

The Story of Patient #10

By Susan Levine
Washington Post Staff Writer
Tuesday, July 31, 2001; Page HE01

To this day, Patient #10 has no regrets.

Far from it, he says, for he would do it all again. He would sign the consent form and submit his body to a potentially dangerous treatment, knowing with chilling clarity what can happen -- what did happen -- when the unexpected risks of medical research overwhelm even the most important possible benefit.

Eight years ago this summer, he and six other participants in a clinical trial at the National Institutes of Health (NIH) became sick. Extremely sick. Within days researchers realized that an experimental drug the volunteers had been taking for hepatitis B had killed more than that virus. In fact, it had poisoned and begun destroying major organs throughout their bodies. By July 30, four people were dead. Another was dying.

Patient #10 was poised perilously near that edge, with a transplanted liver that no one was sure would save his life. His kidneys were failing and a ventilator was forcing air continually into his lungs. Feeding tubes snaked down his nose into his stomach. He was comatose. Doctors had little understanding why.

Never before has he talked publicly about his experience in the clinical trial for the drug fialuridine, which became an unprecedented catastrophe for NIH. Then came news in mid-June that a young woman had died during an asthma study at Johns Hopkins University in Baltimore. In mid-July, government regulators suspended all Hopkins medical trials involving human subjects; while reversing that order last week, they nonetheless maintained severe restrictions that will hamper many studies for months.

The Hopkins tragedy again brought into focus the tightrope on which much medical research operates, and it persuaded Patient #10, a retired educator, to finally recount what he went through, to reflect aloud on the impact it had.

Perhaps the biggest surprise is not that he survived, but that he remains committed to medical research despite his near-death experience.

"Someone has to go out and do it, and so you volunteer for these things," he says. "There will be accidents, and there will be problems. . . . But when there's nothing else [as treatment], are you just going to sit there?"

The Volunteers

Fundamental differences distinguish the NIH trial from the project that was underway at Hopkins until 24-year-old Ellen Roche fell ill in early May. She was one of nine healthy volunteers on whom a chemical was being tested for its ability to block neural signals involved in airway constriction; that physiologic response, if better understood, might lead to a cure for asthma. Roche and the others stood to profit little beyond researchers' appreciation and \$365 for their time.

By contrast, the drug known as fialuridine, or FIAU, was being studied in 1993 for its possible therapeutic value. While the NIH participants had no symptoms of hepatitis B, they definitely carried the virus and it is easier to understand why they agreed to serve as guinea pigs. Their disease is maddeningly untreatable, and chronic infection

can linger for years before causing severe liver damage, scarring, cancer or death. They would have been among the millions to gain had FIAU lived up to the tremendous optimism that marked the trial's start.

"This was basically going to be the answer to help 300 million people around the world," Patient #10 remembers.

Excepting the gold medical-alert bracelet on his right wrist -- alerting strangers that he is a transplant recipient -- Patient #10 bears no obvious sign of the events that followed. He is today a sturdy man of 71, deeply tanned and constantly on the go. He lives in Arlington, not far from his two grandchildren -- and that, he says, is all strangers need to know about his current life, which is why he remains identified as Patient #10 in this story's telling.

He does not know where or when he contracted the hepatitis that eventually led him to the liver disease researchers at NIH, but he readily acknowledges enthusiastically enrolling as a study participant -- not once, not twice, but five times between 1988 and 1993.

"I told them, if something comes along that looks promising, sign me up," he explains. "When you have a disease that's incurable and it's going to progressively get worse, I just felt, hey, I'll jump in."

A Dramatic Success

His first three trials with other drugs produced a variety of bodily aches but made little research headway against the disease. Then he heard that NIH needed 24 people for a 28-day trial of FIAU. He again enrolled. And for just shy of a month, he squirted a cherry-flavored dropper of liquid into his mouth once per day.

He washed it down with water. He suffered no immediate side effects. But the results were spectacular. Tests indicated that the virus was being routed, dramatically so.

"We were so excited," his wife recalls. "We talked about it all the time."

The results were so promising he feared only that he might not be chosen for NIH's next phase of testing, which began in the spring of 1993 and was to last six months. Ten people were accepted. He was the tenth. Like the others, he signed a consent form that laid out in detail the potential adverse consequences of FIAU, including nausea, upset stomach, seizures, and pain and numbness in the arms and legs. The list went on for nearly two pages. The arm and leg pains, it noted, "can be severe and last for weeks to months. In some cases, a permanent decrease in nerve function is found." Death was not mentioned.

Despite the wording, he admits to having had a false security that no significant problems would arise. It's why he dismissed a passing comment from one NIH physician that he'd already "given enough to science" and should take a break. He believes the NIH researchers were completely upfront with him. He describes Jay Hoofnagle, the study's principal investigator, as brilliant and compassionate.

What happened next was nobody's fault, he insists: "I hold no grudges against anyone."

Sudden Reversal

What happened next became horribly clear in a single weekend in late June after one of the volunteers was hospitalized, critically ill, with liver failure. At that point, the group had been on FIAU for as long as three months. That was long enough for the drug's previously unknown and unanticipated toxicity to emerge, damaging -- or destroying -- mitochondrial cells that produce energy for the body. The result was a massive buildup of lactic acid,

which caused multiple-organ collapse. Critics later would say the warning signs had been overlooked or disregarded.

Patient #10 was feeling severely nauseated and exhausted when Hoofnagle called him at home and told him not to take any more medicine. The doctor's voice was urgent: We want to see you Monday morning. Plan on staying overnight.

As it turned out, it would be nearly Halloween before he and his wife returned home. "They told me every cell in my body had stopped functioning," he says. He thinks about that now, wondering what made the difference in his case, why he survived. "How come I made it? I should have been gone."

The scene that Monday morning at NIH was quiet, desperate crisis. Some of the assembled families were in shock, others venting anger. Over the next several days, the patients began to be transferred out of town for transplants. Two didn't even live long enough for those operations to give them a chance.

Patient #10 was flown in early July to the University of Virginia Health Sciences Center in Charlottesville. By week's end, with no liver available, doctors were preparing his wife for the worst. "They told me they didn't think they could save him through the night," she says. He slipped in and out of consciousness. His legs swelled to twice their normal size because of fluid buildup as the kidneys stopped functioning. His stomach bloated. In intensive-care rooms around him, similar battles were being waged. And lost.

And then, unbelievably, another liver was found. But the July 19 transplant surgery seemed to change little. Patient #10 faded deeper into a coma, and doctors feared possible brain damage. They worried whether lingering traces of FIAU would affect the transplanted organ.

"You felt like the Dutch boy with his finger in the dike," says surgeon Timothy Pruett, who leads the transplantation division at the Charlottesville medical center. "He was very, very sick."

August faded into September. He had brief fragments of awareness. During one, he asked whether they'd ever located a liver for him.

"Yes," his wife replied, "and you've had it for two months."

Lingering Effects

In the end, seven of the 10 people in the original protocol group were hospitalized for significant FIAU toxicity. Five died.

The only other transplant survivor left the hospital within a matter of weeks; he now lives in the South and chats every so often, comparing notes, with his Arlington counterpart.

The drug's toll reverberated through NIH -- and still sobers scientists there and across the country. It changed the way many people thought about clinical trials, made them rethink the question of risk vs. benefit and how to better reconcile them, Pruett says. Even today, mention those four letters "and everyone gets a little hushed."

No researcher was affected more than Hoofnagle, a highly regarded liver specialist who remains a senior investigator at the National Institute of Diabetes and Digestive and Kidney Diseases. He will share few thoughts on the impact the trial's outcome had on him: "Personally, it was a nightmare for me, and I have to live with it every day of my life."

In the wake of the recent Hopkins death, federal officials identified numerous problems with how that university was supervising medical research and for four days stopped virtually all of its trials with human subjects. The repercussions of the FIAU trial were less harsh. Inquiries were conducted by the Food and Drug Administration (FDA), the Institute of Medicine, which is part of the National Academy of Sciences, and an independent panel of experts assembled by NIH. Though the FDA criticized the NIH investigators and the drug's manufacturer, Eli Lilly & Co., citing violations of federal reporting regulations, the other two groups exonerated them and ruled the tragic outcome an unavoidable accident in which neither negligence nor carelessness played a role.

Not that such conclusions help the public understand the difficult dimensions of clinical research. In its final report on the FIAU trials, which was laced with references to the grief of the families and the "private and public soul-searching" of scientists, the Institute of Medicine noted the "erroneous public perception that new treatments can be developed and tested free of risks only if enough care is taken."

Michael Gottesman, deputy director for intramural research at NIH, wishes risk indeed could be eliminated. But doing so would have other consequences, he says. "We probably could make incremental [medical] advances, but not big ones. The big leaps do require the brave to participate."

Patient #10 returned home to Arlington in late October 1993 -- four months after he had packed that overnight bag for Bethesda and 80 pounds lighter. He then spent more months in rehabilitation, charting goals such as being able to walk to the bathroom independently. He will remain on Cyclosporine to minimize the chance of his body rejecting his liver, and every two months he receives an intravenous injection of immune globulin. A kidney transplant someday could be in his future because of the damage to his own.

"They learned a lot from me," he says of NIH scientists. "They learned a lot from all of us."

In the balancing of contributions and sacrifice, Patient #10 knows the other FIAU families may not share his sentiments, and above all he does not want to cause them new pain. He realizes that his own family might feel far differently about clinical research were he not alive today. He remains in a follow-up protocol with Hoofnagle, and he admits to being more cautious, more questioning, whenever a new treatment is proposed.

Yet he still believes as he does, strongly, forthrightly. "You can't go forward without trials. You can't give [a drug] to cats and dogs, and then give it to humans and say it worked on cats and dogs. Sometimes trials don't pan out. And then people are going to get hurt."

Eight years later, he considers himself lucky, and blessed. The FIAU nearly killed him, but apparently it also accomplished what was intended.

The doctors at NIH cannot find any evidence of hepatitis in his body.

Susan Levine is a reporter for The Post's Metro section.

© 2001 The Washington Post Company