharmaceutical company and $2.6 million in two private stock offerings. The Hutch antibodies were the company's main assets. A written pitch to investors touted the development of antibodies to diagnose and treat infectious disease and cancer.

Genetic Systems raised an additional $6.6 million in an initial public offering. In its first quarter, the value of the stock the Hutch doctors had received was $875,000 for Hansen, $350,000 for Thomas, $35,000 for Martin, and $175,000 for the foundation.

During Protocol 126, The Hutch adopted a rule barring scientists from work in which they have financial stake.

Changes raise more concerns

Hansen began spending more and more time at Genetic Systems. He gave Martin, a postdoctoral student in his early 30s who had spent two years in the lab refining the antibodies, the title of principal investigator in Protocol 126.

This would be Martin's first experiment involving humans.

The initial results proved next to nothing. About half of the first group of subjects got GVHD - exactly as would be expected without T-cell treatment.

The antibodies alone hadn't killed T-cells in people as they had in mice. Then the researchers asked the review committee to approve major changes in the experiment. They wanted to add enzymes known to make the antibodies more lethal to T-cells. And they wanted more and healthier patients as subjects, people strong enough to survive years after a transplant so they could monitor the long-term results.

When the experiment went back to the Human Subjects Review Committee in April 1983, one member, Dr. Robert Bruce, a UW cardiologist, raised an alarm: One of the antibodies in the new proposal had been associated in another study with the emergence of unexpected new cancers.

Bruce recommended continuing Protocol 126 if and only if Martin established rigorous criteria to stop the experiment immediately if such problems occurred.

"The informed consent should at the very least indicate that some unexpected adverse effects have occurred," Bruce wrote. "The risk of fatality from an additional malignant process ... can hardly be overlooked in the statement of potential risk."

But the consent form wasn't changed. And there is no evidence the new review panel was ever told about the broader objections raised by its predecessor. The concerns Kennedy had raised

about the role of T-cells in grafting and relapse were not addressed.

On May 26, 1983, the next stage of Protocol 126 was given a green light. The research doctors started looking for new patients to enroll.

Later that year, The Hutch's Board of Directors adopted a conflict-of-interest policy. It said scientists "shall not participate in any (research) involving the Center in which the member has an economic interest," including any form of ownership or any outside pay.

Hansen and Martin say they were never told about the policy. And even if they had known, they insist, their work at The Hutch had no bearing on business prospects at Genetic Systems.

The company was developing products to diagnose disease, they say, not to treat it. Given that, they say, the T-cell experiment could not possibly have benefited Genetic Systems or their stock.

Yet the company's own filings with the Securities and Exchange Commission from that period show plans to use antibodies to treat cancer. And Nowinski told The New York Times in 1983 that he expected to move from diagnosis to treatment.

The doctors' business partner, Blech - who was later convicted of securities fraud in an unrelated case - said in a recent interview that the big money was in treatment, and that was where Genetic Systems had planned to go.

Martin and Hansen insist Genetic Systems was not involved in Protocol 126. But Hansen was a full-time employee and director of Genetic Systems at the height of the trial. He is listed as a co-author of the study every step of the way; he participated in major decisions and tracked results.

Martin was working for a Genetic Systems official intimately involved with the conduct, results and funding of the experiment.

Further, the doctors' agreements with Genetic Systems obliged them to give the company the fruits of their research on company products, even if the company did not formally sponsor the research.

New panel raises questions

In September 1983, The Hutch signed up a new group of volunteers for the Human Subjects Review Committee, combining it with a similar group at Seattle's Swedish Medical Center, where Hutch doctors treated patients.

The committee was given a new title: the Institutional Review Board, or IRB.

Dr. Henry Kaplan of Swedish Medical Center, featured here on a Seattle Magazine cover, saw problems as soon as he was appointed chairman of an experiment-oversight board in 1983.

Dr. Henry Kaplan of Swedish, who would become one of the Northwest's leading oncologists, was appointed chairman. Dr. John Pesando of The Hutch was recruited to be a member. Pesando was reluctant because of the demands of his own research but agreed, hoping the volunteer work would help his chances of promotion.

Pesando says he and Kaplan "walked in and found problems everywhere we looked."

"These included unsafe ongoing protocols," Pesando said. "So we had double jeopardy of not only putting the brakes to new research, but trying to stop things that had already been approved."

The experiments that raised their eyebrows, and their concerns, the highest were the tests of new monoclonal antibodies.

Kaplan complained that antibodies were being used in "a completely uncontrolled fashion," and that animal testing had been insufficient. He wasn't told that similar objections had already been raised and ignored.

In one of his first acts as chairman, Kaplan wrote to Thomas asking about rumors that researchers had financial interests in a company that would use the findings from Protocol 126.

"What checks and balances are utilized to deal with potential conflicts of interest between academic and financial considerations of the staff?" he asked.

Thomas replied with a strongly worded letter denying any financial conflicts of interest and refusing the IRB's request to review each antibody separately for human safety.

"I think Committee members have not only an obligation to review the ethical aspects of this work, but also an obligation to assist us and not impede our research, which is directed toward solving some of those problems that are killing the children and young adults who come to us with fatal disease," he wrote.

In fact, the IRB had no such duty to assist research. Federal law gave the panel a single, pointed mission: "Protect the rights of the human subjects."

Nevertheless, Kaplan said he got a clear message from the future Nobel Prize winner who ran The Hutch. "It certainly didn't appear that we had the power to investigate anything once I got that letter from Thomas."

But what Thomas wrote was mild compared with some of what Pesando heard in the hallways. Thomas and others were enraged with the challenge to their research, Pesando said.

"Dr. Thomas had a fearsome reputation," Pesando said. "You crossed him at your peril."

'Who the hell are YOU?'

IRB members felt unable to do a proper scientific assessment of Protocol 126. They felt they didn't have the information or the power to do their job.

Six weeks after Thomas' letter, Kaplan, on behalf of the IRB, asked Hutch President Dr. Robert Day to set up a new, independent body to consider the merits of all the monoclonal antibodies under study. The IRB termed them "entirely new, experimental drugs" which had not met normal safeguards.

Day

"We saw this coming, that we would eventually be unable to resist the people who controlled our lives, careers and salaries," Pesando said. "That's why we wanted an outside review."

Day refused to set up an outside panel, saying it would cost too much and reveal secrets to The Hutch's competitors.

Kaplan also contacted the National Institutes of Health for advice on how the panel could act, but got no help.

In January 1984, IRB members heard that two patients in the newest version of Protocol 126 had failed to engraft transplanted marrow. Normally, properly matched marrow was accepted 99 percent of the time, so these rejections were alarming.

They meant patients might actually die from their treatment before they would even reach the point where GVHD was a possibility.

Pesando started warning patients to stay out of the protocol. Some did; some did not.

Day summoned the senior clinical staff to a meeting with Kaplan and Pesando. Day would not curb the protocol or start an outside review. But he agreed to one demand: The lowest-risk patients, who had the most to lose from graft failures, would not be allowed to enroll in Protocol 126.

"We got something - granted, not very much, because we had no power - but we got the best patients out," Pesando says.

The research team did not appreciate those efforts. Pesando says Thomas asked him at a scientific staff meeting, "Who the hell are YOU to question what we do around here?"

Graft failures, relapses high

Death by leukemia occurs as cancer cells crowd out normal cells in the blood. Victims suffer infections, bleeding and oxygen deprivation.

Death by graft failure after a bone-marrow transplant is an accelerated but no less agonizing process. The victims, weak from Hiroshima-dose radiation and chemotherapy, fail to accept the marrow that could save their lives. They suffer all the effects of a destroyed immune system and die of infections and bleeding.

Graft failure is extraordinarily rare in normal cancer work, occurring 1 percent of the time in tissue-matched transplants between siblings.

Deaths related to T-cell depletion in Protocol 126
Protocol 126 consisted of multiple stages. The first stage of the experiment added the antibodies alone to donor marrow and had no effect on killing T-cells...

But of the 20 people enrolled in Protocol 126 between June 1983 and March 1984, at least seven of them died from graft failure.

At least five patients suffered relapses of their cancers, which was also an unusually high rate, believed to be caused by the absence of T-cells to fight off stray cancer cells.

The dead included people who stood a good chance of being cured with standard therapy. Among them:

• Ruth Agnes Fisher, a Los Gatos, Calif., computer programmer. She was 38 years old when she learned she had leukemia.
It was a relatively mild form that could be bothersome but not fatal for many years. She also had a perfectly matched sibling donor for a bone-marrow transplant. With the standard treatment, she had a 60 percent likelihood of being cured.

But Fisher was enrolled in Protocol 126. Her bone-marrow transplant failed to engraft and she died of cardiac arrest on Jan. 27, 1984.

"The whole thing was sort of a blur," her widower, Joe Fisher, says today. "T-cells - I thought that's what makes the transplant work."

• Jacqueline Couch, 31, an attorney for the city of New York who lived in Summit, N.J. She, too, came to Seattle for a transplant with a relatively good prognosis. She, too, was signed up for Protocol 126.
She, too, died of graft failure almost certainly caused by the experiment.

Her brother, Richard Stanford Jr. of Yardley, Pa., who donated his marrow, says today, "For some reason - we were told the doctors didn't know why - it all of a sudden stopped producing cells."

No one ever told the family what went wrong. "It took me a long time to get over that," Stanford says.

• Lourdes Caridad Llera, 32, a homemaker from Tampa, Fla. She died in May 1984 after graft failure.
• Carolyn Sue Obermeyer, 37, a homemaker from Oldenburg, Ind. She died in September 1984 after graft failure.

• Lawrence Haspel, 48, a New York orthodontist. He died after graft failure and a second transplant attempt.

• Bina Bidasaria, 31, a homemaker from India. Ten months after a transplant with a brother's matched marrow failed to engraft, she tried a second, then died in Seattle a month later. Her widower, Mahavir Bidasaria, says he doesn't remember talking about T-cells and wasn't told why she had graft failure. "All those terms were not very familiar to us."

• Paul Mahler, 41, chairman of the anthropology department at Queens College of the City University of New York. He suffered graft failure, tried a second transplant after the first one failed and died in Seattle seven weeks after that.

The Seattle Times identified these people through death certificates and public records.

Fisher and Couch had been Pesando's patients for a time when he worked on the transplantation ward. Their deaths affected him deeply. He believed they could have survived a standard bone-marrow transplant.

In retrospect, Martin concedes the results of the experiment on chronic leukemias at that point were "awful."

"A lot of rejection, a lot of recurrent malignancy," he said in an interview. "And so it didn't work. It was a bad idea."

'Something's really fishy here'

The Hutch didn't have to report these patient deaths to the federal government. Experimental drugs that do not cross state lines are not regulated by the Food and Drug Administration.

The Hutch didn't alert the King County Medical Examiner, either, despite state and county requirements to report unexpected deaths associated with medical procedures.

Martin was required by federal and Hutchinson rules to report the deaths to the IRB, but he did not.

Inside the corridors of The Hutch and Swedish, however, word of the unusual deaths spread. And the drumbeat against Protocol 126 intensified.

Dr. Rainer Storb - the Hutch co-founder who had opposed the experiment from the start - says he spoke out in staff meetings time and again over the years.

"It was becoming evident on the wards that, you know, something's really fishy here," Storb recalls. "You have to have a very keen eye and bring the whole thing to a screeching halt if something goes wrong."

Storb had long been The Hutch's top expert on GVHD. In the same hallways and at the same time that patients were dying in Protocol 126, Storb was perfecting a better treatment against GVHD.

He had found that a combination of two FDA-approved drugs, methotrexate and cyclosporine, prevented GVHD and treated its effects.

Storb had started enrolling patients in his own clinical trial in August 1983, just as the most dangerous arm of Protocol 126 began.

He published his work in the New England Journal of Medicine. He had cut rates of acute GVHD from 54 percent to 33 percent and had raised the 18-month survival rate from 55 percent to 80 percent. He had had no problems with graft failures or relapse in 93 patients.

Storb came closest to a public attack on Protocol 126 when he cited it twice in passing in his New England Journal article, noting "survival rates that were poorer than those seen among patients who received untreated marrow."

Storb's regimen has stood the test of time. It remains the gold standard for treatment of GVHD to this day.

There is no evidence any Protocol 126 patient was ever told about the Storb treatment, even though its positive results had emerged. Instead, they were told there was no alternative to Protocol 126 to prevent GVHD.

It was a careful choice of words. Thomas' wife, Dottie, a program aide who helped with Protocol 126, argued in a memo that the Storb method was "treating" GVHD but only Protocol 126 was "preventing" it.

As the failures and deaths mounted, Protocol 126 was altered again and again, but new patients still weren't told the risks.

New theory on failures

By mid-1984, Martin and Hansen began to discuss their setbacks in seminars. An issue of the medical journal Blood includes an article in which they note the high graft failure in their experiment - 40 percent at that point - was "a highly unusual outcome."

But not, apparently, reason enough to end the trial.

The Blood article outlined their plan: While eight of 11 patients with the best prognoses had failed to engraft, only one of the other nine patients had failed. The authors theorized that the higher radiation given sicker patients had weakened the immune system enough to let the donor marrow take hold.

Fred Hutchinson Cancer Research Center
Dr. Paul Martin (in tie) stands behind Dr. E. Donnall Thomas, a Hutch co-founder, in a photo taken in the mid-'80s, during Protocol 126.

The IRB, still headed by Kaplan, instructed Martin to change the patient-consent form before Protocol 126 could proceed. "Specifically, the risk of loss of graft should be more clearly stated," the panel said.

The form being shown to patients said: "To the best of our knowledge, (Protocol 126) does not damage the cells necessary for engraftment."

A revised form conceded that the treatment "may damage cells necessary for engraftment," then continued with its previous assurance, "In this case, a second marrow transplant would be necessary."

Again, it didn't say that second transplants fail 95 percent of the time. It didn't say there was a higher risk of relapse, nor did it disclose the Storb alternative, nor the financial interests.

Pesando thought the IRB, under duress, had surrendered. And Pesando said they never knew at the time that Storb, too, opposed Protocol 126.

Kaplan, assured by president Day that there would be a scientific review and that the experiment would stop immediately if it had two more graft failures, approved Protocol 126.1, the next stage of the trial, on behalf of the IRB on June 1, 1984.

Those graft failures came quickly.

Dr. John Draheim, 36, a physician for the U.S. Navy in Bremerton, and Seci Cay, 31, owner of an export-import business in Turkey, came to The Hutch for chemotherapy, radiation and transplants in the fall of 1984. When their T-cell-depleted marrow failed to engraft in December, the trial was halted again.

Kaplan wrote Day "once again" objecting to the protocol on scientific and ethical grounds.

"Monoclonal antibodies are being used in what appears to be a completely uncontrolled fashion ... " Kaplan wrote. "Alternative therapy seems downplayed in importance. ... In addition, the board is concerned about authorizing protocols in which the apparent successful use of an agent could be potentially beneficial financially to many of the investigators listed on the study."

Appelbaum

Dr. Frederick Appelbaum, head of the clinical-research division, replied on Day's behalf, telling Kaplan to stop complaining about financial conflicts. He said the IRB must either express concern about all types of financial conflicts, such as the possibility of researchers losing their jobs if patients stopped enrolling in the experiments, or "accept the fact that those of us in cancer research are intrinsically honest individuals who are trying our best."

Martin proposed further human experiments. Admitting "graft failure represents a highly unusual outcome," Martin said he would add methotrexate, one of the drugs Storb was studying, to aid engraftment.

In January 1985, the IRB approved Protocol 126.2, the next stage.

Two weeks before that approval, Draheim died, with Hansen himself the attending doctor. Two weeks afterward, Cay died. They were at least the eighth and ninth victims of graft failure caused by the treatment.

"Each successive protocol was a variation on some aspect of the treatment, with the goal of asking would this change make a difference in the outcome," Martin said later. "And recurrently, the answer was no."

In other words, no matter what they tried, the treatment wasn't helping patients.

'She never got better'

Elizabeth Almeida, 35, was a strong-willed single woman about to adopt her foster child, a 13-year-old boy, when she was diagnosed with leukemia.

While the first patients were dying of T-cell depletion in Seattle, she was undergoing chemotherapy in Boston, about an hour from her home in New Bedford, Mass. The cancer disappeared, then re-emerged, then disappeared after more chemo, but the prognosis was grim.

Her doctor told Almeida that her best chance for survival was a bone-marrow transplant at the Hutchinson Center in Seattle. She had a perfectly matched sibling, James, to donate bone marrow. If she could survive even more chemotherapy and radiation, James' donated blood could help her start manufacturing new, clean blood.

Almeida and her mother and brother traveled across the country in March 1985. In a conference with a Hutch doctor, they were offered the "informed-consent" documents for Protocol 126.2.

That form had not been updated as the IRB had ordered, a technical violation of federal human-protection rules. Again, it described graft failure as merely possible and correctable, and failed to mention the higher risks of new or recurring cancers.

Though Protocol 126 was a highly experimental procedure, the statement of risks on the patient-consent form was more serene than the warnings on many drugstore medicines.

The Times, with the family's permission, obtained Almeida's 1,833-page medical file. It offers no evidence that anyone ever told her or her family about the then-obvious risks of dying from the treatment, nor of the availability of Storb's more successful alternative treatment.

After some initial hesitation, and after being promised a conference with Martin, which she never got, Almeida agreed to participate in the experiment. She entered Swedish Medical Center in outward good health, with her disease in complete remission.

"Delightful," a nurse described her. "Looks well."

After a week of drugs and radiation, she grew weak and nauseated, then developed severe mouth pain, fevers, pneumonia and kidney failure.

Transplants have been compared with killing patients and then bringing them back to life. Almeida never came fully back. Her marrow never did restore its blood-making capacity after she got her brother's cells.

She recovered enough to return to Massachusetts, but the transplant ultimately failed to engraft and the leukemia returned.

"She never got better," Billy Tatro, a longtime friend, recalls. "When it was obvious the transplant was failing, it really wasn't apparent to anyone why. The doctor said there was only one possibility, and that was a second attempt. So he sent her back to Seattle."

Almeida was pale, frail and feverish when she checked back into Swedish.

"Bright, frightened woman," a social worker wrote.

She never got the second transplant. She died first, on Oct. 3, 1985.

Annmarie Ridings of Mattapoisett, Mass., didn't know her sister Elizabeth had been part of any experiment, let alone one with such a grim record.

"As you can imagine, this information has upset my family," she says.

"My family continues to feel the effects of her death fourteen years ago. I do not believe that my sister would have agreed to participate in a study that she knew had such a high failure rate."

A 100 percent risk of relapse

Among the people Elizabeth Almeida had met in the leukemia ward were the couple from Alabama, Pete and Becky Wright.

Becky was a mother of three, a runner, a dancer, who had been diagnosed with chronic myelogenous leukemia in March 1985. Like Almeida, she and her husband came to The Hutch for the best treatment money (about $200,000) could buy.

Buckner

Dr. C. Dean Buckner discussed treatment options with the Wrights. His dictated notes were released by Swedish Medical Center with permission of Pete Wright.

Buckner told Becky she would not be cured by conventional chemotherapy, but stood a good chance of survival with a bone-marrow transplant. More than half the patients with diagnoses similar to hers were still alive after getting transplants, he said.

Buckner predicted only a 15 percent probability of leukemia recurring over the next two to three years for Becky. However, he added, she had "high probability" of getting GVHD because of her age, 37, and he suggested she enlist in Protocol 126.

Pete Wright recalls: "We had been out there for a month waiting for a bed, and I remember talking about the protocol. We were told this was the best way to avoid GVHD, and from some of the pictures we'd seen and the things we'd heard, we definitely wanted to avoid that."

The consent form the Wrights were given emphasized the benefits. Under "Risks," it said: "Graft rejection has occurred following such treatment. In this case, a second marrow transplant would be necessary."

Pete Wright says - and the records indicate - that Buckner mentioned the risk of graft failure but did not say that more than a quarter of the transplants in Protocol 126 so far had failed. Nor did he say that second transplants were 95 percent fatal. He apparently did not mention the risk of relapse or new cancers at rates significantly higher than in standard transplants.

Buckner now says he was "one of the bigger skeptics" about Protocol 126 but "I didn't find anything unscientific or unethical about any of this. We were all trying to make people better. And at that time, it was felt that T-cell depletion was the greatest thing since sliced bread. And it wasn't."

In fact, as Martin, Thomas, Buckner and other Hutch doctors outlined in a journal article on chronic myelogenous leukemia published three years later:

"The actuarial relapse risk 2.5 years posttransplant was 100 percent in patients administered T-cell-depleted marrow as compared with 25 percent in patients administered unmodified marrow."

A 100 percent risk of relapse. Every patient like Becky Wright, if he or she lived long enough, saw the nightmare of leukemia return.

The statistic shocked Pete Wright when he saw it years later. The relapses in Protocol 126 included eight patients before Becky walked in the door, and six afterward. She was not the only one, nor was she the last.

Pete Wright said Becky didn't give much thought to the protocol, trusting doctors to act in her best interest. She signed most of the forms before even talking with Buckner.

"She knew this was her one shot to live," Pete Wright said. "She was upbeat. She was psyched up and ready to go."

'The pain never really dies'

Becky Wright told Pete she never imagined she would feel so bad.

Chemotherapy not only kills cancer cells, it assaults normal tissue in hair follicles, the mouth, the digestive system and the bone marrow. Wright suffered painful lesions, systemic infections, diarrhea, organ damage.

But if she could be cured, it would be worth it.

On June 17, 1985, she received her sister's marrow, which had been treated with the eight antibodies and was devoid of T-cells.

She was luckier than some: The graft took; her white cells propagated and her sores and infections healed. Becky Wright checked out of the hospital a month after the transplant and flew home to Heflin, where life more or less returned to normal.

But when she flew back to Seattle the following year, a checkup showed her leukemia had returned. Doctors recommended a second transplant, this time with T-cells. She got it, but was too weak to survive a graft-versus-host reaction and bloodstream infections.

"I can hardly take deep breaths; it's too painful," she told a nurse.

She missed her children. She wanted to go home to Heflin. There was nothing The Hutch could do to help her. And on the day before Mother's Day, 1987, Becky Wright hemorrhaged and died in a hospital bed in Birmingham, Ala.

Whether she would have survived with standard treatment will never be known. But based on the evidence, her widower feels his wife was deprived of her optimal shot for survival.

At the very least, he said, they were deprived of crucial information they deserved to know.

Earlier this year, Pete Wright was shown Pesando's letters and studies on T-cell depletion. The understated risks and undisclosed financial interests infuriated him.

"My grandfather was a doctor, an active doctor for 62 years," Wright said. "He would be doing back flips in his grave if he heard about this."

Pete Wright is remarried and trying to move on with his life. He doesn't want Becky's ghost to haunt his new family. But he says, "The pain never really dies. The truth definitely needs to come out on this."

The experiment ends

In October 1985, Bristol-Myers bought Genetic Systems for $294 million, or $10.50 per share. The purchase raised the value of Hansen's original stock holding to $1.8 million, Thomas' to $1.05 million, Martin's to $105,000 and the foundation's to $502,000.

Protocol 126 lasted 12 years - an extraordinarily long time for a clinical trial - even as deaths mounted.

Each new phase tested slightly different combinations of chemotherapy, radiation or immune-system suppression, but all were built around the same antibodies.

The later versions of Protocol 126 ended with graft failures in two of 12 patients, two of nine, two of eight, two of nine, two of two, and one of one, respectively. Overall graft failure was at least 24 percent, vs. the expected 1 percent.

And even when the transplants took, the cancer came back. Of those with chronic leukemia, 100 percent suffered relapses, vs. the expected 25 percent.

As the failures mounted, the description of the study in filings with the National Cancer Institute changed: It began as an experiment in whether T-cell depletion would prevent GVHD. It ended as an experiment that showed T-cells were necessary to engraft and to fight spare leukemia cells.

The consent form in the final phase of the study, approved by The Hutch in 1991 and 1992 for up to 20 patients, warned that patients "often reject the marrow," leading to death, and that T-cell removal "may increase the risk of relapse."

Finally, it revealed: "In this situation, there is a high chance of infections, bleeding and death."

The first patient in the final phase, a 30-year-old man with a mismatched donor, experienced graft failure. The protocol was ended forever.

Records reflect that at least 20 patients died from graft failure in the experiment between 1981 and 1993. The first seven of those had forms of cancer with a cure rate of about 50 percent with standard treatment.

In the end, the experiment was almost uniformly fatal.

Martin, Hansen and Thomas never did write a final report on Protocol 126. Martin says he discarded his files when he moved to a new office in 1998.

But Martin disclosed the final toll: 82 people from around the world enrolled in the Seattle experiment; 80 of them are dead today. And the Hutchinson Center has become a leading voice against T-cell depletion.

"We worked very hard to remove every T-cell from the graft and we found out that wasn't a bright thing to do," Martin says now.

He wishes he had set up a better mechanism for ending the stages of the experiment as they proved unsuccessful. He blames his inexperience, and a lack of guidance from The Hutch.

"I don't know that I was trained as well as I would have liked at the time," he says. "Nobody told me what to do."

Martin passionately insists, though, that his persistence down the path of T-cell depletion was motivated by science, not by business.

"I want to assert definitively that the clinical trials were motivated by scientific evidence suggesting that the results of bone-marrow transplant could be dramatically improved by removing the T-cells from the graft," he said.

Martin's mentor, Hansen, is less emphatic in his denial of financial motivation. Asked whether the doctors' personal investment in Genetic Systems affected the experiment, he replied: "I don't think so. I don't think so."

Asked if Genetic Systems stood to make money if the antibodies proved successful, Hansen said: "Well, of course that was the idea. You start a company to make a profit."

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The Hutch is a major player in cancer care and research

Harley Soltes / The Seattle Times
In the 1990s, The Fred Hutchinson Cancer Research Center moved to a new campus at South Lake Union, 1100 Fairview Ave N., which it built for more than $150 million.

THE FRED HUTCHINSON Cancer Research Center in Seattle has saved thousands of lives in its 25 years of existence.

The Hutch performs about 450 bone-marrow and stem-cell transplants a year on patients whose cancers were once thought to be incurable.

It is the largest bone-marrow-transplant center in the world, and, in the words of leukemia experts such as Dr. Richard Shadduck of Pittsburgh, it is "the Mecca."

"Everyone would agree the Seattle program took off not only numerically but scientifically and blazed trails in the field," he said.

The taxpayers have helped: The Hutch leads the nation in funding from the National Cancer Institute (NCI) - a notable achievement for a place specializing in blood cancers, which account for just 10 percent of the new cancer cases in the United States each year.

The Hutch received $69 million from the NCI in fiscal 1999 (the latest figures available) - more than Johns Hopkins, Sloan-Kettering, M.D. Anderson or any other well-known cancer center.

In all, The Hutch got $142 million in 2000 - about two-thirds of its total revenue - from the federal government. Of the remainder, about $40 million comes from patient fees, $25 million from direct public support and $12 million from other sources.

Fred Hutchinson
Cancer Research Center

Established: 1975
Employees: 2,300
Volunteers: 1,400
Clinical Research Division
staff: 943
Budget: $204 million
National Institutes of
Health grants (2000):
$142 million

The center is named for a former major-league baseball player and manager from Seattle who died of cancer in 1964. Fred Hutchinson's brother, Bill, a Seattle surgeon, knew U.S. Sen. Warren Magnuson of Washington, the longtime chairman of the Senate Appropriations Committee. Magnuson pushed through a $5 million grant, and The Hutch was on its way, opening in 1975.

It is one of 38 federally designated Comprehensive Cancer Centers in the United States and the only one in the Northwest.

Over the years, The Hutch has spawned seven major biotechnology companies, including Immunex and Cell Therapeutics, making Seattle the nation's fifth-largest biotech center by employment.

In the 1990s, The Hutch built a new campus at Seattle's South Lake Union for more than $150 million.

In 1998, The Hutch, Children's Hospital & Regional Medical Center and the University of Washington formed the Seattle Cancer Care Alliance, described as "the new front door to comprehensive oncology services in the Pacific Northwest." The alliance's seven-story outpatient clinic was built next door to The Hutch.

The Hutch is also becoming a leading center for stem-cell transplants, a safer procedure in which immature cells that give rise to other blood cells are used instead of bone marrow to rebuild the body's immune system after massive chemotherapy and radiation.

The procedure left two-thirds of patients cancer-free after two years, compared with 45 percent of bone-marrow patients, according to a Hutch study recently published in The New England Journal of Medicine.

Dr. William Bensinger, director of the study, said stem-cell transplants could help thousands of patients worldwide who are treated for blood cancers, especially those with advanced disease.

In addition, Dr. Rainer Storb is preparing a paper about a revolutionary new "minitransplant" that activates the body's own immune reaction to attack cancer. The procedure can be done at low cost without hospitalization, and Storb is reporting remarkable preliminary results.

The center's mission is vast and simple: "eliminating cancer as a cause of human suffering and death."

He saw the tests as a violation of 'trusting, desperate human beings'

By Duff Wilson and David Heath
Seattle Times staff reporters

FOR NEARLY two decades, Dr. John Pesando sounded the alarm over what he saw as a dangerous and unethical human experiment at Seattle's Fred Hutchinson Cancer Research Center.

In the 1980s, he complained from the inside: As a member of an oversight committee at "The Hutch," he repeatedly objected to the clinical trial in which leukemia patients were dying at unusually high rates.

In the 1990s, he complained from the outside: In letter after letter - to members of Congress, to federal and state agencies, to newspapers - he said "many good people needlessly lost their lives" in the leukemia experiment, which lasted from 1981 to 1993.

"Trusting, desperate human beings were used as laboratory rats," he wrote to state authorities in 1994. "One should not assume that these patients would have soon died anyway because they had cancer, and that it was therefore not possible to do any harm. Many of these patients were correctly told that they could expect cure rates of approximately 50 percent (with standard treatment) ...

"Real people lost their lives, and there was no way to stop it."

What happened
A timeline of doctors' complaints and officials' responses.

For the most part, Pesando was received as Hutchinson Center officials have portrayed him: a disgruntled former employee with an ax to grind. But a Seattle Times investigation supports most of his allegations and finds his concerns shared by some of the most respected cancer doctors in the Northwest.

Seventeen years passed between the time Pesando and other doctors first objected to Protocol 126, as the experiment was labeled, and yesterday's revelations in The Times of deaths, misleading assurances and potential financial conflicts surrounding the experiment.

In those years, the doctors' complaints were largely rebuffed, rejected or ignored. Finally, under incessant pressure from Pesando, they were taken up by federal and state agencies but never fully investigated.

Underlying all of this, Pesando and other doctors believe, was a reluctance to challenge an institution as respected and powerful as the Hutchinson Center. That reluctance was all the greater because one of the people behind Protocol 126 was Dr. E. Donnall Thomas, a Hutch co-founder and co-winner of the 1990 Nobel Prize in Medicine.

As Pesando puts it: "They were all afraid of taking on the 800-pound gorilla."

Experiment already under way

Harley Soltes / The Seattle Times
A snapshot of Ruth Fisher who died in January 1984 after a graft failure and second transplant

John Pesando came to Seattle and The Hutch in 1982 as a 36-year-old magna cum laude graduate of Harvard University with a medical degree and Ph.D. from the Albert Einstein College of Medicine in New York. Pesando was board-certified in oncology and internal medicine; his research focused on tumor immunology. He had taught at Harvard and had worked for four years as a cancer doctor and researcher at the Dana Farber Medical Center in Boston.

At Harvard, Pesando had discovered an important antibody marker in tracking and treating leukemia, and conducted the first-ever clinical trial with a monoclonal antibody, treating five leukemia patients.

He was recruited to The Hutch by one of its co-founders, Dr. Rainer Storb. Soon after joining the staff, Pesando was asked by his bosses to serve on the Center's Institutional Review Board.

That board was required by federal law to review all proposed human experiments at The Hutch. Its members were to ensure that risks to patients were minimized in relation to potential benefits, and that patients fully understood those risks before agreeing to participate in clinical trials.

Pesando was reluctant to take on the unpaid duty of policing his colleagues, some of whom were in a position to affect his future. But he believed deeply in the need for such policing, he says, so he swallowed hard and served.

Also joining the review board was a new chairman, Dr. Henry Kaplan, from Seattle's Swedish Medical Center, where some Hutch patients were treated. He is now one of the Northwest's most highly regarded oncologists.

From their first days on the board together, Pesando and Kaplan were concerned about Hutch researchers using unproven new antibody drugs.

In Protocol 126, researchers were testing antibodies to see if the elimination of certain cells in the blood, called "T-cells," would make bone-marrow transplants safer. The researchers theorized that killing off the T-cells in the marrow of donors before injecting it into patients would help stave off a troublesome complication known as graft-versus-host disease, or GVHD.

The experiment was directed by Don Thomas; Dr. John Hansen, head of a tissue-matching lab and later clinical director; and Dr. Paul Martin, a young oncologist. The trial was funded by the National Cancer Institute.

From the time the experiment was first brought to the oversight committee early in 1981, some committee members had challenged it, saying:

•The science behind the experiment was dubious. While mice benefited, some felt there had been inadequate prior research on dogs before moving on to tests in humans.
•Some thought T-cell removal might actually prevent donated bone marrow from engrafting, or taking hold in the recipient's bones, and some thought it might open the way for the return of the cancer.

•While GVHD was bothersome and uncomfortable, it was seldom fatal. And the proposed subjects of Protocol 126 - those with siblings whose tissue type matched theirs - were the least likely to get it. Besides, there were other ways to effectively treat GVHD.

•Unlike most cutting-edge medical research, Protocol 126 proposed experimenting on the healthiest, rather than the sickest, patients. Committee members saw no need to subject those patients to undue risk.

•The "informed-consent" form for the experiment - the required document outlining risks for patients - was misleading.

Despite all these concerns, the previous oversight board had approved the experiment in April 1981. By the time Pesando and Kaplan joined the board, the experiment was well under way.

Financial conflicts of interest

Within their first few months on the Institutional Review Board (IRB), the new members suspected that Protocol 126 wasn't working. Patients enrolled in the experiment were dying - including some people who otherwise would be expected to live.

Kaplan and Pesando raised many of the same questions their predecessors had on the medical and scientific aspects of the experiment. They received lots of assurances but no answers.

Meanwhile, a new concern emerged: Rumors were rampant in hospital hallways that the researchers - Thomas, Hansen and Martin - all had financial interests in Genetic Systems, the Seattle biotechnology company that owned rights to some of the drugs being tested in the experiment.

When Kaplan asked Hutch officials about the rumors, he was told the researchers had no financial conflicts. What he was not told was that not only did those researchers all hold stock in Genetic Systems, they all held advisory or actual working positions with the company. Nor was he told that The Hutch itself had stock in Genetic Systems.

"We didn't even know which investigators were connected with which companies," Kaplan recalls now. "We never got the opportunity to ask about the decision-making process. I guess the fair thing to say was John (Pesando) was absolutely convinced there was a problem, and the rest of us thought there was enough to raise questions about. They were not answered satisfactorily in the time I was on the board."

Meanwhile, the early stages of Protocol 126 were proving a failure, and patients were dying - some, apparently, as a direct result of the experiment. Among the dead were two patients Pesando himself had treated.

When their two-year terms on the Institutional Review Board ended in 1985, Kaplan and Pesando were told again by the president of The Hutch, Dr. Robert Day, that their concerns about both medical and ethical problems with Protocol 126 would soon be addressed.

They trusted that assurance, and went on to focus on their careers. Kaplan built one of the most successful private oncology practices in the Northwest; last year, he was the cover subject of a Seattle Magazine feature entitled "Top Doctors."

Career hits a snag

Pesando, meanwhile, went about trying to land a long-term position doing cancer research at The Hutch. That didn't happen. In 1987, his contract expired and was not renewed. Storb says Pesando "didn't work out. He was removed by Don (Thomas) for a number of reasons. I agreed with them. He was not an active member. He led a sheltered life. He was very paranoid about sharing data. He didn't bring in grants. He left under poor circumstances."

Pesando has another explanation: his run-ins with Thomas and the other people behind Protocol 126. He recalls Thomas confronting him after one particularly tense session, barking: "Who the hell are YOU to question what we do here?"

(Thomas refused to be interviewed by The Times for the articles running this week.)

Pesando doesn't deny that he struggled at The Hutch. He says that was because he was unable to get support from his bosses for research he proposed.

He tried unsuccessfully for a time to find a good position elsewhere in his specialty areas of leukemia and lymphoma - "They (would) go to The Hutch for recommendations" - then decided to take another path. He began working as a consultant for the Social Security Administration and for biotechnology companies.

He and his wife settled into a hundred-year-old Victorian home on Capitol Hill and raised their daughter.

Over the years, Pesando tried to put Protocol 126 out of his mind. He might have succeeded, had he not picked up a book entitled "Magic Bullets" in 1991. In it, Seattle author Grant Fjermedal describes the invention of new antibodies to seek out and destroy cancer.

Among the companies Fjermedal wrote about was Genetic Systems. He outlined the company's relationship with The Hutch and its doctors, and quoted Day, Hutch president, on why such financial interplay was a positive factor in medical research, not a negative.

Pesando was incensed to see this apparent confirmation of what he and Kaplan had suspected all along: that Protocol 126 was driven not only by science but also by money. And Day's position was a signal that nothing had changed.

Pesando contacted Fjermedal, a longtime science and medical writer, who was struck by Pesando's knowledge of the situation and by his passion.

"What you've got in this guy is a rarity," Fjermedal said in a recent interview. "You've got somebody who has the credentials. He's seen all this, he's on the inside, and he's coming forward. That's very, very rare."

Fjermedal encouraged Pesando to take his complaints to the proper authorities.

For the rest of the decade, that's precisely what this lonely warrior did - only to be repeatedly frustrated.

Federal agencies take a look

President Day successfully defended The Hutch, but in the end a state official said, 'There still remained some doubt in our mind.'
Pesando began firing off letters in various directions in 1991. He wrote to members of Congress, to federal and state agencies, even to The New York Times.

Finally, a letter to the federal Office of Protection from Research Risks (OPRR), a unit of the Department of Health and Human Services, caught someone's attention.

"Basically," Pesando wrote, "senior clinicians at the Fred Hutchinson Cancer Research Center in Seattle conducted clinical trials with high therapy-induced mortality rates while they were major stockholders in the company with commercialization rights to those therapies."

Admitting to feeling "much anger," Pesando concluded, "The seriousness of this issue and its implications for future patient care continue to make it very difficult for me to take the expedient course of doing nothing."

In May 1993, the OPRR opened an investigation of the case. Thomas Puglisi, chief of the agency's compliance department, assigned investigator Kamal Mittal.

Mittal got Pesando's permission to use his name, and three months later, sent a copy of Pesando's letter to Day, the Hutchinson Center president.

Two months after that, Day responded with a 24-page letter and 2-inch stack of attachments. In that package, he defended The Hutch and its researchers vigorously.

He insisted that a successful outcome to Protocol 126 would not have benefited Genetic Systems or its stockholders - ignoring the fact that some of the chemicals being tested were licensed to Genetic Systems, and that the very existence of the experiment had increased the company's value.

He insisted that any risks "were fully disclosed to and discussed with the patients." However, the consent form underplayed the risk of graft failure and failed to mention the likely outcome - death - if a second transplant were necessary.

He insisted that the IRB had the power to address any concerns - ignoring the fact that Pesando and Kaplan had pushed for an outside review.

And he insisted that concerns about conflicts of interest "were addressed promptly" by a policy adopted by the Hutch Board of Trustees in March 1983. That policy barred employees from participating in research in which they or a family member had an economic interest of any type. However, the policy was not enforced and resulted in no changes in Protocol 126. In fact, Hansen and Martin say they were never told about it.

(Day, who retired as Hutch president in 1997, refused to be interviewed by The Times for the articles running this week.)

The Hutch also hired the best medical-ethics defense lawyer at the then-biggest law firm in Washington, D.C.: Barbara Mishkin of Hogan & Hartson, who phoned Puglisi and met with Mittal briefly.

Pesando had no opportunity to respond to Day's claims. He called the OPRR several times to offer help and information but never heard back.

Frustrated, he went to the top, writing to Health and Human Services Secretary Donna Shalala. The result: more frustration.

Pesando did receive a response, from Wendy Baldwin, acting deputy director for extramural research at the Public Health Service. Baldwin wrote that she recognized "the very serious nature of the issues you have raised" and promised to review the case.

But that promise was an empty one, e-mail released to The Times under the Freedom of Information Act shows.

That e-mail, between Puglisi of the OPRR - the actual author of the letter signed by Baldwin - and Dr. George Galasso of the National Institutes of Health, indicates that top federal officials had already decided there was "nothing wrong" with conflict-of-interest issues in Protocol 126. An e-mail from Galasso suggests they send it to another office as "sort of CYA (cover your ass)."

Investigation is dropped

Meanwhile, other federal documents show, the primary investigator, Mittal, was far from convinced there was no problem. He had several pointed questions he wanted to ask Hutch officials:

•Did the IRB feel compromised or strong-armed?
•Was the risk/benefit ratio in favor of the patients?

•Were patients fully and correctly informed of risks?

•Did the doctors violate the conflict-of-interest policies? (Mittal added: "Answer appears to be yes!")

•Was it proper to develop products with federal funds that would profit a private company and doctors?

"To get answers to these questions, it may be necessary to arrange a site visit to speak with various individuals including the members of the IRB at the time period in question," Mittal wrote.

But then Mittal, who'd been brought in as temporary help, asked to be transferred to another job and was removed from the case.

"I left it almost in the middle," Mittal recalls.

Pesando's complaint lay untouched in Washington, D.C., for a year after that.

"It was just a matter of our workload being overwhelming at the time," Puglisi said.

The OPRR was absorbed in a fertility-clinic scandal in California. It was chronically understaffed. At one time it had about 70 open investigations being conducted by one full-time professional staff member and two or three part-timers, the House Committee on Government Reform found.

Eventually, Pesando and Day both wrote, separately, to ask for a progress report. Puglisi assigned a senior staffer, William Dommel, to write a report based on information in the file, nearly all of it provided by The Hutch.

That report, dated Sept. 5, 1995, and signed by Puglisi, concluded that the complaint was "unsubstantiated" and that The Hutch was not at fault since its own Institutional Review Board had failed to stop the activities. The OPRR blamed the Hutch IRB for not doing more to stop the study.

The federal investigators never interviewed Pesando or Kaplan, both of whom had tried to stem the study, or any other IRB members.

They never interviewed Thomas, Hansen, Martin, Day or any other Hutch officials.

They never interviewed any of the families of the trial subjects.

They never asked for a single tape of a single IRB meeting, nor ever spoke with a single outside expert on the risks of T-cell depletion and second transplants.

Pesando was stunned.

He wrote again to HHS Secretary Shalala and to Harold Varmus, director of the National Institutes of Health. Steam rose from his rhetoric.

"In late 20th century America, prominent physicians at a major cancer center knowingly risked the lives of unsuspecting patients in pursuit of financial gain, successfully bypassed regulatory bodies, and repeatedly silenced opposition. ... Yet there could hardly be less concern if laboratory rats had died instead."

He called the investigation "arrogant, chilling and totally unacceptable."

Shalala and Varmus never replied. Baldwin of the Public Health Service wrote to Pesando on their behalf.

"After careful examination of the OPRR's findings, I am convinced that the investigation was exhaustive and conducted with objectivity and due consideration for the rights and welfare of human subjects involved in research," Baldwin wrote.

A fax obtained by The Times, however, suggests there was no such "careful examination" by Baldwin. Instead, it shows that Dommel - the very person who wrote the findings about which Pesando was complaining - had drafted the response for Baldwin to sign.

Pesando wrote to Varmus again: "The NIH's handling of this matter suggests that it was afraid of finding something, and the profound apathy of those at the top to misconduct in the field helps to explain why such problems exist."

This time, Pesando got no response.

State panel takes on the case

While he was waiting for Washington, D.C., to act, Pesando took his crusade to Washington state officials.

He wrote to Dr. Larry Bryce, chairman of the state Department of Health's Medical Quality Assurance Commission, in December 1994, repeating his complaint:

"In essence, financial conflict of interest led to highly unethical human experimentation which resulted in at least two dozen patient deaths. Oversight committees were misled, lied to, and kept uninformed while in an atmosphere of fear and intimidation ...

"I have done my part, and more, to correct this problem. I would like to see someone else show some interest."

The state commission showed some interest in the complaint but decided to wait for the federal findings.

Nine months after federal officials dropped the case, the state opened its own investigation. In June 1996, a year and a half after Pesando's filing, the case was assigned to Dr. Robert Miller, physician staff member of the state commission, and investigators James Smith and Bill Crowell.

Their investigation went much further than the feds' had. They interviewed Hutch officials, Kaplan and Pesando.

Kaplan had forgotten many details of his own role by then. For instance, he said he wrote one letter of objection, rather than the three The Times has found, and received just "a one-sentence letter of reply" from Thomas, rather than the lengthy missives Thomas, Day and Dr. Frederick Appelbaum, head of The Hutch's clinical-research division, sent him in the mid-1980s.

The state investigators didn't interview the researchers involved but obtained written statements from Thomas and Hansen.

Thomas' letter, marked "CONFIDENTIAL," was his only written response since the flat denial of conflict in 1984.

"The decision as to whether or not these studies should or should not continue was not made by me," Thomas wrote.

Storb and Pesando say Thomas, though technically not a member of the review panels, was influential in continuing the studies.

"I have never exposed any patient to treatment risks for reasons which were not ethically and medically appropriate, and I did not do so in the matter into which you are inquiring," Thomas wrote.

In his letter, Hansen noted he was not the principal investigator on Protocol 126, and in fact had "no involvement" in it while working for Genetic Systems.

However, Hansen was named as the second author in several papers on the clinical trial. He was Martin's mentor and supervisor. And he received copies of all the key correspondence from The Hutch even while he was working at the private company holding commercial licenses for the antibodies.

In September 1997, with the case still unresolved, Miller left the state Medical Quality Assurance Commission and its investigating team.

With his departure, this investigation died.

The commission closed the complaint, citing "no cause for action," in January 1998, three years after Pesando's letter.

Miller says he was "saddened and alarmed" by the lack of follow through.

At a minimum, he said in an interview, the commission should have acted on ethical violations by Thomas and Hansen for influencing a study of materials licensed to the company in which they owned stock.

"To me, what Dr. Thomas did and the other doctor did was a clear conflict of interest," Miller said in an interview. "I think that's a pretty obvious, well-known ethical principle."

Dr. David Williams, an internist who chaired the state Medical Quality Assurance Commission at the time, was one of two doctors who personally reviewed the case. He says now that he, too, was not satisfied with the outcome.

"There still remained some doubt in our mind," he said. "I was never truly satisfied that the protocol had been written in a manner that was truly appropriate."

'Just trying to do our duty'

Through it all - unresponsive bureaucrats, half-baked investigations, patronizing letters - John Pesando, now age 55, persisted. He was both haunted and motivated, he says, by the memory of two of his patients who died in the experiment - Ruth Fisher, a 40-year-old computer programmer from California, and Jacqueline Couch, a 32-year-old lawyer for the city of New York.

He took it personally when people died on his watch and when he was, in his view, pushed out of The Hutch for raising his voice in favor of ethics and patient safety.

His quixotic quest both frustrated and frightened his wife, Patricia, who worried about his reputation.

But he kept pushing. Pushing until he got the attention of reporters at The Seattle Times, who took up the investigation.

Survivors of patients who died in Protocol 126 are grateful for that persistence.

Pete Wright of Heflin, Ala., whose wife, Becky, died in 1987, said: "I might slough this off to sour grapes if I didn't know Dr. Pesando. But I have nothing but respect for him."

Wright says that while caring for his wife, Pesando never talked about conflicts of interest or research misconduct, though he did try to talk them out of enrolling in the experiment on medical grounds.

"We were not looking for trouble," Pesando said. "We were just trying to do our duty and take care of patients."

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With a year or two to live, woman joined test in which she was misled — and died

By Duff Wilson and David Heath
Seattle Times staff reporters

DYING OF BREAST CANCER at age 48, Kathryn Hamilton pinned her hopes on the wisdom of doctors at the world-renowned Fred Hutchinson Cancer Research Center in Seattle.

Kathryn Hamilton, left, and her daughter, Elisabeth. Hamilton had twice beaten cancer, but after it made a third appearance, in 1990, she sought a stem-cell transplant at The Hutch.

With conventional treatment, those doctors told her, she would live another year or two. They urged her to consider an alternative: an experimental treatment that might kill her cancer without killing her.

The experiment, labeled Protocol 681, featured new drugs that physician-researchers at "The Hutch" theorized could protect a patient's vital organs from the ravages of extraordinarily high doses of chemotherapy.

Hamilton, desperate to spend as much time as possible with her husband and three children, agreed to enlist in the clinical trial, based on what her Hutch doctors had told her.

Here's what they hadn't told her:

• The Hutch had a financial interest in the "rescue drugs" being tested.
• The experiment had caused the premature death of one woman, from the high-dose chemotherapy.

• One of the rescue drugs being tested wasn't available in intravenous form, the only form Hamilton could tolerate and which they had assured her she could have.

• There was evidence the rescue drugs might in fact do more harm than good, and Hamilton's doctors were working on a medical-journal article saying so.

The drugs didn't work.

Forty-four days after entering the hospital, weakened by failing organs and bleeding from the eyes, Hamilton grabbed her husband tightly and pleaded, "Don't you dare let me die."

Within hours, in the late afternoon of Feb. 19, 1993, she did.

The cause of death: Fred Hutchinson Protocol 681.

Six days later, Hamilton's doctors submitted the journal article documenting what they had known for more than a year: The primary rescue drug didn't work.

Hamilton's case is further evidence that doctors at The Hutch have at times failed to fully inform patients of the risks and implications of clinical trials, as required by law.

As with Protocol 126, the blood-cancer experiment described Sunday and yesterday in The Seattle Times, this trial reveals a lack of accountability and communication in a system where other interests can compromise the care of patients.

What happened
A timeline of events in Protocol 681.

The Hutch and some of its doctors had a financial stake in the drugs being tested in Protocol 681, just as they had with Protocol 126.

But the potential for profit was not as clear-cut in this instance. In fact, this experiment continued long beyond the point where any money could be made from it.

The trial appears to have taken on a life of its own, being completed for completion's sake rather than for meaningful science or for the benefit of patients. The complete findings of the study were never even published.

Ethics experts astounded

Medical-ethics experts are astounded by certain decisions made in Protocol 681.

For example, after Hamilton and the first victim died from high-dose chemotherapy, the researchers persisted - actually increasing the doses they gave other women.

Oncologists, ethicists and drug-development experts said such a decision would be extraordinary. Some said they had never heard of a clinical trial in which doses were increased after a patient had died from the drugs.

"I can't imagine such a scenario occurring," said David Lepay, who directs the scientific-investigations division of the Food and Drug Administration.

"I have never, ever heard of a trial - and I'm talking about thousands of trials here - where people would escalate the dose until people died. It would be unethical," said Bert Spilker, an expert on drug development at Pharmaceutical Research and Manufacturers of America, an industry group.

However, Spilker and other experts became more cautious when asked specifically about this Hutch experiment.

"It's a very complex answer," Spilker said. "For 99 percent of the drugs in the world, you would never escalate a dose beyond where it killed someone."

After Hamilton, at least two more women died from the treatment, according to the doctors' own notes. In all, Hutch researchers attributed four deaths out of 68 patients in this experiment to "regimen-related toxicity," meaning that the treatment rather than the cancer killed them.

Regimen-related deaths are rare in these types of cancer trials, happening in an average of one out of every 200 patients. In Protocol 681, however, the rate was nearly 12 times higher: one out of 17.

"You'd have to have a really powerful, overwhelming reason in any situation to keep pushing the dose in the face of death at lower doses," said Arthur Caplan, director of the Center for Bioethics at the University of Pennsylvania. "It's hard for me to imagine situations in which that would be morally acceptable to do."

Treating advanced breast cancer
The difference between standard treatment and the experiment

Most of the rest of the patients in the experiment died of cancer. Major studies have now shown that bone-marrow and stem-cell transplants are no better than conventional treatment at saving lives of breast-cancer patients.

The physician who supervised Protocol 681, Dr. William Bensinger, declined to discuss the study.

"I don't really have time to go back and look at the issue," he said. "I honestly don't think it's going to help me and the Hutchinson Center in any way."

Hamilton's survivors are hurt and angered by what they've learned about Protocol 681 — facts their mother never knew.

"If she would have known these things I doubt she would have gone forward" with the experiment, said her son, Chris Addicott. "It would have been suicide."

More knowledgeable than most

Kathryn Hamilton was not a typical patient.

She had a master's degree in health administration and had been coordinator for emergency medical services in Bellingham. When she came to The Hutch, she was the manager of human resources for three medical centers in Spokane.

Those who knew her describe her as strong-willed, sharp and unafraid to speak out.

Hamilton believed her cancer was caused by radiation leaked from the Hanford nuclear reservation in Eastern Washington, near where she grew up. Her father had worked at the plant, helping secretly make plutonium for the first atomic bombs.

She first detected a lump in her breast when she was 32, but it wasn't diagnosed until two years later. After a lumpectomy, radiation and chemotherapy, she thought she'd beaten the cancer.

She made it past the critical five-year mark. Then 10 years. Cancer seemed just a bad memory.

But in the 11th year, her back started to hurt. She blamed it on a bad mattress but soon was told the cancer had returned, this time to her bones. After more surgery and radiation, the cancer went away but was back two years later.

The news was devastating; it meant she was dying.

But Hamilton wouldn't go quietly. She had a lot to live for.

For one, she had become the lead plaintiff in a class-action lawsuit related to the Hanford plant, a case later consolidated into a suit on behalf of 3,000 plaintiffs. She was preparing to testify before Congress.

And there was her family - especially her 14-year-old daughter, Elisabeth, the one child still at home.

Hamilton's best hope, it seemed, was a stem-cell transplant at The Hutch, one of the leading institutions for that procedure. Bone-marrow and stem-cell transplants had been successful in treating leukemia, and researchers were experimenting on breast cancer. There was no proof it would work, but there was hope.

"She mostly wanted to do it for Elisabeth's sake," said Hamilton's mother, Mary Lee Thorpe.

Stem-cell transplants are similar to bone-marrow transplants, except that patients are infused with immature cells, taken from circulating blood, that later become bone-marrow cells.

Both types of transplants save patients by nearly killing them first. A patient is given extremely high doses of chemotherapy or radiation, killing the cancer cells but also wiping out the spongy, delicate marrow, leaving the body unable to produce new blood cells.

Without a stem-cell transplant, the patient would die.

Even with a transplant, there's a limit to how much chemo patients can withstand. The chemicals can cause other vital organs - such as the liver, kidney, heart or lungs - to fail.

As the 1990s began, The Hutch was looking for ways to protect these organs. A solution would make bone-marrow and stem-cell transplants safer and potentially useful in treating more common types of cancer.

The miracle drug that wasn't

In late 1990, two years before Kathryn Hamilton came to The Hutch, a 34-year-old researcher there wrote about a possible breakthrough in bone-marrow and stem-cell transplants.

With federal funding, Dr. James Bianco had done a preliminary study of 30 patients and concluded that an innocuous little drug used for treating leg cramps could shield the liver, kidney and soft linings of the digestive system from the toxic damage of chemotherapy.

Pentoxifylline, or PTX, held promise as a miracle drug.

The results were so amazing that not everyone at The Hutch believed them. Amazing discoveries, such as penicillin, are rare events. Lloyd Fisher, a biostatistician, said of Bianco's PTX findings, "It was awfully hard to believe that things were that good."

Fisher's instincts were right. A second study by Bianco produced far different results.

In the first study, only 3 percent of patients taking PTX suffered kidney damage from chemotherapy. In the second, 39 percent did.

That was greater than the percentage - 36 percent - who suffered kidney damage from chemo and a placebo sugar pill. What's more, PTX patients had significantly more cases of severe kidney damage.

By January 1992, one year before Hamilton was admitted, Hutch researchers knew those results. Not only was PTX not a miracle drug, evidence indicated it might make patients sicker.

But Bianco wasn't ready to give up on PTX. He started delving into the way the drug broke down inside the body. He theorized that the key wasn't PTX but a compound created when PTX metabolized in the body. Genetic differences might explain why some patients seemed to benefit in the first study.

Bianco pulled the medical charts of patients who in addition to PTX had been given other drugs known to alter the way drugs metabolize. He found 10 patients who, in course of being treated with PTX, had also been given the antibiotic Cipro and a steroid called prednisone.

Again, he touted amazing results: None of the 10 patients had suffered damage to her kidneys, livers or lungs. These findings would be used to help justify the experiment Hamilton would enroll in a year and a half later.

By scientific standards, pulling 10 cases from files proves little. Even so, Bianco said he was so confident about the direction of the research that he and colleague Dr. Jack Singer decided to start their own company to develop this treatment.

Not everyone involved in the research was so confident. Anthony Shields, a doctor who worked side by side with Bianco and Singer on their pentoxifylline research, said, "They started the company on a drug that wasn't really panning out. I always thought that was funny."

The company was born on ferry trips to the San Juan Islands. Singer had a vacation home next to Dr. George Todaro, who had done groundbreaking research at the National Institutes of Health.

Todaro introduced Singer to New York investment banker David Blech, who, as a young entrepreneur a decade earlier, had started Genetic Systems, the company involved with Protocol 126, the leukemia experiment.

Bianco and Singer founded Combined Therapeutics Inc. in September 1991. The name, which would soon be changed to Cell Therapeutics Inc., or CTI, came from the fact that they planned to combine two drugs.

The two doctors left The Hutch three months later to work on their new company full time.

The Hutch's president, Dr. Robert Day, wanted the cancer center to be compensated for their plan to commercialize their research. A deal was cut: The Hutch would receive about $20,000 in stock shares and $50,000 a year in licensing fees. That would increase to at least $100,000 plus a percentage of sales if the company successfully sold its treatment.

The Hutch stood to make millions if the drugs worked.

Bianco also recruited two prominent doctors, both Hutch co-founders, for CTI's scientific advisory board: Dr. E. Donnall Thomas, who had just won a share of the Nobel Prize in medicine, and Dr. C. Dean Buckner, who would later become Hamilton's doctor. Both received stock options.

Review board wasn't told all

Meanwhile, another researcher, Dr. William Bensinger, was experimenting at The Hutch to see whether stem-cell transplants could save patients with advanced breast cancer.

He hadn't gotten far before a high dose of anti-cancer drugs killed two of four patients. Bensinger knew about Bianco and Singer's research and wondered whether their drug combination would allow him to safely administer high-dosage chemotherapy.

Buckner, who would soon join the Cell Therapeutics board, was working with Bensinger on Protocol 681. He said they knew PTX alone didn't work, but they hoped combining it with Cipro would make a difference.

Notably, however, proposals Bensinger submitted to The Hutch's Institutional Review Board (IRB) before beginning the new study or when making modifications to it made no mention of negative findings on PTX.

Bianco, who had left The Hutch to start CTI, was the second researcher listed on the protocol. However, he insists he was never involved in it.

In fact, he is critical of the study. There was no proof that PTX and Cipro worked, Bianco said, and until that was known, Bensinger wouldn't be able to tell whether his patients were

tolerating higher doses of chemo because of the drugs or despite them.

Bianco himself quickly gave up on PTX and Cipro.

For starters, the FDA resisted the idea of combining two drugs into one. As specialists there pointed out, Bianco and Singer were trying to use one drug to change the way another drug broke down inside the body. The drugs might interact differently in different patients, so the plan to combine the drugs wasn't reliable.

What's more, using an antibiotic such as Cipro was risky. Patients might develop a resistance to antibiotics, making it more difficult to treat infections.

And there was another problem: Competing pharmaceutical companies owned PTX and Cipro, and didn't like the notion of combining them. So even if Bianco and Singer could prove the drugs worked, they might not be able to profit from them.

Cell Therapeutics was at a crossroads. At the urging of its scientific advisory board, chaired by Nobel winner Thomas, the company made a critical decision: It would dump PTX and Cipro and patent a compound that these two drugs created when mixed.

The company filed for that patent in September 1992. It called the new drug Lisofylline.

Bianco said this information was passed on to The Hutch in the company's quarterly and annual reports. Anyone on the Cell Therapeutics advisory board, such as Thomas or Buckner, would have known that Bianco was no longer backing PTX.

Others were abandoning PTX, also. On Nov. 15, 1992, the medical journal Blood published a study by Austrian and German doctors who had tried to duplicate Bianco's first PTX study on 31 patients. They concluded that the drug didn't work.

Bianco and Singer responded in the same issue. Although they knew that their own follow-up study had even worse results, they didn't mention that. Instead, they defended their first PTX study, speculating that the European study came to different results because it relied on the intravenous version of PTX, which Bianco and Singer said wasn't as effective.

The timing was critical for Cell Therapeutics. The company was wrapping up its first major stock sale, raising $38.5 million.

Investment banker Blech, who recalls skepticism over the science involved, was managing the deal.

"There were some very big claims made about a Cell Therapeutics drug," Blech said. "Half the world believed them, and half the world didn't believe them. It was a very controversial company."

Chad Waite of Olympic Venture Partners, a Seattle venture-capital firm that invested in biotechnology companies, said: "The science was controversial. There were people who just absolutely swore by it and there were people who thought it was bunk."

Cell Therapeutics would not release the documents it used to entice investors for the private stock placement. However, The Times obtained a copy of a memorandum for another stock deal in June 1993, seven months later. In it, the company reports research results that suggest that PTX and Cipro were wonder drugs.

Cell Therapeutics claimed that 74 percent of the most seriously ill patients taking these drugs lived one year after treatment, compared with 7 percent of those who didn't take the drugs. It also claimed that after two years, 75 percent of the surviving patients were cancer-free, compared with 38 percent for those who didn't take the drugs.

Robert Kupor, a stock analyst at Seattle-based Frasier & Co., said at the time, "The commercial value of such a product would be hard to overstate. Anyone who had convincing proof would have a market cap (financial backing) of a billion dollars."

But no convincing proof was ever published in medical journals. And biostatisticians say the findings defy belief.

"You don't see changes like that in cancer studies," said Geoffrey Norman, a statistician at McMasters University in Canada. "If it was that big of an effect, there's no way that it wouldn't be published."

Dr. John Nemunaitis, an oncologist who worked with Bianco and Singer on PTX-Cipro research and now practices in Dallas, said he doesn't recall any study with those findings and added, "It almost seems too good to be true."

Cell Therapeutics recently declined to comment on this research, on the advice of its attorney.

Choosing to take 'a lethal dose'

So even as Cell Therapeutics was touting its PTX research, it was shutting down that research. That led to The Hutch losing its supply of the intravenous, liquid form of PTX.

The intravenous (or IV) form of PTX was not approved for use in the United States. While at The Hutch, however, Bianco had obtained permission from the FDA to use the IV form in clinical research. Bianco held onto that permission after leaving The Hutch, agreeing to supply the liquid to Hutch researchers for their continuing studies.

But on Nov. 10, 1992, Cell Therapeutics notified The Hutch that it was cutting off the IV supply of PTX.

Bianco said he no longer had a use for the IV form. But all Bensinger had to do, he said, was ask the FDA for permission to use it.

Instead, Bensinger decided to stop using the IV form of PTX in his study. He sent a revised protocol to the Hutch's Institutional Review Board, which met monthly. On Jan. 5, 1993, the board ordered mention of the IV drug to be deleted from the informed-consent papers given to patients entering the PTX study.

The next day, Kathryn Hamilton and her family met with a Hutch doctor to decide whether she should enter Protocol 681.

Hamilton was far more able to evaluate the trial than most patients. Because of her health-care background, she knew doctors at The Hutch and had persuaded them to give her a confidential document - the research protocol.

Appelbaum

The protocol spelled out the risks involved in far greater detail than the standard-issue informed-consent paper other patients are given. Without the protocol, for example, Hamilton would not have known that high-dose chemotherapy had killed two of four breast-cancer patients in a previous experiment without the rescue drugs.

Hamilton had long discussions with her family about whether to enroll in the trial. For one thing, it would cost $265,000, of which insurance would pick up only a portion.

Hamilton asked her oldest son, Chris Addicott, then 24, to help her analyze the documents. Addicott, now a Seattle attorney, read through the protocol and was prepared to ask questions when the family met with a Hutch doctor for the informed-consent conference.

That doctor was Frederick Appelbaum, soon to be director of clinical research at The Hutch and one of the investigators on Protocol 681. He was also a co-author of two articles about PTX: one that showed promise and another, which was about to be submitted for publication, showing the drug didn't work.

According to Addicott, Appelbaum never mentioned the new findings, even though the informed-consent form incorrectly said, "Recent studies suggest that PTX (pentoxifylline) prevents kidney, lung and liver damage in patients receiving transplants."

Asked recently why this was in the document, Appelbaum looked over the form and pointed out that it also included a warning that doctors didn't know if PTX and Cipro worked when it said, "We plan to see if the combination of these drugs can prevent damage to the kidney, liver and lungs."

Appelbaum told Hamilton she would be given a large dose of anti-cancer chemicals: 18 milligrams of busulfan per kilogram of her body weight.

Addicott remembers being concerned about that amount. He thumbed through the protocol until he came across a passage explaining that five of 10 patients in two previous experiments had died when given a smaller dose, 16 milligrams. The protocol warned that even that dose was "probably too toxic."

Appelbaum's notes from the meeting make no mention of the exchange. But even if it did come up, Appelbaum said, there were too few instances to determine whether the dosage was dangerous.

Besides, the whole idea of this experiment was to see if the rescue drugs would protect the patient from toxicity.

The doctor's notes do mention that Hamilton could expect to feel quite sick from the chemotherapy.

"I explained to Kathy that the inevitable consequences of the (chemotherapy) were nausea and vomiting," the notes say.

That concerned Hamilton and Addicott. She had vomited violently during past treatments of radiation and chemotherapy. What if she could not keep down the rescue drugs, which were given in pill form?

The answer was right there in the informed-consent form: PTX "may be given through your Hickman catheter if your physician thinks you may not be absorbing the medicine when you take it."

The informed-consent papers Hamilton signed mentioned the availability of the IV version of PTX not just once or twice but three times. But in fact, as Hamilton's doctors knew - or should have known - at that point, The Hutch no longer had the IV version.

Addicott remembers telling her, "They're giving you a lethal dose of chemotherapy, and unless you get the PTX, you could die. But you should be OK because if you can't keep the pills down, they'll give you the PTX in intravenous form."

"I think that's what bothers me so much about this," Addicott says now. "She was relying on me to help interpret and understand the science of what was going on. I did that, and I think I did it correctly. But I think I was given wrong information.

"Nobody in their right mind would go into a study like this knowing they wouldn't get PTX."

Hamilton signed the papers that day and was admitted immediately. At 6 p.m. Jan. 6, 1993, she took her first pink pill of PTX. That night, she became nauseated and threw up. At 7 a.m. the next day, she was given her first dose of chemo.

'I can feel it. I'm going to die'

Hamilton would finish taking the high doses of chemo within her first week in the hospital. It would then be up to a stem-cell transplant and the rescue drugs to give her her life back.

She was supposed to take PTX for 31 days, but that didn't happen. Hamilton struggled with nausea and vomiting from the first day, and nurses began noting Jan. 12 that she was throwing up the PTX virtually every time she took it.

Her husband, Allan Berman, remembered the whole pink pill would come up. She threw up almost every day, sometimes several times a day.

Addicott didn't talk about it with his mother at the time, but he would leave the room and ask nurses why she wasn't getting the IV form of PTX. They told him the FDA had withdrawn approval of the drug.

But when Addicott finally talked to a doctor in charge of the floor - he doesn't remember whom - he remembers being told not to worry. She had gotten down a little bit of the PTX, and it wasn't clear that the drug did much good anyway.

He never told this to his mother.

Appelbaum said The Hutch didn't ask the FDA for permission to use the IV form because it would have involved a lot of paperwork. However, Bianco had first obtained the liquid drug on an emergency basis by making a telephone call to the FDA. The Hutch could have done the same.

On Jan. 15, 1993, Hamilton underwent a stem-cell transplant.

Within days, she developed a fever, a sign of infection.

Berman remembers his wife's fear.

"She said, 'I'm not going to live,' " he recalls. "I said, 'Yes you are.' She said, 'I can feel it. I'm going to die.' Every night it would be a struggle. Something would happen, then fever would come back."

Hamilton's skin became yellow, and doctors found signs of liver damage. She had problems breathing. The blood vessels in her eyes, ears and nose began leaking, causing her to bleed.

But Hamilton hung on. Then, on the evening of Feb. 18, things turned much worse. Her kidneys were failing.

The next morning, Berman talked to his wife for the last time. She pleaded with him not to let her die.

It was too late.

Bad results don't stop testing

Six days after Hamilton died, a group of 17 Hutchinson Center researchers submitted an article to the journal Blood - an article they had been working on for months. It said PTX was not effective in protecting against the toxic effects of chemotherapy. Among the authors listed on the study were Bensinger, Appelbaum, Bianco and Singer.

Yet they continued Protocol 681. The study didn't prove that PTX plus Cipro didn't work, said Buckner. And, he said, the protocol allowed them to continue even if patients died.

Deaths from high-dose chemotherapy

Medical experts are baffled as to why researchers at the Fred Hutchinson Cancer Research Center kept escalating the amount of high-dose chemotherapy they gave breast-cancer patients even after it killed some of the women...

But that's not clear. The study was designed to find the maximum amount of chemotherapy which patients could tolerate. A dose would be tested on four women and then escalated if none of these women died or suffered life-threatening complications from the chemo. If two women died or suffered serious complications, the protocol stated, researchers must drop to a lower dose.

But the protocol didn't explicitly say what to do if one patient died.

A number of experts said that in all clinical trials they've known, a dose is considered lethal if a patient dies from it. At that point, doctors stop the trial or continue to test at a lower dose.

"I would not want to be one of those patients who received a higher dose after one of four suffered a regimen-related toxicity death," said Steve Piantadosi, an oncologist at Johns Hopkins Medical Center.

Eventually, enrollment in the study slowed. In the first three years, Bensinger and Buckner enrolled 54 women in the breast-cancer study. But in the last three, they enrolled only 14.

In 1998, Bensinger shut down the study, one week after Cell Therapeutics reported disappointing results for its drug derived from the rescue drugs used in Protocol 681.

Four women, including Kathryn Hamilton, had died from the experiment that they had hoped would cure them.

Bianco and Cell Therapeutics, meanwhile, moved on to developing other drugs. Today, the company is worth more than $764 million.

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Many patients think that joining testing will help them, but often they're mistaken

By Duff Wilson and David Heath
Seattle Times staff reporters

THE BEDROCK ETHIC of any human research is that a patient must fully understand an experiment before participating in it.

Yet the nation's top enforcer of human-research ethics says that the biggest problem in research today is that, often, this is not happening.

"Too often individual research participants will enter a study believing that they are perhaps being treated when in fact they need to understand that if they are participating in research, treatment might not be part of that," said Dr. Greg Koski, director of the federal Office for Human Research Protections.

Studies bear this out, suggesting that patients often don't understand what they are getting into when they sign up for clinical trials. They often don't realize that there is little chance the experiment will benefit them.

A survey of cancer patients at the University of Chicago found that 93 percent said they understood what they were told about the trial in which they were enrolled. Yet only a third were able to explain the main purpose of their trial accurately.

It's the job of researchers and institutional review boards to make sure patients understand their studies. Critics say they often fail to do an adequate job.

The federal Office for Protection from Research Risks (the former name of the Office for Human Research Protections) found that 90 percent of the cases it investigated had problems with informed consent.

Written in 'gobbledygook'

Abbey Meyers, founder of the National Organization for Rare Disorders, a patient-advocacy group, reviewed scores of informed-consent documents from research centers throughout the country. She was appalled at how incomprehensible they were.

"They are often written in scientific gobbledygook," Meyers said. "The rules say that they are supposed to be written in plain English, but people just ignore the rules."

Meyers was particularly appalled that many of the consent forms she reviewed held out the hope of a cure to terminally ill patients even in trials designed only to test for a safe dose of an experimental drug.

In the first phase of drug trials, researchers are testing doses that have never been tested in humans before. So they don't know if the drugs will be effective.

Even when a cancer drug is effective, it usually works only at a precise dose. Give a patient too little and nothing happens. Give too much and it can kill.

Phase-one trials a real concern

Studies have shown, and experts agree, that the chances of a patient getting better in a phase-one study are remote. A major review of 211 phase-one cancer trials involving 6,639 patients found that tumors responded to the experimental drugs less than 5 percent of the time.

Yet patients don't seem to understand this. According to surveys, people enroll in phase-one trials not for the good of science but for their own good. One study reported that 85 percent of patients signed up because they expected the treatment to make them better, 11 percent acted on the advice of a doctor and 4 percent felt pressured by their family.

If patients enrolled in dose-escalation trials for altruistic reasons, there would be less of an ethical dilemma, says Christopher Daugherty, the University of Chicago oncologist who conducted the study.

For that reason, he and others insist, researchers should be more blunt.

"It should really be put in terms that you will not benefit from your participation in this study," said LeRoy Walters, a bioethicist at the Kennedy Institute of Ethics at Georgetown University. "You will be taking part for the benefit of others."

Sprinkled throughout the informed-consent document that Kathryn Hamilton signed at The Hutch were suggestions that she could be saved by it.

"This new treatment program has been designed with the hope that it will prove to be much more effective than standard treatments now available. We hope that your life will be lengthened by this treatment," the consent form reads.

In fact, this study was designed to see how much chemotherapy patients could tolerate. Patients had already died from doses lower than that Hamilton was to be given.

Not all ethicists agree

Not all ethicists agree that patients have to be told they are enrolling only for the benefit of others. Even if the chances are remote that a patient will benefit, that may be better than the certainty that they will die if they don't enroll, said R. Alta Charo, professor of law and medical ethics at the University of Wisconsin.

"When you've got a disease that is absolutely untreatable by all measures, and you've got a patient who's willing to try anything instead of giving up, there's a strong libertarian bent that says why should anyone tell me no," she said.

Some research advocates worry that emphasizing the dangers might discourage anyone from signing up for clinical trials, bringing medical research to a halt.

"But that's all right," said Georgetown's Walters. "I'm all for medical progress, but only if it's done in an honest way. If that's the upshot of being honest to patients, I'm willing to accept that.

"We can't be hoodwinking people about what they are getting into."

He helped create the biotech boom and when it went bust, so did he

By Duff Wilson and David Heath

Seattle Times staff reporters

Harley Soltes / The Seattle Times
David Blech exercised in the swimming pool at his Chelsea apartment as therapy for his depression.
NEW YORK - The father of Seattle's biotechnology industry has a probation officer.

He lives in a modest, cluttered apartment in Manhattan's Chelsea neighborhood, 3,000 miles from the glass-and-steel temples of the companies he helped create. A continent away from the houses of doctors who, with his help, turned their positions with the Fred Hutchinson Cancer Research Center into personal fortunes.

And only two miles but a world away from the $3 million penthouse where he lived in 1992, when he was on Forbes magazine's list of the 400 richest Americans.

Meeting with a Seattle newspaper reporter, David Blech wears sweat pants, a sleeveless T-shirt and beat-up white tennis shoes with loose laces. He looks like a disheveled Billy Crystal, curly hair cut close, jaw unshaven.

He takes lithium for manic depression and has spent time in a mental hospital.

But things could be worse: At least the federal judge who sentenced him for securities fraud in 1999 allowed him to stay out of prison.

Blech's precipitous fall from grace is no more fascinating than his ascension as a brash 24-year-old who turned a family dream into reality. He helped build an industry whose products have saved lives and made lots of money.

And, as a Seattle Times investigation being published this week has revealed, Blech helped create a situation at the Hutchinson Center in which the care of cancer patients might be compromised by business relationships.

The get-rich-quick dream of 1980 - after plastics, before the Internet - was biotechnology. With talk of the potential of a cure for cancer, the industry's economic possibilities seemed unlimited.

Blech, a songwriter and fledgling stockbroker, watched Genentech, a company with no profits and no products, sell shares for $35 apiece and double the price to $70 by the end of its first day on the market.

"I can do that," Blech told his father, a rabbi and stockbroker, and his brother, a public-relations man.

The three started with a name: Genetic Systems.

"The ideal catch-all but say-nothing name for our new biotechnology company," Blech recalls.

Next, they needed to find a scientist brash and respected enough to head the company.

Among their candidates: Dr. Robert Nowinski, a young, rising star at the Fred Hutchinson Cancer Research Center in Seattle. They had just read about him in an article entitled "Immunizing Immortality."

They called him, and for some reason - perhaps because he, like the Blechs, was from New York - Nowinski listened.

In fact, he told them, he had already been talking about setting up a company. He'd been in discussions with Bob Johnston, chief executive of Cytogen, and investor Charlie Allen of Allen & Co.

Blech says Nowinski told him, "I'm going into the monoclonal antibody business."

"So am I!" Blech responded. He persuaded Nowinski to fly to New York for a meeting.

Blech's father picked up the Seattle scientist at JFK International Airport and took such a roundabout way from Queens to Manhattan that, Blech recalls, Nowinski was sorry he'd ever come.

Blech concedes that Nowinski thought he'd been taken in by "a bunch of amateurs."

Blech didn't even have a credit card. He was a kid - wiry, fast-talking, high-strung, super-ambitious. In some ways, a lot like the 35-year-old Nowinski.

Blech won Nowinski from Johnston and Allen with the promise the scientist could do good work, get rich and stay close to "The Hutch" in Seattle.

Allen had wanted Nowinski and 11 other Seattle scientists to move to New Brunswick, N.J. Blech told Nowinski that was crazy.

"That was the best observation of my career," Blech said. "It's unusual that two kids from Brooklyn and their rabbi-stockbroker father could get a company away from Bob Johnston and Allen & Co., but we did. We used to call the company `Genetic Balls.' "

The Blechs had $10,000 apiece. Blech says they told Nowinski they'd borrow to put $200,000 in escrow for him to keep if they didn't raise $3 million within a year.

They raised $40 million.

Nowinski was given 1.2 million shares of stock at a penny a share. Under Blech's tutelage, Nowinski sprinkled shares around The Hutch like manna from heaven.

His brilliance and the penny stocks helped Nowinski recruit his boss, Dr. John Hansen, as medical adviser for Genetic Systems and his boss' boss, Dr. E. Donnall Thomas, as a key member of the company's scientific advisory board.

Then Genetic Systems struck a deal with Hutch officials for commercial rights to 37 drugs.

Three of those drugs were antibodies that were to be used in a Hutch experiment called Protocol 126, an experiment in which Hansen and Thomas were involved. As described in The Times earlier this week, that experiment was controversial within The Hutch, with some doctors complaining that the welfare of patients was compromised by the researchers' ties with Genetic Systems.

In 1982, when Genetic Systems went public at $1.25 a share, the Blechs, Nowinski, Hansen and Thomas all made lots of money. Three years later, the company was bought by Bristol-Myers for $10.50 a share.

Bristol-Myers hurried in to buy Genetic Systems for $294 million in stock two weeks after Eli Lilly, its rival, had bought Hybritech, another monoclonal-antibody company, for $350 million. Blech liked to brag that Genetic Systems sold for 15 times its original public-stock value, while Hybritech merely doubled its value.

Blech made $30 million on the Genetic Systems deal. Nowinski's stock at that point was worth more than $10 million and Hansen's $1.8 million. Assuming Thomas had kept his original stake, which is unknown, his share - in Bristol-Myers stock - was worth $1 million.

"I always took great comfort how the scientists made a million dollars each," Blech said.

As Rose Beer, then a company official, recalled, "We had a very high profile at Genetic Systems. Without any due diligence, Bristol Myers came in and bought us for about $300 million. And then did their due diligence. And what Bob (Nowinski) sold was his dream of what this company would be.

"Oh, man, if they only knew!"

They found out soon enough that the dream was brighter than the financial reality. In 1991, Bristol-Myers resold part of the former Genetic Systems for $20 million and closed the other part, taking a $274 million bath.

Despite that, Bristol-Myers has gone up six fold since then, increasing even further the value of the doctors' stock.

Selling vision and credentials

Blech became known as the nation's most aggressive biotech financier. He took high fees and a lot of stock for seed money, and he took the companies public fast.

While most biotechs had one or more products in Food and Drug Administration-sanctioned trials before they took their stock public, most of Blech's did not. That made the scientific studies and credibility of medical doctors on board all the more important.

The Hutch's Thomas, who won a share of the 1990 Nobel Prize for his work on bone-marrow transplants, was recruited by Blech for the advisory boards of three other companies.

Dr. James Bianco, founder of Cell Therapeutics, a company now worth $485 million.
And Blech helped two other Hutch scientists, Drs. James Bianco and Jack Singer, start Cell Therapeutics Inc.

"Bianco came to us," Blech recalls. "He told us this story about these amazing clinical results he was seeing."

Some scientists doubted the research, which touted unbelievably good results with a little-known drug shielding vital organs from harm during cancer chemotherapy. Blech says he knew the research was thin but he sold the vision and the credentials of the company's supporters, especially Thomas.

"Ultimately, the drug failed," Blech said. "I don't know why." But Cell Therapeutics tried another drug, then another. Recently the company rose from near-death to huge gains with an arsenic drug to fight blood cancers.

"They were constantly reinventing themselves," Blech said. "That's the wonderful part of dealing with (stock in) life and its frailties."

Major deal-maker in biotech

In 1989, the Blechs helped create Icos Corp., joining Nowinski and Dr. Chris Henney, who had left The Hutch to co-found Immunex.

The Blechs put up $1 million of borrowed money. They wanted PaineWebber to sell the stock; PaineWebber wanted the Blechs to recruit George Rathmann, founder and chairman of the largest biotech company in the nation, Amgen, of Thousand Oaks, Calif.

Rathmann had taken Amgen from $4 a share to $60 and sold $190 million in products in 1989.

Ken Lee of Ernst & Young said Rathmann, 65, was "one of the most important guys in biotech in the country." Landing him was a coup for Blech and Nowinski.

"George had a fantastic career at Amgen, you know; he was the king of biotech," Blech said. "Luckily, he had one more deal in him."

The board of Icos was amazing for a start-up company. It included the former chairmen of Citibank (Walter Wriston), IBM (Frank Cary) and General Foods (James Ferguson), a former secretary of commerce (Alexander Trowbridge), and David Blech and his brother, Isaac.

Icos had the largest start-up financing in biotech history, $33 million. The Bothell-based company went public at $8 a share in 1991. David Blech owned 7 percent, and made a quick $10 million.

Rathmann described Blech as a "pure-greed" venture capitalist, and one who was very important to Seattle biotech. "It's because of his very venturesome personality. You have that kind of mindset," he said.

In the next few years, Blech helped set up about 20 other companies, mostly outside the Seattle area, including Celgene of Warren, N.J., with Nowinski, and Incyte Pharmaceuticals of Palo Alto, Calif.

He was a master salesman, whipping out lists of investors and trust funds, spinning academic cachet into cash. He sold hope: You could find a cure and make a mint.

Picking up `fallen angels'

Research doctors from the Fred Hutchinson Cancer Research Center started at least 10 major companies, many with help from The Hutch and New York financiers David and Isaac Blech.

At the height of his power, Blech estimated his personal fortune in 1992 at $310 million.

But Genetic Systems never did make a product to help cure cancer. Neither did Cell Therapeutics.

"I made a lot of money in the companies in Seattle but the products didn't quite get there," Blech said. "So I guess I entered the '90s feeling a little guilty about all that. So I started putting money into `fallen angels.' "

That's how he referred to young biotech companies that had spent at least $100 million on research but didn't have a product ready by the time they were out of money.

Blech picked them up when nobody else would.

"People get tired, you know," he said. "A lot of bright stars become fallen angels before they shine again."

He saved NeoRx of Bothell with $10 million cash, helping it raise $31 million in licensing deals.

He saved Microprobe (now Epoch Pharmaceuticals) of Bothell, personally financing operations for 16 months. He wrote monthly checks and guaranteed the salaries for six executive officers.

He bailed out another dozen companies across the nation. He was sure his name would mean gold.

"I'm not telling you there wasn't an element of greed in it for myself," Blech said. "I'm sure that played a role in it. But my doors were open to everybody - whether it was an Icos with

golden management or a NeoRx that was on its ass and needed $10 million to keep the company open. I tried to save both sectors."

When Blech himself fell, though, many looked away.

Things fall apart

The biotech market soured in 1993. Blech, obsessed with buying undervalued biotech stocks, bought more and more on credit. He shifted funds to hide his mounting losses.

Blech stopped taking lithium. "As a manic-depressive, I'd get real high and low, so I'd buy when prices were high and sell when prices were low, the exact opposite what you should," he said.

The Securities and Exchange Commission investigated whether Blech broke the law by giving cheap stock to money managers and others prior to public offerings. That would inflate the price. Blech denied any impropriety.

For a time, Blech-backed companies held up under the collapse. Then he ran out of cash and the short-sellers pounced.

The first sign of deep trouble was in April 1994, when Blech had to sell his 24 percent stake in NeoRx to avoid a margin call by Citibank on $40 million in loans.

Afterwards, Blech bragged about the money he'd made on NeoRx anyway and the $150 million he claimed was held in trusts nobody could touch no matter what happened to the market, the financial newspaper Barron's reported.

Falling deeper and deeper in debt, Blech admits, he executed sham and unauthorized stock sales. It was outright criminal activity and he knew it, but he said he couldn't stop.

D. Blech and Co. failed to open its doors on Sept. 22, 1994 - referred to on Wall Street as "Blech Thursday." At least 13 stocks for which Blech was the underwriter declined by 23 percent or more that day. One fell 64 percent. The whole biotech sector sagged.

More than 300 brokers lost their jobs when the firm collapsed, and Blech stood sobbing in his trading room at the end of the day.

"A few days after D. Blech & Co. closed its doors on September 22, 1994, Blech entered the hospital due to an emotional breakdown. He never returned to the firm's offices. Within days of the firm's collapse, Blech's wife filed for divorce," according to a National Association of Securities Dealers report. Blech hadn't told his wife he was forging her signature on documents.

The SEC said investors and broker-dealers took $22.5 million in losses because of Blech's stock manipulations.

As the SEC developed criminal charges against Blech, he turned informant. Lloyd Schwed, a Florida attorney for four brokers who sued Blech, was arrested in August 1996 and charged

with shaking down Blech by offering to withhold tapes subpoenaed in the SEC investigation. Schwed told Blech he would destroy two especially damaging tapes if Blech settled the suit with a big payment. Blech had worn a wire for the feds.

In April 1998, Blech was charged with the illegal security actions that led to "Blech Thursday." He pleaded guilty to two counts of criminal fraud. He faced up to 97 months in prison.

He refused to seek an insanity plea, though, even after a court-appointed psychiatrist said manic depression had contributed to his crimes.

Federal prosecutors suggested leniency because Blech had helped them. In October 1999, U.S. District Judge Kevin Duffy sentenced Blech to five years' probation and community service.

The National Association of Securities Dealers fined Blech $20,000, censured him and barred him from associating with NASD members in the future. In addition, the SEC, four former brokers and a class of investors all filed lawsuits against Blech.

Blech had never been well-known in Seattle, and none of this was even reported in the daily newspapers in the city where he'd set up several biotechs and manipulated stocks in others. Blech has not been mentioned in The Seattle Times since 1996, and in the Seattle Post-Intelligencer since 1994.

Hoping for a comeback

Today, Blech is supported by his second wife, Margie, a graphic designer and aspiring actress.

He is trying to sell a manuscript of his life story - "Million Dollar Dreamer" - but publishers aren't buying.

Sally Richardson, president of St. Martin's Press, wrote to him recently: "People don't like David Blech, they don't root for him, and we don't think they would buy his book."

Blech says he thinks about his rise and fall every day. His early times with Nowinski were the best, he says: so young, so easy.

But it's been a long time since Blech has heard from Nowinski, who lives north of Seattle and recently left Vax Gen, a company trying to develop an AIDS vaccine.

Rathmann is about the only one who calls Blech from Seattle anymore. Rathmann and Bianco wrote letters of support to the judge in Blech's federal trial.

Blech hopes to make a comeback someday. Not now, but soon. He's restless. He has a part-time secretary in his home office, a desk in the corner off the living room. He promises to never borrow money again, but watches the market closely.

"I believe I have learned from my mistakes," Blech wrote recently. "I feel good about my legacy. I have helped create over $15 billion in biotech market value, and have been associated with several products which are currently being used in the treatment of AIDS and cancer.

"But, at 44, I am still too young to retire. I may have one more go at it in me. This time, I would try to do it in a more measured way, with only one or two biotech companies. I would not try to save the world."

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No wonder they call the place 'Mother Hutch'

Since the Fred Hutchinson Cancer Research Center was founded as a tax-supported nonprofit a quarter-century ago, it has spawned private companies worth more than $18 billion and an estimated $100 million in personal wealth for its doctors.

At least 20 physician-researchers have left The Hutch to start private ventures based on the government-funded work they did there.

Others, particularly senior managers, stayed at The Hutch but supplemented their salaries with private consulting, stock deals and drug-development rights.

Whether they left, stayed or straddled the fence between business and academic research, the scientists say they were motivated not by the money but by the promise of better science and medicine.

That was the argument that prevailed in Congress in 1980 when the Bayh-Dole Act gave academic centers the right to patent and profit from their discoveries. Supporters thought this would spur innovation and discovery, and it has.

Here, based on financial records in the public domain, are some of the progeny of "Mother Hutch":
Who left The Hutch... Who stayed...

More and more, though, the financial benefits are ending up with individual scientists and their investor backers. And some experts worry that the motive for profit could compromise the free exchange of ideas for scientific progress.

They question the wisdom of joint ventures between publicly funded academic research and corporations. And they cite the importance of maintaining public trust in the integrity of medical research unmotivated by profit concerns, particularly when the research is performed on human volunteers.

Dr. Rainer Storb, an orignal member of The Hutch and current head of transplantation biology, said he is thankful for public funding of biotech research, and proud to be working for scientific progress rather than profit. Storb said he has never believed government-financed scientists should take money from private companies.

The late Dr. Bill Hutchinson - founder of The Hutch and brother of the man for whom the center is named - reportedly felt much the same way.

Clearly, though, many doctors at The Hutch feel differently. Over the years, the center's conflict-of-interest policy has been weakened and walls between taxpayer-funded science and for-profit science have crumbled.

"Actually a lot of people in the community call us `Mother Hutch,' " said Rose Beer, who moved from a Hutch lab to private industry - 18 years at Genetic Systems, Icos and Targeted Genetics - before returning to The Hutch in 1998.

Beer now works at the center's Office of Technology Transfer, its bridge with companies.

"When I came back, everyone went, `You're going back to the Mother.' The womb."

The Hutch zealously guards its secrets

By Duff Wilson and David Heath
Seattle Times staff reporters

Dr. John A. Hansen kept about $10 million stock and broke conflict-of-
interest policy Dr. E. Donnall Thomas took stock worth $5 million today, if he kept it, which he won't say. Donated the $350,000 for his Nobel Prize to The Hutch.

Dr. Robert Nowinski started three big biotechs. Sold one to Bristol-Myers for $295 million. Dr. James Bianco owns $5.1 million stock after two products flopped then a third took off. THE INTERNATIONAL reputation of Seattle's Fred Hutchinson Cancer Research Center was forged with a courageous and sometimes defiant approach to conventional medicine.

It was built by doctors empowered to try new weapons against cancer, even if it meant some patients might die sooner than they would have with conventional treatments.

The center's most respected researcher, Dr. E. Donnall Thomas, won a Nobel Prize for persevering on bone-marrow transplants despite the doubts of peers and the deaths of patients.

In his seminal work between 1969 and 1974, he performed bone-marrow transplants on 54 cancer patients. Forty-eight died, but six lived.

In the quarter-century since, "The Hutch" has continued to improve those methods, which have saved thousands of lives around the world.

But now, in the wake of articles in The Seattle Times this week, some doctors, medical ethicists and patient advocates are questioning whether the swagger that put The Hutch on the map in the 1980s and '90s has created a culture that is unduly insulated from public accountability.

The Hutch's approach to ties with industry, its policies on financial disclosure and its stance on public access to its activities, while not unique, differ significantly from those at some other respected institutions.

The result: a system in which patients pondering whether to enter a clinical trial may have little information - and little choice but to trust the center, even when financial connections might raise legitimate questions about the experiments on which they're betting their lives.

"The issues that are raised in this (series), whether they occurred 10 years ago or today, are of critical importance in our system of human research," said Dr. Greg Koski, director of the federal Office for Human Research Protections.

Nowhere is the combined success and secrecy of The Hutch so plain as in its partnerships with biotechnology companies.

As The Times has outlined, the center and many of its doctors, including Thomas, have linked their research to the for-profit business world of biotech, spinning off private companies worth more than $18 billion today and producing some $100 million in personal wealth.

Those financial relationships create the potential for conflicts of interest in the conducting of human experiments. But patients and the public have had little opportunity to even ask such questions, let alone to have them answered.

The lack of openness has been highlighted this week in The Times' investigation of two failed clinical trials in which patients died prematurely. In both experiments, The Hutch and its doctors had financial connections to some of the drugs being tested. Patients were not told of those ties, nor were they fully informed of the experiments' risks.

In one of the experiments, at least 20 patients died from causes attributable to their treatment; some of them would have likely lived a full life with conventional treatment. In the other, at least four died from their treatment.

The newspaper was led to one of these clinical trials by a doctor who had been on the inside as a member of a Hutch internal review board, and to the other by the son of a woman who died from treatment.

Whether other clinical trials at The Hutch - including those that are ongoing - have had similar issues is unknown. The Hutch operates in extraordinary secrecy - justified in the name of commercial confidentiality, grown from its maverick roots.

Dr. Howard Shulman, a pathologist in the clinical division at The Hutch, says he and others have questioned whether the center should have such close ties to companies. But Shulman said he was told by Dr. C. Dean Buckner, an original member of The Hutch: "We lost our virginity a long time ago."

Partnerships with business

Supporters say partnerships with business provide incentive, reward and seed money for innovative medical research. But numerous academic studies show that medical research may be impacted, at least subconsciously, by private financial incentives.

In a 1986 article in The New England Journal of Medicine, Dr. Richard Davidson analyzed reports on drug trials in five leading medical journals. He found that when drug companies sponsored the trials, researchers were significantly more likely to favor the drugs being tested.

Dr. Marcia Angell, editor of the prestigious journal, warned last year of "a Faustian bargain" when research centers "make available their precious resources of talent and prestige to carry out research that serves primarily the interests of the companies."

Angell asked, "How can they justify rigorous conflict-of-interest policies for individual researchers when their own ties are so extensive?"

The Hutch won't disclose financial connections of its research doctors or of the center itself. It won't say what stock it owns. It won't say what experiments it is performing for the companies whose stock it owns. It won't say what inventions and patents it is licensing to those companies, or for what prices.

To do so, Hutch President Dr. Lee Hartwell says, could violate confidentiality agreements with private companies.

Several clinical researchers at The Hutch who hold patents have written about their discoveries without disclosing their financial interest in print, a Times review of more than 1,000 medical journal articles has found.

Some journals require such disclosure, and Johns Hopkins University, among others, requires all of its researchers with financial interest to publicly disclose them.

The Hutch does have a policy regulating conflicts of interest, but that policy has been weakened over the years.

In 1983, during Protocol 126 - one of the experiments described in The Times earlier this week - the policy said no Hutch scientist could participate in any study or patient care in which he or she had any outside interest.

That policy was not enforced in the case of Protocol 126, as all three of the researchers had ties to a company that owned licensing rights to some of the drugs being tested.

Today, the policy says only the "principal" investigator must avoid financial holdings that can be affected by the experiment.

Appelbaum
Other researchers involved in studies and patient care can hold interests in private companies whose products they are testing as long as they report them to Dr. Fred Appelbaum, the director of clinical research. There is no limit on the amounts they may own - and no required disclosure to the subjects of their experiments.

Appelbaum says fewer than 10 percent of the clinical doctors at The Hutch have had conflicts. He says he has had to "manage" three or four situations. Citing privacy, he won't talk about details.

Some have stricter rules

The Hutch's current policy matches a 1994 guideline by the National Institutes of Health, and many research centers nationally have similarly loose restrictions.

But some major centers - among them Harvard University, Johns Hopkins University, UCLA, the University of Minnesota, the University of Kentucky, the University of Nebraska and even a Hutch partner, the University of Washington - are tougher.

To begin with, a few of them require research doctors to tell patients when they have private financial interests.

"It's the appropriate thing to do," said Steve Peckman, associate director for human-subjects research at UCLA. "If an investigator has an interest in the product or the company sponsoring the study, any reasonable subject would probably want that information."

A typical disclosure might say, "Dr. Smith received payment from Jones Company, sponsor of the study, for giving presentations."

Hartwell, Hutch president, says, "It's such a complicated issue that I'm not sure it makes sense to ask a patient to decide whether that's relevant or not. I don't think that's the way to handle it. I think the way to handle it is for the institution to be sure that no financial interest has an opportunity to have an influence on the outcome of the study."

The University of Washington Medical School, which works closely with The Hutch, doesn't give such information directly to patients. But unlike The Hutch, the UW does make its corporate sponsors, licensing deals and medical professors' reports of outside income available as public records, available on request.

Harvard Medical School flatly prohibits faculty from owning more than $20,000 in stock in companies whose products they are testing. Harvard reaffirmed the strict policy last year despite warnings it could lose some star faculty who wanted to make more money.

New York's renowned comprehensive cancer center, Memorial Sloan-Kettering, has far fewer spinoffs and potential conflicts of interest than The Hutch, despite having a faculty five times larger.

"Our board is very conservative," Senior Vice President James Quirk explained. "They're still concerned about what (private work) does to the faculty, meaning does it divert their attention from the work they do here."

While The Hutch has spawned more than a dozen private biotech companies, only one has spun out of Sloan-Kettering. Quirk said it was started because no vendor stepped forward to market a vaccine the hospital needed.

Sloan-Kettering requires all scientists to report potential or actual conflicts of interest internally. Quirk says only two scientists in 18 years have exceeded the limit of $10,000 or a 5 percent interest, and neither was in the clinical division, where human experiments are conducted.

Sloan-Kettering hasn't had institutional conflicts of interest with owning biotech stock, Quirk says, because it rarely asks for stock and always sells it fast.

"We feel it's cleaner," he said. "It's much easier for somebody who would ask you, `Do you have stock in that company?' We say, `Absolutely not.' "

Hartwell, meanwhile, says The Hutch should get more, not less, stock from biotech companies with which it is involved.

The Hutch sold $50 million in stock between July 1998 and July 1999, taking $3.6 million in profits, an IRS report shows. The center apparently acquired other stock and was left with about $40 million in corporate securities. It has repeatedly refused to discuss its stock dealings.

Rosetta Inpharmatics, a $250 million company co-founded by Hartwell and Dr. Stephen Friend, gave The Hutch 352,000 shares of stock for a licensing and research deal. Hartwell, hearing grumbles in the hall, gave The Hutch his own 283,200 founder's shares to avoid a personal conflict of interest.

The role of the review board

Hutchinson doctors today give two levels of scientific review to clinical trials and say they spend at least two hours with each prospective patient. But the primary safeguard against ethical and medical problems at The Hutch remains its Institutional Review Board.

The IRB, as it is known, is required by law for federal funding of any medical experiment involving humans.

Each month, two groups of about 10 people gather around tables in the E. Donnall Thomas Building on the Hutch campus.

Before each of the members is an imposing packet of papers stamped "confidential." The packets can't leave the room. They are carefully collected at the end of each meeting.

Inside are the details of 25 or so medical experiments on human beings. Five or six are new; the rest are ongoing.

The IRB's job is to ensure that subjects of medical experiments are treated in an ethical and humane manner, are fully informed, and that the potential benefits of the experiment outweigh the risks. It's a daunting task.

Waiting to speak to them are the center's most respected doctors - the ones who bring in millions of dollars in grants.

Down the hall is Dr. Thomas, a living legend who at 80 still works part time in an office in the building named in his honor.

The IRB members are all unpaid volunteers. The Hutch keeps their identities secret, but they include a housewife with a science background, a human-resources consultant, an attorney, a finance officer at a research institute and a risk-management expert. The others are doctors, nurses and pharmacists.

One former IRB chairman said the board was tough when going over patient informed-consent forms. For instance, "We made sure not to have polysyllabic words when a monosyllabic would do." But he refused to be quoted by name or to answer further questions unless, he said, The Times got a court order.

Center spokeswoman Susan Edmonds has for months refused to say who sits on the IRB. "We have nothing to hide," she said, asserting that members want to keep their identities secret to avoid being bothered by reporters' calls.

The Times did learn that two board members designated as "nonaffiliated community members" - which the federal government requires - were, in fact, being paid by The Hutch to perform legal work.

Suzanne Kelly Michael sat on the IRB from 1994 to 1998. Court records show Michael represented The Hutch in a major lawsuit in 1997 and 1998, while she was on the IRB.

Asked about that, Michael said that when she joined the board, she didn't personally work for The Hutch, though her firm, Lane Powell Spears Lubersky, did. The Hutch refuses to say how much Michael or the firm was paid during the time she sat on the IRB.

Paul Nordsletten replaced Michael in July 1998 as the "nonaffiliated" member. He works for The Hutch as an attorney on employment cases.

"At least in my own mind it's never made a difference because the two things are so different," he said, adding, "My work for them is sometimes very substantial and other times is not." Nordsletten lists The Hutch first among his clients in a lawyer directory.

After The Times raised questions about these lawyers' work as "nonaffiliated" members of the key review board, IRB administrator Karen Hansen said she asked all members of the IRB to study the statement of nonaffiliation and to report any problems. Hansen said the two lawyers then did so. She said some other people were "close" but not disqualified.

Helen McGough, IRB administrator for University of Washington research, where names of IRB members are public, said the UW "would not consider a person who has any financial relationship to be a nonaffiliated member." The purpose is to be "an outsider to the institution," she said.

At The Hutch, not only are the IRB's meetings closed, but also the meetings of the center's Board of Trustees. Although 68 percent of the center's funding - $140 million last year - comes from taxpayers, Hutch officials say they feel no legal or ethical obligation to open the meetings.

That attitude, and The Hutch's insulated approach, should be reassessed by its leaders, said Mary Faith Marshall, director of the program in bioethics at the University of Kansas Medical Center.

"I hope that approach will change," said Marshall, who is chairing the National Human Research Protections Advisory Committee, a blue-ribbon panel looking at such issues at research centers across the country.

"The model should be one of transparency. There should be no secrets."

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System's serious flaws have led many to call for regulatory reform

By Duff Wilson and David Heath
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IT'S BEEN MORE than a half-century since horrifying human experiments by the Nazis prompted the first code of ethics for medical research. Yet enforcement of ethics today remains largely an honor system.

On the agenda

Here's what's on the agenda in the national effort for reform of medical research:

• Sunday through Tuesday: Medical Research Summit, a privately sponsored forum in Washington, D.C., for industry and regulators, on the regulation and ethics of medical research in the U.S.

• April 9-10: Second meeting of the National
Human Research
Protection Advisory
Committee, a panel appointed by then-Secretary of Health and Human Services Donna Shalala.

• Late April or early May: one or two days of hearings on human research and financial conflicts of interest, by a subcommittee of the U.S. Senate Commerce Committee.

In this country, government regulators leave it to research centers to police themselves. And even when regulators learn that rules have been broken, they rarely mete out stiff punishments.

This has led to inconsistent, lax standards - and, sometimes, patients dying in questionable experiments.

Birth defects caused by the drug thalidomide, prescribed without patients always being told it was experimental, led in 1962 to the first U.S. law requiring informed consent for medical research. A decade later, news that 399 black men in Tuskegee, Ala., had been deceptively denied treatment for syphilis as part of a government experiment ultimately led to major reforms.

Yet the system still has serious flaws.

"Unfortunately, because the current system of protections has, in large measure, been cobbled together in the wake of abuses, it is both more cumbersome and less effective than it must be both to support research and protect participants," the National Bioethics Advisory Commission, appointed by then-President Clinton, said in a recent report.

But critics fear that pharmaceutical and biotechnology companies, which pay for much medical research these days, will be able to thwart major reforms. Abbey Meyers, president of the National Organization for Rare Disorders, expected few results from the myriad commissions and studies calling for changes.

"I think we're probably headed toward another catastrophic event like a Tuskegee experiment" before that will happen, Meyers said.

'The science has been lost'

Of particular concern these days is the relationship of physician-researchers and their medical centers to for-profit companies.

Since Congress in 1980 made it much easier for universities and researchers to cash in on their discoveries, "the science has been lost in the rush for money," said Dr. Thomas Bodenheimer of the University of California, San Francisco, who decried this trend in The New England Journal of Medicine.

Momentum to reform conflict-of-interest rules has grown since the highly publicized death of a young man in a clinical trial at the University of Pennsylvania.

Eighteen-year-old Jesse Gelsinger agreed to participate in a gene-therapy trial even though it offered him no benefits. He slipped into a coma after being infused with a gene-therapy substance and died four days later on Sept. 17, 1999.

Unknown to Gelsinger, the researcher, Dr. James Wilson, owned 30 percent of Genovo, whose gene-therapy substance he was testing. Wilson reportedly made $13.5 million when the company was later sold to Targeted Genetics of Seattle.

Gelsinger's death has prompted many universities and medical-research centers to rethink their financial-conflict policies. Most follow federal rules requiring researchers to disclose financial conflicts to someone in administration, but none ban such conflicts outright.

Critics worry, too, that financial conflicts are compromising the validity of medical research.

"Teaching hospitals and medical schools are becoming increasingly compromised in that they are behaving like research outposts for the pharmaceutical industry," said Marcia Angell, former editor in chief of The New England Journal of Medicine.

A report in The New England Journal said 96 percent of studies in medical journals advocating the use of heart and blood-pressure drugs called calcium-channel blockers were funded by the drug manufacturers. Only 37 percent of the studies critical of those drugs had financial ties.

Another study said that in medical journals, only 5 percent of studies sponsored by the makers of six oncology drugs were critical of the drugs, vs. 38 percent of independent studies.

Review boards are pressured

The burden of protecting patients falls to so-called institutional review boards, or IRBs. But these local boards, appointed by the institution they police, are often overwhelmed and lack expertise.

And even if an IRB wants to get tough, its members may lack the time to do it. Studies by the federal General Accounting Office and the Department of Health and Human Services (DHHS) have found IRBs to be severely overworked.

"In some cases, the sheer number of studies necessitates that IRBs spend only one or two minutes of review per study," said a 1996 GAO report. For continuing studies, "these reviews are typically either superficial or not done at all."

An IRB member at one institution explained to federal investigators that for continuing studies, he usually just checks to see if there have been any deaths.

"If no patient has died, then he generally will not raise questions," said a 1998 DHHS report.

There are also financial pressures to approve research because delays could cost an institution grants or commercial partnerships. One federal report described the process used by some pharmaceutical companies as "IRB shopping." A drug company shops around for an IRB that will give it quick approval on proposed research.

Two years ago at the University of Illinois at Chicago, 10 members of the IRB quit, complaining that they felt pressure from the school not to interfere with lucrative studies. One said, "They thought we were overly scrupulous, nitpicking obstructionists who were spoiling the research-enterprise system."

The federal Office for Protection from Research Risks (OPRR), under fire for rarely inspecting research centers, signaled a new get-tough attitude in May 1999 when it temporarily shut down federally funded research at Duke University because the school wasn't adequately tracking experiments to ensure the safety of patients. It later suspended research at several other universities, including the University of Illinois at Chicago.

Dr. Greg Koski, director of the revamped Office for Human Research Protections, the federal successor to the OPRR, said that shutting down Duke and other universities caught the attention of academic centers and led to better compliance.

When the National Institutes of Health recently reminded grant recipients they were required by contract to report any deaths or other "adverse events" in gene-therapy trials, more than 500 previously undisclosed problems were reported.

However, no such reports are made public in the many clinical trials that don't involve gene therapy. The Food and Drug Administration treats those as confidential "trade secrets."

Efforts toward reform

Many of the reforms being proposed nationally focus on educating and certifying anyone involved in research and on accreditation for research centers. There's also a push to reduce paperwork.

"The mindless way to try to protect from any injury to subjects is to build a wall that's higher and thicker that makes it more difficult to do research," said Koski.

"By and large, most human research is done by very well-intentioned individuals according to high standards. The institutional review boards by and large take their responsibilities very seriously."

A U.S. Senate subcommittee is expected to hold hearings on human-research protection this spring.

Previous efforts to reform the system have fallen short. There have been several stinging reports about the failure of IRBs in recent years, including one by the DHHS in 1998.

Last year, that office issued another report, saying that virtually none of the changes it had recommended had been made.

Said Dr. Sydney Wolfe of the consumer group Public Citizen, "They are almost begging for deaths and serious injuries as the prerequisite to making further changes."