Informed Consent

Alan Milstein says he wants to rescue us from unscrupulous doctors, undisclosed risks and greedy institutions. But is he a shining knight,or an enemy of medical progress?

By Jennifer Washburn Sunday, December 30, 2001

At one end of the long conference table sat the lawyer, a tall man with silver-and-black hair, prominent cheekbones and a Baltimore accent, dressed in a charcoal-gray suit and white pin-stripe shirt with monogrammed cuffs. The others seated at the table wore lightweight dresses, bluejeans, overalls, cowboy boots and trucker caps. Their faces were somber and expectant. Some had driven hundreds of miles to Tulsa to be here.

The lawyer began the meeting with two questions. "Why did you decide to enroll in this trial?" he asked, his dark eyes sweeping around the table. "What did Dr. McGee tell you about the vaccine being tested?"

Phyllis Friesner, an elderly woman with arresting blue eyes, was among the first to respond. Her late husband, James, had been diagnosed with advanced-stage melanoma, a deadly skin cancer. He had seen the vaccine -- offered in a melanoma experiment at the University of Oklahoma Health Sciences Center -- as his last hope. According to Michael McGee, the director of the experiment, the purpose of the medication was to prevent the melanoma from recurring after it had been surgically removed. But shortly after the injections began, Phyllis Friesner said, "Jim's tumors started growing rapidly."

"I asked Dr. McGee, 'Just how good is this vaccine?' " she recalled. "He said it's the greatest; it's better than any of the vaccines out there. He told us he was having a 70 to 75 percent cure rate.

"The lawyer nodded his head. "A 70 percent cure rate?" he asked. "Was anyone else told that?"

Jeff and Paige Teel, a young couple seated at the far end of the table, recalled that they had heard the same reassuring figures. Jeff had been diagnosed with melanoma as well. "We were also told that the side effects would be minimal," he said.

A chorus of people responded affirmatively, "Uh-huh."

Despite McGee's assurances, Jeff Teel went on, the vaccine injections had made him violently ill. After each one, his temperature rose rapidly; he broke out in a cold sweat and started to shake uncontrollably. For two or three days he would vomit continually. The anxiety attacks were terrible," he recalled. "I felt like my throat was closing; I could hardly breathe.

"Mark Gaffney, a quiet man with a narrow face, deep bags under his eyes and a forest-green baseball cap, said he, too, had suffered terrible symptoms after each round of injections. Rolling up his sleeve, Gaffney asked the group whether anyone else had experienced swelling. His arm was nearly double its normal size, the pale skin covering his hand and fingers puffed out like a balloon.

The lawyer looked up from his yellow legal pad. "Who's your physician?" he asked. "We haven't found another doctor," Gaffney's wife responded.

This, the lawyer knew, was the reason that many of those around the table had enrolled in the clinical trial. They didn't have health insurance, they were terminally ill, and here was a prestigious university offering them treatment for free. But what most interested him were the things his clients had not been told. They weren't told the test vaccine had been manufactured by untrained

staff in a small, cramped room at the university without proper sterility testing or quality controls. They weren't informed that the study was unlikely to cure its subjects. When the clinical trial was terminated, federal investigators noted that the informed consent document each patient had signed had overstated the potential benefits.

Nor were they warned that the vaccine and another drug that McGee introduced during the research trial could be harmful to a fetus. Dawanna Robertson, a young woman with olive skin and brown hair, told the group that she and her husband had notified McGee immediately when they learned she was pregnant. "I didn't want anything to hurt my baby," she said. "Dr. McGee told me that it would be okay, that the vaccine wouldn't reach the fetus because it was in a sack."

Soon afterward, however, she developed severe reactions. "One time my throat swelled up so bad I had to go to the emergency room because I couldn't swallow my own saliva," she said. "Now, I'm really worried about my baby, Sydnee. She's sick all the time. When you go to the doctor, you trust him. Just as a human being, I feel betrayed; I feel like he took advantage of my child, and that's a big deal to me.

"As the meeting drew to a close, the lawyer told them that he would do everything he could to hold the University of Oklahoma accountable. What had happened to them, he added, was not an isolated case but an example of a broader trend, which was why their lawsuit was beginning to attract national media attention.

"The whole country," Alan Milstein promised, "is watching this case."

He is an improbable crusader in the world of medical research. An attorney with Sherman, Silverstein, Kohl, Rose and Podolsky in

Pennsauken, N.J., Alan Milstein knew little about clinical research before he filed a much-publicized lawsuit against the University of Pennsylvania last year. Prior to that case, he had never even filed a medical malpractice suit.

But since then, Milstein has become the man to see when it comes to medical research abuses. His scorched-earth tactics -- suing anyone even remotely implicated in harming his clients -- have unnerved his academic opponents, among them some of the nation's most prestigious medical schools and research institutions. Drawing a connection between these modern-day violations and the abuses perpetrated by Nazi doctors convicted at Nuremberg after World War II, Milstein is pursuing an aggressive legal strategy that intimidates and infuriates many in the clinical research world.

Milstein has found a fertile field. Experts estimate that nearly 3 million Americans volunteer annually to participate in 50,000 to 60,000 ongoing clinical trials. These trials are critical in determining whether the vast array of new drugs and therapies developed in the nation's laboratories will prove effective in curing diseases and saving lives. But there has been growing concern about whether the human subjects who volunteer for these trials are adequately protected.

In the past four years, federal regulators have restricted or shut down research at 20 institutions for violations of rules designed to protect participants. The crackdown has come at a time when funding for biomedical research has been skyrocketing, many more clinical trials are being conducted and an already-weak oversight system of institutional review boards (IRBs) has been staggering from the strain of too much work.

It is in this context that Milstein has jumped into the fray. In the past 15 months, he has filed three major lawsuits against

university-affiliated research centers. His first case was filed on behalf of the family of Jesse Gelsinger, an 18-year-old who died in a gene therapy experiment at the University of Pennsylvania and whose death prompted a national investigation that uncovered abuses at dozens of other institutions. More recently, following reports of multiple deaths and research violations, Milstein filed suit against the Fred Hutchinson Cancer Research Center in Seattle, a world-renowned cancer institute affiliated with the University of Washington. Finally, there is the class action suit he has filed jointly with Oklahoma lawyer Robert Seacat against the University of Oklahoma.

Milstein has several other cases in the works -- including a recent lawsuit on behalf of soldiers ordered to be inoculated with a controversial anthrax vaccine -- and it's no wonder: Until the September 11 attacks drove most other stories from the headlines, fresh revelations concerning medical research violations seemed to emerge every few weeks. Over the summer, federal authorities opened an investigation at the University of Michigan after receiving complaints that two studies there were performed without the subjects' consent. The same month, authorities charged senior officials and investigators at St. Jude Children's Research Hospital in Memphis with failing to report "serious unanticipated problems involving risks to subjects.

"One month earlier, Ellen Roche, a healthy, 24-year-old woman, died in an asthma experiment at the Johns Hopkins School of Medicine in Baltimore, one of the most respected medical schools in the country. A federal investigation found that Hopkins researchers had failed to obtain information on the links between a drug they were administering and possible lung damage, even though data showing this connection were readily available. Investigators also discovered widespread deficiencies in Hopkins's oversight system and ordered the suspension and reevaluation of thousands of clinical trials. In another instance, last month Hopkins

moved to discipline a scientist who had been operating a cancer trial in India without approval from the university or the Food and Drug Administration.

To be sure, universities and their affiliated teaching hospitals have faced medical malpractice suits against individual doctors before. But Milstein is attempting to hold the entire institution liable -- everyone from the president of the university to the individual IRB members to the bioethicists who advise institutions on ethical issues. In Milstein's view, the only way to protect human subjects and bring about reform is to hit universities where it counts: in their pocketbooks.

Milstein's lawsuits are wreaking havoc in the halls of academia because of the high stakes and the ethical questions they raise. The lawsuits are also focusing public attention on aspects of the research world that many universities and scientists would prefer to keep private, such as their growing financial ties to corporate sponsors. At both the University of Pennsylvania and the Fred Hutchinson Cancer Center, the principal researchers -- and the institutions themselves -- had financial interests in companies that stood to profit from their experiments. The prevalence of the ties has prompted questions about whether university research centers are bending the rules and cutting corners on safety in order to make profits.

"Universities are afraid," says Kendra Dimond, a Washington, D.C., attorney who represents the health care industry. "Most of them are public institutions, or supported by public and philanthropic funds, so they can ill afford to have a lot of bad publicity -- and Milstein knows that.

"Medical research usually begins with extensive laboratory testing in animals. If the results appear promising, investigators generally file a new-drug application with the FDA and navigate through

three phases of testing on humans. The first phase, usually performed on 20 to 100 subjects, tests toxicity -- the way the drug is absorbed into the body, and what dosage levels are safe. The second phase, conducted on up to several hundred people, tests whether the drug is effective. According to the FDA, only about one-third of experimental drugs successfully complete both phases. Drugs that make it to the third phase are tested on several hundred to thousands of subjects to establish a more thorough understanding of their effectiveness, benefits and side effects.

The system is intentionally rigorous in an effort to ensure that only drugs that are safe and have proven health benefits are released to the broader public. "Clinical trials are very important to our lives," says Larry Medley, acting CEO of the Association of Clinical Research Professionals. "We wouldn't be able to live as long as we do if it weren't for the appropriate study of new drugs and devices.

"Too often, however, these experiments are conducted with meager oversight and without proper informed consent. The main mechanism for protecting human subjects is the institutional review board, federally mandated for most experimental research. Typically, all large research institutions have their own IRB composed of faculty members, administrators and at least one independent representative from outside the institution. But according to a report last year by the inspector general's office at the Department of Health and Human Services, "IRBs are inundated with protocols and adverse-event reports. With limited personnel and few resources, many IRBs are hard-pressed to give each review sufficient attention.

"Federal oversight is not much better. The General Accounting Office found that during a recent eight-month period, the Office for Human Research Protections failed to make any unannounced spot checks of research sites. Even when federal agencies do inspect a site, it rarely happens while a clinical trial is taking place;

if any violations are found, it is often too late for the human subjects involved.

"Too many researchers are not adhering to standards of good clinical practice," wrote Donna Shalala, then secretary of health and human services, in an editorial in the New England Journal of Medicine last year. "These were not isolated incidents on the fringes of science. Instead, these troubling problems occurred at some of our most prestigious research centers and involved leaders in their fields of study.

"While acknowledging problems exist, many clinical investigators contend that waves of litigation, and the negative publicity that inevitably follows, could have a chilling effect on research and impede advances in medicine. "Litigation certainly gets everyone's attention," says Robert M. Nelson, chairman of the institutional review boards at Children's Hospital of Philadelphia. "But getting a monetary award eight years later doesn't do any good for changing practices at the time of the trial.

"Milstein is unimpressed with that argument. "Everyone accuses me of wanting to shut down research and slow medical progress," he says. "I'm not trying to shut down research; I'm just trying to make sure it's done ethically.

"The case against Milstein often gets personal. Boiled down, it is that he's a plaintiff's lawyer out to make money in a field whose nuances and moral quandaries he fails to comprehend. Arthur Caplan, a prominent Penn bioethicist who acknowledges he's still bruised from being one of the early defendants in the Gelsinger case (he was dropped eventually from the suit), makes the argument: "No one in bioethics takes [Milstein] seriously. He simply has no background and no understanding of Phase I and II studies or anything else in human experimentation ethics . . . He is simply clueless about the area that he happened to find himself

litigating with respect to Gelsinger.

"But Paul Gelsinger, Jesse's father, sees things differently. "I've done all I can do to change the oversight system: speaking out, attending hearings. And where is it now? Hung up in limbo," he says. "It's been my fear all along that time and money will kill the whole awareness brought about by Jesse's death. I think Alan's lawsuits are appropriate; they are keeping this issue alive.

"Alan Milstein keeps framed photos of John F. Kennedy and Bob Dylan on display in his South Jersey law office, and a Grateful Dead wine bottle (labeled "Dead Red") on his shelf. It doesn't take much prodding for him to pull out his modest collection of O.J. Simpson memorabilia, including a T-shirt signed by Johnny Cochran ("I'm a big Johnny Cochran fan"), a Rose Bowl jersey signed by O.J., and snapshots of Milstein and his legal partners on the L.A. murder scene tour.

Like his early idol, Dylan, Milstein enjoys thumbing his nose at the establishment. Does it concern him that his lawsuits might damage the reputation of prestigious institutions like the University of Pennsylvania? "I went to law school at Temple," he replies. "I could care less."

But like his other idol, Cochran, Milstein is making good money pursuing his personal brand of legal morality. He drives a silver Toyota MR2 Spider convertible, and his suits are comfortably stylish. Those are about the limits of his ostentation. "The impetus is not to make money," he says of his medical research work. But he can't help adding a few moments later, "Do I believe we are going to make lots of money? I do. It is a pleasant collateral result."

Sometimes it's possible both to moralize and to make a healthy profit. In the Gelsinger case, the facts were relatively

straightforward; Milstein brought a traditional medical malpractice claim arguing that Jesse, a young, healthy volunteer, had died as a direct consequence of the experimental treatment. The university settled quickly -- without acknowledging wrongdoing. While the amount is confidential, observers knowledgeable about such cases estimate it was between $5 million and $10 million. Milstein's share: 33 percent.

Any good lawyer might have succeeded with Gelsinger. But elsewhere in the medical research field, the question of liability is far more complex. In the Oklahoma case, for example, most of the patients enrolled in McGee's study had advanced-stage melanoma -- a usually fatal condition for which there are few treatment options -- making it much harder to prove that any permanent physical harm was caused by the experiment. Searching for other legal arguments, Milstein has accused the university of breaching "the right to be treated with dignity," and the right to be fully informed about the potential benefits and risks of experimental research. He finds the source of these rights in the 14th Amendment's guarantee of life, liberty and property, though his claims have yet to be tested in court.

Stephen Hanlon, an attorney who has filed a similar "dignity claim," did so in a class action lawsuit filed in 1990 against the University of South Florida. The suit alleged that researchers at a public clinic serving low-income women with high-risk pregnancies had failed to inform patients of all their medical options and used a consent document written well above the average patient's reading level. The case was settled out of court last year for $3.8 million.

"Most lawyers want cases where they can go in and say, 'This is what juries across the country have awarded; this is what we should be compensated,' " says Hanlon. "Dignity harm is still an embryonic legal theory -- it has yet to be upheld in court."

Hanlon says the odds are stacked against Milstein. "They are going to fight him as hard as they fought me -- they fought me for 10 years -- because there are huge stakes here. It involves pharmaceutical companies, biomedical research institutions -- the amount of money involved is simply staggering."

"Before the Gelsinger case, I had a lot of cases that didn't really have any political context to them," Milstein recalled one day as he sat in his sunlit office. "Sometimes I was on the right side, sometimes on the wrong side. I enjoyed being a trial lawyer and the challenges of that. But here was a cause I really believed in."

Milstein, who is 48, grew up in a middle-class household in Pikesville, a predominantly Jewish suburb of Baltimore. His father owned a liquor store; his mother was a homemaker. After graduating from high school in the early '70s, Milstein attended the University of Maryland, where he soaked up the atmosphere of the counterculture. He grew his hair long and wore bell-bottoms. He became obsessed with the Beats -- he still enjoys quoting from Allen Ginsberg's poem "Howl."

It was a major stretch for Milstein to imagine that he would one day become a lawyer. After graduating in 1975, he got a master's degree in American studies at the University of Kansas, where he taught courses on the 1950s and '60s, examining each decade through the lives of prominent artists and dissidents: Jack Kerouac, Jackson Pollock, Billie Holiday, Kurt Vonnegut, Jasper Johns, Bob Dylan.

When he moved back east to Philadelphia, Milstein worked as an art critic for a small newspaper. "Art history was my passion," he says. "But after I had a kid, I realized I better start making some money. So I went to law school.

"Over the course of two decades, he became a specialist in

insurance litigation, computer software disputes and product liability, joining Sherman, Silverstein in 1991 to become chair of its litigation department. Then one day in December 1999, a banker who had been a longtime client of the firm brought his brother, Paul Gelsinger, a contractor from Tucson, to discuss the death of Paul's son, Jesse. Three months earlier, Jesse had died in a novel gene therapy experiment at the University of Pennsylvania designed to help find a cure for a genetic liver disorder.

Jesse's involvement in the study was strictly humanitarian. He stood to derive no benefit from the study since his own rare liver condition was already effectively controlled through medication and a restricted diet. Both Jesse and his father had been led to believe that Penn's investigators were on the brink of finding a cure for infants who suffered a more deadly form of Jesse's disease. "My son knew the study wouldn't benefit him," Gelsinger told Milstein, "but he thought there was a good chance it might cure the babies.

"But the experiment went badly wrong. The large dose of genetically engineered viruses that researchers infused into Jesse's liver in September 1999 caused a massive reaction. His liver failed, his blood thickened into jelly, and his kidneys, brain and other vital organs shut down. Four days after the initial infusion he was brain-dead. His death was the first reported fatality in the gene therapy field -- a much-vaunted new science with heavy Wall Street financing -- and made international headlines.

Paul Gelsinger told Milstein that for several months after Jesse died, he had defended the scientists at Penn, trusting that they had done what they could to save his son. Later, however, he began to question the circumstances of Jesse's death. It particularly troubled him that the scientists at Penn were now publicly stating that the gene therapy "treatment" they were testing was still in such an early stage that they had no proof of its effectiveness. Gelsinger

said he would never have allowed Jesse to volunteer for the study if he had known that.

Milstein was hooked. Despite his lack of expertise in the field, he took the case immediately. He read everything he could about the history of biomedical ethics and human experimentation. He became particularly interested in the brutal experiments performed on Jews, the mentally ill and Gypsies during the Holocaust. He delved into the darkest chapters of medical research in the United States, such as the Tuskegee experiment, in which treatment was deliberately withheld from black men with syphilis between 1932 and 1972, and the human radiation experiments conducted by the U.S. government during the Cold War. He began to draw a direct link between these gruesome experiments on unwitting victims and modern medical abuses. "The history of medicine and science is littered with subjects sacrificed for the 'greater good,' " he says. And what began as an intriguing but straightforward legal case was fast becoming a personal crusade.

By the time Milstein was ready to file his legal brief against Penn on the anniversary of Jesse Gelsinger's death in September 2000, federal investigators had unearthed most of the evidence he would need. The FDA reported that monkeys given gene-transfer injections similar to the one Jesse received had died or suffered serious adverse events, yet Penn's investigators had neglected to notify the agency of those occurrences until after Jesse died and failed to include this information on patient consent forms. Federal auditors also found that Penn's researchers had failed to halt the study and alert the FDA, as required, when volunteers suffered serious toxic reactions prior to Jesse's participation. And although Jesse's blood ammonia levels were too high to meet the criteria for enrollment, investigators admitted him anyway. (University President Judith Rodin, in a letter to alumni, has written: "It is extremely important to recognize that none of these lapses appears to have had any connection to the tragic event of Gelsinger's

death.")

Beyond these violations, Milstein's suit highlighted the extensive financial conflicts surrounding the experiment. Early on, news articles revealed that both James Wilson, the principal investigator, and the University of Pennsylvania held stock in a biotechnology company, Genovo Inc., founded by Wilson, which provided approximately 20 percent of the annual research budget for Wilson's lab. In exchange for this funding, Genovo had exclusive rights to develop Wilson's research into commercial products. Both Wilson and the university stood to profit financially if the experiment was successful.

No one has proved that Wilson's or Penn's financial stake contributed directly to the mistakes and misconduct discovered in Wilson's lab -- indeed, Wilson and Penn strongly deny any link. Still, numerous internal Penn documents reveal that university officials had extensive discussions about the possible dangers of such financial entanglements.

In early 1995, for example, the school convened a Conflict of Interest Standing Committee to review the matter. "The Genovo case might be the most important case which the CISC will ever deal with," noted Neal Nathanson, then Penn's vice dean for research and training.

One of the first questions the committee raised: "Since Dr. Wilson's research efforts will be directed towards the solution of a problem in which he has a financial interest in the outcome, how can Dr. Wilson assure the University that he will not be conflicted when making decisions that could have an impact on . . . his intellectual property?" The committee never answered this question.

The committee raised another prescient question: "How can Dr.

Wilson and the University avoid liability for any damages if a patient died from any products produced or studied at the University?"Even after Penn settled with the Gelsinger family in November 2000, nagging conflict-of-interest questions remained. Despite the negative publicity surrounding Gelsinger's death, Genovo was eventually sold to a larger company, leaving Wilson with stock options reportedly worth $13.5, and the university with an equity stake valued at $1.4 million.

In a written statement, Penn's director of university communications, Lori N. Doyle, said that the school has placed new limits on the involvement of faculty members in drug studies when they have an equity stake in companies sponsoring their research. The statement also called Jesse's death "a terrible tragedy," adding, "Our goal is to establish -- and to continually improve upon -- a national model for clinical research and, in this way, honor Jesse Gelsinger's memory." According to Doyle, the university has instituted steps to improve oversight and monitoring of human subject research, including strengthening its institutional review board.

The Gelsinger case brought Milstein instant fame, and punched a hole in the hype and optimism surrounding the hot new field of gene therapy. It also forced federal regulators to pay closer attention to what was happening in the clinical research world. What they discovered was startling.

A few weeks after the Gelsinger case first made headlines, the National Institutes of Health sent out a circular reminding all gene therapy investigators that adverse events and deaths must be reported. To their amazement, officials were suddenly flooded with 652 new adverse-event reports from some 80 institutions. Although they thought that Jesse Gelsinger was the first person to die as the result of a gene therapy experiment, it turned out that at least seven earlier deaths had not been reported to NIH. Further

inquiry revealed that many investigators and their corporate sponsors considered adverse events "confidential commercial information," and were reluctant to disclose them.

Public dismay over the extensive financial entanglements in the Gelsinger case triggered congressional hearings and a two-day NIH symposium on conflicts of interest. Here again, Penn was not an isolated case. Academic medical centers have long received research grants from the pharmaceutical industry. But since 1980, when Congress passed the Bayh-Dole Act, the line between academic research and business has grown increasingly blurred.

Bayh-Dole allowed universities to patent federally funded research and license campus-based inventions to private companies. The results have been dramatic. At virtually every major research university in the country, professors began launching their own start-up companies, schools invested capital and bought equity in these new ventures, and administrators eagerly awaited the next breakthrough discovery that would bring profits to the university and its researchers. Milstein calls the phenomenon "Nasdaq medicine."

Ties with industry now permeate academic institutions. The Massachusetts Institute of Technology, for example, has a five-year, $15 million collaboration with Merck & Co., which grants the firm patent rights to any joint discoveries. Dana-Farber Cancer Institute, a Harvard-affiliated teaching hospital, has a similar deal with Novartis Pharmaceuticals for research related to new cancer drugs. Harvard's Beth Israel Deaconess Medical Center recently solicited bids from 40 companies to conduct joint research at a new medical facility, where they would have first rights to any discoveries.

Academic administrators say that rising competition for research funds and limited public support make such relationships

necessary. They have a point. Today 80 percent of clinical trials are funded by private industry, not by government. Cutbacks in Medicare support for teaching hospitals and the financial limits imposed by managed care have left academic medical centers seriously strapped for clinical-research dollars. To top it off, beginning in the 1990s -- precisely when medical colleges began feeling the financial crunch -- the pharmaceutical industry started to shift a large portion of its research dollars away from academic medical colleges to an array of new for-profit research companies that contract out with physicians in private practice.

Faced with this heightened competition, some 30 academic medical colleges have recently set up centralized clinical-trial offices, modeled after those in the private sector, whose purpose is to streamline academic research, adjust to industry's faster deadlines, and win back industry grants. Marcia Markowitz, director of the Office of Clinical Trials at Penn, told an industry trade publication that "one goal [of her office] is to increase the number of trials, and thereby increase the revenue."

Heightened competition has also intensified the quest for human subjects. "The difficulty here is that the drug and device manufacturers want to get the clinical trial completed as quickly as possible," says health care industry attorney Kendra Dimond. She says companies typically obtain patents for a potential new drug before research trials begin. Those patents have 20-year expiration dates. "The longer the clinical trial, the more it eats into their ability to market the product."

The drive to speed up clinical trials has induced many companies to "replace careful patient screening practices with a crude reward system," says Vera Hassner Sharav, president of the Alliance for Human Research Protection, a nonprofit group based in New York. Industry now commonly pays doctors financial incentives ranging from $1,000 to $6,000 for each new patient recruited; top recruiters

earn somewhere between $500,000 and $1 million a year. At this year's annual meeting of the American Academy of Allergy, Asthma and Immunology, an industry representative told a group of investigators, "No longer will you get $2,500 per patient; you will get X dollars if you recruit 5 patients before week four, and if you don't, that's it and we are going to close the site."

"In a highly competitive marketplace, with few rules or guidelines governing recruitment," warned an HHS report last year, such aggressive practices "could compromise long-valued human-subject protections."

Others worry that the growing dependence on corporate dollars could erode academic autonomy and the impartiality of scientific investigators. "The boundaries between the academic medical colleges and the drug companies are becoming ever more porous," argues Marcia Angell, a former editor of the New England Journal of Medicine. "It used to be that academic medical colleges said, 'Okay, we will take this industry grant and do the study, but our researchers are going to design the study, they are going to retain the data, they are going to analyze the data.' Now this arm's length relationship has broken down."

Indeed, numerous studies indicate that industry-sponsored research tends to favor the sponsor's interests. A recent report in the Journal of the American Medical Association, for example, found that nonprofit studies of cancer drugs were eight times more likely to reach unfavorable conclusions than industry-sponsored studies.

Considering how many researchers now stand to profit from the experiments they conduct, it's not surprising that trial lawyers have begun to take notice. "Alan Milstein has found an issue that of course will resonate with a jury: 'This doctor was making money by putting the subject at risk, and he killed 'em!' " says the Rev. John Paris, a bioethicist at Boston College."

You know, it is one thing if the researcher's interest is the advancement of science for the benefit of mankind. It's a significantly less attractive proposition when the researcher has stock options in the development of the drug or technique he's testing. What Milstein is doing is sounding the alarm."

On the same day he met with his clients in Tulsa, Milstein had breakfast at his hotel with Cherlynn Mathias, the woman responsible for blowing the whistle on the University of Oklahoma's research violations.

Seated in a large pink booth, Milstein asked Mathias how her job search was going. When she alerted federal authorities to the problems at the university, Mathias instantly became an outcast in Tulsa's tightknit medical community. Unable to find work, she told Milstein, she was preparing to put her house on the market.

After the waiter brought over breakfast, Milstein got down to work, pulling a large pile of documents out of his briefcase. "What does this one refer to?" he asked, peering over a pair of black-frame glasses low on his nose. It was an office memo from Mathias updating the staff on her efforts to track down death certificates for patients enrolled in the mela-noma trial."

I was trying to pull together complete records on which of the subjects in the trial had died," Mathias began. "We didn't even know how many people were dead! I mean, that's sad."

Mathias, herself an OU graduate, had taken the job as a nurse coordinator at the university's health sciences center in the spring of 1999. At first it seemed like a dream job, she recalled, helping Michael McGee, a respected surgeon and cancer specialist, oversee the testing of an experimental vaccine for melanoma victims.

But things went wrong almost from the beginning. "On my first

day of work, I noticed they were enrolling patients who were not eligible for the study," she recalled. When she took up the matter with a colleague, she was told, "Oh, you haven't seen anything yet . . . Dr. McGee enrolls whoever he wants to in his clinical trials."

One of Mathias's central duties was to organize the medical charts for patients enrolled in the study. Mathias told Milstein she originally thought she could accomplish this by centralizing the data from various different sources. Eventually, however, she realized that crucial records -- such as reports of adverse reactions suffered by patients in the experimental program -- simply did not exist.

As her misgivings about the research program grew, Mathias said, she went directly to McGee. He assured her everything was in proper order. But reading up late at night on federal drug safety regulations, she became more and more convinced procedures were amiss. She eventually went to Thomas Broughan, chairman of the university's surgery department. He ordered an independent audit that revealed safety problems in the manufacture, distribution and testing of the vaccine that were far graver than anything Mathias had imagined. In March 2000, university officials shut down McGee's study. Still, she said, they failed to report the auditor's safety concerns to federal regulators. In his annual report, McGee falsely stated that the study was being shut down due to "insufficient staff and our inability to release adequate amounts of vaccine . . . There were no significant safety issues." A similarly misleading letter went out to former patients.

When she read the letters, Mathias said, she was so sick with concern that she consulted with her priest. She told him she was afraid that if she blew the whistle, she'd lose her job and be ostracized. "And what's the alternative?" he asked.

"I can't live with what I know," she replied.

"Well, you know what you have to do."

If Mathias hadn't disclosed what she knew to federal authorities, there's no telling whether any of the problems at the university would have come to light. The university's institutional review board, which was supposed to oversee the research experiment, was chaired by Daniel C. Plunket, a colleague of McGee's who frequently approved major changes to the study protocol under expedited review without any discussion by the full board. When 11 out of the first 18 subjects enrolled in the trial did not meet the inclusion criteria, Plunket unilaterally approved these deviations retroactively, according to a subsequent audit. "The average IRB meeting appeared to take one hour and included dinner to follow," noted one auditor. "Given the number of active protocols, safety reports, etc. processed by the chair, it is clear that no deliberative review could have taken place."

Plunket's lawyer said of these findings, "Those statements are inaccurate."

Federal authorities apparently weren't watching events any more closely. Two years earlier, an FDA inspection of the IRB found problems remarkably similar to those identified after Mathias lodged her complaint. Yet there was no federal follow-up and the violations were never corrected.

McGee's attorneys in the past have characterized Mathias as a disgruntled ex-employee whose allegations are false. Because of the pending litigation, Michael Atkinson, McGee's current lawyer, said the doctor has no comment to make at this time. "I plan to vigorously contest the lawsuit and expect Dr. McGee will be completely vindicated," said Atkinson.

The University of Oklahoma has acknowledged many of the federal government's findings but refuses to discuss the lawsuit.

Many of the top administrators involved have either resigned, retired or, like McGee, are in the process of having their tenure revoked. In a written statement, the university said it has taken corrective action, such as restructuring its IRB and establishing an education and training program for all investigators. "The university realizes that there were problems in [the melanoma] study and the oversight of the IRB and that is why we have taken the steps that we have," said Gary Raskob, associate vice president for clinical research, in an interview. "Certainly new and cutting-edge research is a key priority at our university, and in that sense we do want to grow and evolve that activity, but we feel that that has to be done in a way that first and foremost does not compromise the safety of the subjects."

Milstein's lawsuit on behalf of 18 of the research trial's patients and their families is still pending -- and Cherlynn Mathias has moved to a different state, where she works as a clinical trials auditor.

The Gelsinger lawsuit is over, but Alan Milstein and his crusade still seem to haunt the University of Pennsylvania. Earlier this year, he was a featured speaker at a conference on campus attended by prominent bioethicists, physicians, lawyers and students. Although it seemed somewhat incongruous for him to appear at the institution he had sued, Milstein was invited to speak on "litigating ethics and injury." He appeared comfortable enough -- and eager to do verbal combat. He quickly stirred things up with a blanket statement: "It's unethical to ask someone to be a martyr for science."

"If the risks are too great, then you can't do the experiment," Milstein told the packed audience. "I don't care if somebody volunteers to participate. If that experiment is too risky -- well, it is my position that the subject doesn't have the right to participate."

An audible gasp rippled through the audience. But Milstein then

went a step further, questioning whether terminally ill patients -- who make up the vast majority of the subjects enrolled in early-phase research -- can ever give truly informed consent. His skepticism is rooted in a phenomenon known as "therapeutic misconception." Researchers have found evidence that even when terminally ill patients are explicitly told that they will likely not benefit from Phase I and II research, many continue to believe the experiment will help them.

A medical student stood up to challenge Milstein. "Are you saying that . . . we cannot allow anybody to enroll in what we codify as early-phase research because by definition there is no intent for therapy?"In effect, Milstein replied, that's what he was saying.

One of those in the audience that day was Arthur Caplan, the Penn bioethicist. "There is a horrible dilemma in early-phase research," he said later. "You have to take the sickest and most vulnerable and tell them that all medicine can offer is experimentation and the chance to help others. Very few people want to hear that, and very few researchers want to say that. But Milstein believes there should be no experiments done unless there is some possibility of benefit to the subject. Most research in its early stages can't do that. If you could promise that, then you wouldn't be doing research."

Caplan agrees with Milstein that the protection system for human subjects is broken. But he believes lawsuits can only make things worse. If Milstein's approach catches on with other lawyers, Caplan warned, universities will go running to Congress shouting that "we want relief from the trial lawyers. Universities are mad about these suits. They are angry like hornets. They're all on the phone to some congressional aide saying, 'Give us relief or you are going to choke off your own golden goose, and you're going to wind up losing cures.' "Indeed, when government regulators suspended clinical research at Johns Hopkins in July following

Ellen Roche's death, Hopkins administrators lobbied hard with federal regulators and Maryland's two senators to get the suspension lifted, charging that the government's actions were "unwarranted, unnecessary, paralyzing and precipitous" and "an extreme example of regulatory excess." Within days, HHS's Office for Human Research Protections relented, allowing Hopkins to resume many of its testing programs.

Federal efforts to rein in financial conflicts in human subject research have met with a similar resistance from academia. Earlier this year, when HHS asked for public comments on a draft statement of conflict-of-interest principles, many prominent education associations -- including the Association of American Medical Colleges and the Association of American Universities -- immediately called for the proposal to be withdrawn. Rather than work within the government framework, the organizations were adamant that universities should be left to develop conflict-of-interest policies of their own.

Milstein insists he would be much less of a threat to universities if they cracked down on research abuses. So long as they don't, he says, he intends to go right on suing. In March, Milstein filed suit against the Fred Hutchinson Cancer Research Center after an investigative series in the Seattle Times reported that a failed blood cancer experiment, known as Protocol 126, was riddled with research violations and instances of improper informed consent. Officials at the center have denied there was any impropriety in the conduct of the trial and labeled the newspaper reports unfair and inaccurate.

But in pursuing the Hutch and other institutions, Milstein wants to go one giant step beyond a traditional civil lawsuit: He hopes to establish a new precedent in human rights law by invoking the Nuremberg Code as the basis for a constitutional claim in U.S. courts.

Adopted in 1949, the code was part of the verdict issued by U.S. judges in the famous "Doctors Trial" at the Palace of Justice in Nuremberg, Germany. During the trial, Karl Brandt, Hitler's personal doctor, and 22 other physicians and administrators were charged with war crimes and crimes against humanity for a series of barbaric experiments they performed on Jews, Gypsies and other targeted minorities.

Establishing Nuremberg as a legally enforceable standard of conduct for medical research is "the most interesting part of what I'm attempting to do as lawyer," says Milstein, who hopes his efforts will one day lead to a Supreme Court review of one of his cases.

Many in the medical community are duly alarmed. "Invoking the Nuremberg Code is very problematic," argues Jonathan Moreno, director of the Center for Biomedical Ethics at the University of Virginia. "The code came about under very extreme circumstances: the Holocaust. It is not at all clear that it was intended to apply to all medical research, in particular clinical research."

Moreno and other scholars believe that the code's first principle -- "the voluntary consent of the human subject is absolutely essential" -- is simply too restrictive for some kinds of research. "There are a lot of subjects who cannot give informed consent: children, people with mental disorders and dementia," he argues. "Whole groups would be ruled out of research." He and other ethicists endorse standards proposed in recent years by the National Bioethics Advisory Commission to enhance protections of human subjects. But if investigators' hands are tied too tightly, they contend, it could deter breakthroughs in areas such as drug treatment of mental illness.

Other prominent legal scholars defend Milstein's approach. "It makes absolutely perfect sense to use Nuremberg as a cause of

action in U.S. courts," says George Annas, chairman of the Health Law Department at Boston University's School of Public Health. "The provisions of the Nuremberg Code were not articulated exclusively as war crimes," Annas argues. "They are crimes against humanity, and a series of U.S. courts have already adopted the code," most recently in two federal district court rulings in 1995 and 1999.

In Milstein's view, the code's association with the Holocaust enhances rather than diminishes its value as an ethical standard. "I'm not saying that doctors who perform unethical experiments today are Nazis." Still, he insists, "I think it is important that out of the ashes of the Holocaust there is something that emerges that's going to forever change the way these experiments are conducted."

What about the fear that Milstein's ethical absolutes would eliminate most early-phase drug research? "That's not my problem," he replies. "They'll find a way to continue research."

Both the Tulsa and Seattle cases are bogged down in pretrial motions and maneuvers. But Milstein forges ahead. He has filed suit on behalf of another human research subject in the same University of Pennsylvania gene-therapy experiment that led to the death of Jesse Gelsinger. And in late October, he filed a multimillion-dollar lawsuit against BioPort Inc., the nation's sole producer of an anthrax vaccine, alleging negligence in its manufacture and testing of the vaccine and injury to U.S. military personnel who were inoculated during and after the Gulf War. BioPort has already come under heavy criticism from government regulators for chronic manufacturing deficiencies. Now Milstein's lawsuit alleges that the company neglected to inform soldiers that the vaccine "was unlicensed for use to prevent inhalation anthrax" and "no animal studies or human clinical trials demonstrated either the safety or effectiveness of the vaccine." BioPort spokeswoman Kim Brennen Root said the company had just received the suit, and

its policy is not to discuss pending litigation. She added that "we have been working over last two years to fully meet the rigorous standards of the FDA at our renovated vaccine facility. We expect that within the next four to six months we will have FDA approval."

On a frigid day in November, Milstein traveled to Lansing, Mich., to speak at a small rally of Gulf War veterans and their families. "On this Veterans Day," he proclaimed, "particularly during this time of war, America should be treating its soldiers as heroes, not as guinea pigs."

Later, speaking by phone, Milstein acknowledged that he believes the anthrax case could either help advance the cause of reforming clinical trials, or make him look like an opportunist. "I haven't figured out which," he said.

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