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BIRMINGHAM, Ala. - After Bob Lange spent eight weeks rubbing an experimental cream on the fiery patches on his body, researchers at the University of Alabama at Birmingham told him the drug was defeating the killer inside him. He felt grateful. "I believed it," he recalls. "I actually thought I might be cured."

But it was a lie. The drug had no effect on Lange's rare and potentially fatal skin cancer. And the two key people testing the drug knew it. Lange and 21 other patients were victims of fraud - a scheme made possible by the close ties between the university and the state's most prominent biotech company.

Though promoted as a cure for an incurable disease, the drug in the end produced only disgrace. Two people were convicted last year of defrauding the U.S. Food and Drug Administration. A university physician, one of the nation's leading dermatologists, was banned from testing drugs for the FDA. Investors lost an estimated \$34 million in the company, BioCryst Pharmaceuticals Inc., after the bogus data were discovered. The National Institutes of Health accused the university of poor oversight and suspended enrollment of patients in 550 studies.

Lange, a 55-year-old factory manager, worries that the judgment of those in charge was clouded by their financial stake in the outcome.

"If you can't trust the medical profession or the people creating these things to benefit humanity - if they're going to sell out for profits, who is there left to trust?" he asks.

Today, Lange's question echoes in the halls of Congress, in the pages of top medical journals and in university laboratories across the nation.

The public relies on America's medical research centers, subsidized by tax dollars, to serve as independent authorities on drugs and therapies. Like the Birmingham school, many institutions have become business partners in recent years with pharmaceutical and biotech companies, forming what critics call the "academic-industrial complex."

For patients, these alliances can speed development of lifesaving treatments. For schools hungry for research money, the payoff can be enormous: Stanford University and the University of California, San Francisco split \$270 million in income from one genetics invention, while Michigan State University earned more than \$160 million from sales of two anti-cancer drugs. The Johns Hopkins University realized how much money is at stake after it passed up a chance to patent a DNA-testing method and then watched a Bethesda company turn it into a \$100 million product.

But moving into the marketplace is radically changing American medical centers. Increasingly, they're committed both to advancing science and making money. This dual mission can threaten the integrity of medical research and the safety of patients, even at elite institutions.

Doctors at the Fred Hutchinson Cancer Research Center let a blood-cancer experiment drag on for years, even though patients were dying at a higher rate than with standard therapy. At least 20 patients died from causes directly attributable to the treatment, the Seattle Times reported this year. The center and some of its physicians had a financial stake in the treatment.

At the University of Pennsylvania, doctors ignored danger signals in a 1999 gene therapy trial that caused the death of an 18-year-old study volunteer from Tucson, Ariz. Both the physician overseeing the trial and the university held stock worth millions in a company trying to develop the therapy.

A University of Pittsburgh scientist whose research was funded by several drug companies has been accused in a lawsuit of manipulating a study of children's ear infections - contributing to the dangerous overuse of antibiotics.

And the FDA reprimanded a Tufts University researcher for improperly treating a cancer patient with a gene therapy that may have caused his tumor to double in size. Both the scientist and a Boston medical center held a large stake in the company developing the treatment.

"The market obviously is corrupting," says Dr. Steven Piantadosi, a professor at the Johns Hopkins School of Medicine. "It's corrupting at every level."

Experimenting with people is always risky and sometimes tragic. This month, a healthy young woman died after participating in an asthma experiment at Hopkins. There is no evidence, though, that the school or physicians involved had any financial interest in the study.

But the BioCryst fraud shows how research can be skewed when scientists and schools have a major stake in the outcome. It raises the question of whether the current haphazard collection of federal rules governing such conflicts of interest is sufficient to protect patients. And it demonstrates how the cozy relationship between money and academic medicine can threaten public health. If a conspirator hadn't blundered, federal officials say, a worthless cancer treatment could have slipped onto the market.

Like Lange, Marcia Houchens was told that her cancer was getting better when it wasn't. She says she was told that the experimental drug was her only hope, though there were proven alternatives. When she complained to university officials, she was told that her protests were being sent to the university president. Soon after, Houchens learned that he had resigned to become president of BioCryst.

She trusted her life to the researchers, the company and the Birmingham school, but she says all three violated that trust.

"They didn't have a right to do this to cancer patients," she says. "I am angry. I will always be angry."

### **Trial of BCX-34**

Courtly, white-haired and professorial, Dr. W. Mitchell Sams Jr. inspired confidence. Chairman of the dermatology department at the University of Alabama at Birmingham, Sams was co-author of a popular textbook and would later serve as president of the American Academy of Dermatology. He prided himself on taking time to carefully explain diseases and their treatment. Patients said he made them feel that they were in good hands.

Sams was an expert on cutaneous T-cell lymphoma, a disease that develops when a type of white blood cell turns cancerous and pools under the skin.

Blotches on the skin blush red, inflict a fierce itch, and turn as dry and flaky as cigarette paper. If the cancer advances, the blotches become raised islands and then mushroom-shaped tumors. Finally, the cancer can spread inward to the bone and vital organs, dooming the victim.

Bob Lange, a bearish man with a deliberate manner, was in his late 40s when he first saw Sams. The physician confirmed that the itchy red splotches blooming on his skin were lymphoma.

For a few years, Lange had received the standard treatment - phototherapy drugs that work in combination with exposure to ultraviolet light. It eases the pain and itching but may only hold the cancer in check. While the cancer progresses slowly in most people, there is no cure.

When Sams asked Lange to test a new cancer treatment in 1994, he was eager to try it.

The drug, called BCX-34, was the first product developed by BioCryst, a young biotech company with close ties to the university. BioCryst was co-founded in 1986 by Dr. Charles E. Bugg, a biochemist at the Birmingham school. Company officials had traded 5 percent of BioCryst's stock to the UAB Research Foundation in return for rights to university patents. Within a decade, the company was paying the university more than \$500,000 a year for research. Faculty members moved between the school and the company.

Birmingham welcomed the biotech industry. Smoke from the steel mills once choked the valley beneath the city's Red Mountain, named for its rust-colored, iron-rich soil. But U.S. Steel cut production in the 1960s as a result of tougher pollution laws and rising labor costs. The city staggered. In 1969, UAB's first president set out to turn the university into a major research center by aggressively seeking federal money and recruiting star faculty.

Just as Hopkins has come to dominate Baltimore's rusting economy, the Alabama school is credited by many with rescuing this city of 243,000.

Today, the school receives \$140 million annually in National Institutes of Health awards - 17th highest in the nation. One magazine survey ranked UAB among the top 25 universities in the country in "technological strength," a measure of the commercial impact of its work. (The nine-campus University of California system was first, Hopkins sixth.) In the 1980s and early 1990s, the Alabama school had a reputation as freewheeling and entrepreneurial.

"It wasn't a school overly burdened with strictures or rules and regulations," says David T. Curiel, now director of the gene therapy program at the university.

BioCryst regarded BCX-34 as a potential cure for a common skin disease, psoriasis, as well as the rare skin cancer. Bugg persuaded Sams, a friend, to conduct two company-funded studies - one on 22 cancer patients at the Birmingham school, the other on 40 psoriasis sufferers. He agreed to pay Sams \$2,000 a month as a consultant.

As with many drug studies sponsored by the manufacturer, the company would retain significant control. Sams provided the patients and oversaw tests. But the company designed the study and analyzed the results.

In an interview with a Montgomery newspaper, Bugg explained the difference between academic and corporate research. "University scientists find a negative result interesting," he said. "A negative result in company research can lead to a press release which drops your stock price."

A lot was riding on BCX-34. BioCryst's losses had risen from \$1.3 million in 1991 to almost \$7 million in 1994. The drug was the closest thing the company had to a product. Because cutaneous T-cell lymphoma is rare, the FDA could waive expensive large-scale tests if early studies produced striking results.

"This study was absolutely critical," Sams would later testify.

### **'Miracle' results**

That summer, Bugg asked Sams to hire Renee Peugeot, a 35-year-old nurse and the wife of Harry W. Snyder Jr., the scientist running the study for the company. Sams agreed, assigning her to help him with the study. Neither Bugg nor Sams seemed concerned that the husband and wife had a financial interest in seeing the trial succeed.

"At the time, I really didn't think anything about it," Bugg says.

When Lange arrived at the Birmingham research center that fall, he was greeted by Peugeot. She was upbeat and buoyant, Lange says, but also someone to be reckoned with, someone who gave the impression of being in charge.

Lange and 21 other T-cell lymphoma patients at Birmingham were given two number-coded tubes of cream and told to use one on a cancerous patch on the left side of their body, the other on a patch on their right. Every few weeks, the patients would come to the hospital for examinations, including measurement of their patches and other tests.

The FDA required so-called double-blind studies of BCX-34. Neither patients nor investigators were supposed to know which tubes held the drug, which the placebo. That information was recorded on "randomization schedules" that were drafted before the trial and locked up at BioCryst.

Those documents served as the keys to secret codes. No one was supposed to use those keys to see any results before the end of the trial, to guard against bias - conscious or not - in evaluating the drug's effects.

### **Unnerving doubts**

Lange sheepishly walked down hospital corridors in a drafty gown, carrying a jug filled with urine for testing. He let Sams take pictures of his thighs and buttocks to illustrate talks at scientific meetings. At one point, Sams summoned Lange to say that a test indicated he might have the virus that causes AIDS. Lange spent a terrifying night before Peugeot reported that it was a false alarm.

Lange now shrugs it off. "It was worth it to me if I could help find a cure for the disease," he says.

Marcia Houchens also signed up for the trial. Her first husband died of cancer in his 40s. Her sister died of cancer. So, when Houchens received a diagnosis of cutaneous T-cell lymphoma, she was frantic. She was referred to Sams, who she said steered her into the BCX-34 study without offering the standard treatments.

"They had me believing this was my only hope," she says.

During examinations, Peugeot and Sams had what some patients thought was the unnerving habit of disagreeing about the size and redness of cancerous patches, or lesions. Peugeot often saw

substantial improvement in the lesions where the physician saw little or none.

"She said that my lesions were gone," Lange recalls, though he could still see them. Houchens, too, was told she was cured. She didn't believe it, either.

Sams was dubious as well. But it was Peugeot's assessments that wound up on patients' charts. She even recommended BioCryst stock to Sams and others at the hospital. Sams said he didn't follow her advice.

"There was no way I would own stock in a company in which I was doing the studies," he later testified. Still, he liked Peugeot's optimistic nature. "She was always enthusiastic and always very positive. It was a breath of fresh air. It was wonderful."

Sams acknowledged that he gave his assistant "total responsibility" for the study. It was a serious breach: The principal investigator in a drug study is the person who must ultimately answer for its conduct.

If Sams trusted Peugeot, others learned not to. Dr. William J. Cook was hired from the university in September as BioCryst's medical director and Snyder's boss. Peugeot overheard Cook ask another BioCryst executive about a missing number in a patient's chart. Peugeot immediately wrote a number in. When Cook asked what she was doing, Peugeot said she recalled the figure from an examination more than a week earlier.

"Did you see what she just did?" the astonished executive asked after Peugeot left the room.

"Anybody knows you can't do that," Cook replied.

Peugeot's husband, Harry Snyder, was a respected scientist who taught at Cornell University's medical school before working in the biotech industry in Seattle. He joined BioCryst in 1993 to help run clinical trials.

More than a month before the BCX-34 studies ended in January 1995, Snyder wrote to colleagues, claiming that the drug was working, even though it was a blind study and he had no legitimate way of knowing the results. In early January, Peugeot and Snyder bought BioCryst stock, adding to their shares and options. At one point, they owned BioCryst stock and options worth \$600,000, court records show.

When Snyder's data were analyzed at the end of the trial, BCX-34 seemed to have had impressive results. The company issued a news release in early February 1995, announcing that the drug had proven highly effective in treating psoriasis and, more important, the skin cancer.

About a week later, BioCryst told the FDA that the drug had reduced or eliminated the cancer in 59 percent of the patients. The company, it appeared, had found a cure for an incurable disease.

As word spread, the stock surged - from less than \$6 a share at the beginning of February 1995 to nearly \$13 months later. One investor snapped up \$5.5 million worth of newly issued BioCryst stock.

The news about the seeming miracle drug cheered many residents of the Birmingham suburb of Mountain Brook. Birmingham's official nickname is "the Magic City," conferred when it was a 19th-century boomtown. Mountain Brook is sometimes called "the Magic Kingdom," because so many of the city's rich and powerful live there. Some were BioCryst investors.

Despite his initial skepticism, Sams boasted about the study results at a dermatology meeting in Chicago in May. That month, he urged his cancer patients to keep using the drug through the end of the year. On consent forms, Sams wrote that most patients were nearly cured and that "it would be considered medically unethical to withdraw therapy with BCX-34."

Lange, Houchens and most others lined up to get tubes of the white cream.

### **The crooked key**

In June, Cook began writing a scientific paper on the psoriasis trial and asked Snyder for the key to the results. Snyder printed out a copy of the randomization schedule from his computer. Cook sat down and did the calculations. He was stunned.

The results didn't match those announced in February.

Suspicious, Cook went to the study coordinator, who worked for Snyder, and asked for the original document, which was kept in a locked cabinet.

When Cook redid the calculations using that document, the results again were different from the February numbers. They also did not match the results from the schedule that Snyder had handed him the day before.

Cook's heart sank when he examined the cancer study numbers as well. Again, the results didn't match.

The documents combined the results from Sams' tests on 22 cancer patients in Birmingham with those from eight patients being treated by a researcher at Washington University in St. Louis.

According to the decoding document Snyder had originally provided, almost 60 percent of the skin cancer patients saw their drug-treated patches improve. About 40 percent saw no improvement, or more improvement in their placebo-treated lesions.

Cook's double-checking showed that the drug-treated lesions got better in only about 30 percent of the cases. In almost 70 percent, the placebo beat the drug or results were the same.

Cook compared the two schedules, noting the pattern of changes. In every case, the changes made the drug look better. None made it look worse.

The next day, Cook confronted Snyder, who assured him that it was all a misunderstanding. Cook kept recalculating the numbers. But they told the same story, and Snyder failed to give a satisfactory explanation.

Three days later - Father's Day, June 18 - dawned hot and sunny in Birmingham. Bugg convened a Sunday meeting of glum executives at BioCryst.

"We knew the stock was going to take a dive," Cook recalls. "We knew we'd lose credibility. It was just a devastating blow to the company."

Bugg muttered about how investors, many of them friends and colleagues, were going to get "creamed."

Snyder told the company officials he'd suspected that some patients had mixed up their tubes of

ointment, so he had scribbled several randomization schedules to see how inadvertently switching tubes might affect the study. He called these handwritten documents "what-if scenarios." Snyder said his study coordinator must have typed up his notes by accident. She would later deny it.

As Snyder talked, the BioCryst executives sat stone-faced. "It strained credibility," Bugg said later.

After Snyder left the room, Bugg turned to the group. "This guy's out of here," he said. "There's no way this guy's coming back."

The next day, BioCryst notified the FDA and the Nasdaq stock market, and issued a carefully worded news release saying that scientists had "reanalyzed the data" from the studies and concluded that there was no "statistically significant ... drug effect." The stock price, which had been nearly \$13, fell to \$8.75.

Why didn't BioCryst executives tell the FDA or the public of the fraud? Executives said they were afraid Snyder might sue.

"To accuse this guy publicly of a felony has all kinds of downsides and no upside," Bugg says.

The scheme, prosecutors said, was simple.

Peugeot and Snyder, they said, wanted to make sure BCX-34 succeeded spectacularly - possibly to get quick FDA approval, certainly to raise the value of their stock. Peugeot's job was to make sure one lesion on each patient appeared to be getting better. For example, she was supposed to outline the patches on tracing paper to record their size. At the start of the study, Peugeot traced some lesions loosely - making them appear larger. Toward the end, she drew the patches tightly, making them seem to shrink.

Afterward, Snyder's role was to forge a randomization schedule that purported to show that "shrinking" lesions had been treated with the drug.

The scheme was nearly foolproof. Adolph "Buddy" Dean, the assistant U.S. attorney who prosecuted the case, said that if Snyder hadn't blundered by giving Cook the wrong document, the fraud would never have been discovered.

"If Dr. Cook hadn't figured this out, would somebody at FDA have figured it out? I don't think so," Dean says.

Robert West, an FDA criminal investigator, says there was a real chance the drug could have been approved - with devastating effects for cancer patients. "To me, that drug did nothing more than what cold cream does."

After learning of the falsified results, Cook met with Bugg and Sams. "Do we or do we not have a drug here?" Bugg asked.

Sams said he was convinced that patients who had continued using the cream after the study were improving. He wrote a letter to the university's Institutional Review Board - the panel in charge of protecting patients taking part in drug studies - notifying it that "errors in the statistical analysis" showed a "reduction" of the drug's effect. He did not tell the board the drug's effect was zero. Neither, evidently, did the university demand further explanation of the "errors."

A company audit of the cancer and psoriasis studies, completed by October 1995, found gaping

holes in the records. Vital data, including biopsy records, was missing. Blood, urine and pregnancy tests were never performed. Over Cook's objections, Sams had left Peugeot in charge of the BioCryst studies until a month before, when he finally moved her to the hospital staff. Now she was fired.

"I trusted her," Sams later testified. "I delegated the responsibility to her."

Bugg, the BioCryst chief executive, acknowledges that the company failed to closely supervise the drug trial, in part because of his relationship to Sams.

"It's a little awkward when dealing with friends to go in like a police force and do all the things that need to be done," he said. "We did a poor job down at UAB really monitoring all the day-to-day activities."

It would take five years and investigations by two federal agencies to straighten out the mess.

## **Songs of sirens**

The FDA heard hints of serious problems with the cancer cream during a routine visit to BioCryst in late 1995. The fraud began to unravel after three agency officials showed up a few months later at the University of Alabama at Birmingham to review its records.

Later, the university's Institutional Review Board was presented with FDA audits detailing major flaws in the BCX-34 studies. It reacted timidly. It never took action against Sams and never removed him from follow-up studies. Neither did the panel notify patients of the problems.

After the initial study, Houchens stuck with the drug. Her body broke out in angry red blotches, leaving her in agony. While using BCX-34, she wasn't to take medicine to control itching.

"That's the main symptom of this disease, this horrendous itching down toward the bone," she says. "You go crazy. People just tear themselves to pieces."

After hearing about "errors" in the BioCryst trial, Houchens finally worked up the courage to ask Sams about it. He reacted angrily, she says, and told her that only the psoriasis study was flawed, not the cancer study. Later, he sent her a letter suggesting the same thing. She begged the university to guarantee her a supply of the cream.

Still, Houchens was increasingly uneasy about the conduct of the trial, especially Sams' supervision. When she called the university's Institutional Review Board, she was told that her complaint would be forwarded to UAB President J. Claude Bennett. Three months later, in December 1996, he became president of BioCryst.

The FDA's investigation escalated into a criminal inquiry. But no one looked into the failure of the university to safeguard patients in the drug trial.

That's because oversight of drug research was fragmented among government agencies with different agendas. The FDA approved new drugs, and the National Institutes of Health was charged with protecting patients' rights and safety in government-sponsored drug trials.

The two agencies have long regarded each other as rivals. The Food and Drug Administration, officials say, felt no need to share information with the National Institutes of Health. The FDA was also under pressure from Congress to speed the approval of new drugs, not bog down the process by

helping launch ethics inquiries.

Eventually, Houchens alerted the NIH's Office of Protection from Research Risks about the problems in Birmingham.

"We were always told that the BCX-34 was doing an amazing job and helping everyone," she wrote the agency. The university "has been silent on all of this disaster; not only with the 'errors' that happened during the study ... but also the blatant conflict of interest with the employees conducting the study."

At first, university officials told NIH that it was Sams' job, not the school's, to notify patients about the failed trials. But in a July 1999 letter, university officials acknowledged that they had "overlooked" doing so.

Citing a lack of oversight in the BioCryst trial and other "fundamental shortcomings," the NIH took the drastic step last year of suspending enrollment of new patients in 550 drug studies at the university. The school was forced to increase staff and take other steps that cost more than \$400,000 a year.

W. Ann Reynolds, the university's president, testified that the suspension was "one of the most incredible and most searing" incidents of her career. One of her biggest worries? She said the bad publicity had cost her school critically needed business - the testing of new drugs such as BCX-34 for industry.

Reynolds declined to be interviewed for this article. Joan F. Lorden, the associate provost for research, blamed the BCX-34 fiasco on Peugeot. "There was nothing that the university did in that case that was inappropriate," she says.

At their trial last year, Snyder and Peugeot testified that the charges against them stemmed from an innocent mix-up of the randomization schedules. But a federal jury was not convinced. It found the couple guilty of conspiracy, mail fraud and making false statements to the FDA. In August, a judge sentenced Snyder to three years in prison, Peugeot to 2 1/2 years and ordered them to pay \$26,000 in restitution. They now live near San Antonio, Texas, and have filed appeals. They did not respond to requests for interviews.

For the volunteers, the drug fraud brought false hopes and bitter disappointment. Later large-scale trials confirmed that the cream didn't work. While prosecutors say that none of the patients' cancers progressed to a more serious stage, several people suffered painful flare-ups. Lange and Houchens said they felt better after returning to standard treatments. By using an experimental treatment, they had risked letting their cancer get out of control. And they did it all for nothing.

"It was worth it to me if I could help find a cure for the disease," Lange says. "But was it worth it for me to go through that embarrassment and humiliation so Renee and her husband could get richer? No, it wasn't."

For Sams, the episode ended his career. In October 1997, the FDA concluded that Sams had failed to properly supervise the studies. It cited numerous instances of missing data, records and forms. Saying that the physician repeatedly violated FDA regulations, the agency barred him for life from testing drugs. Sams did not contest the allegations. "I felt they were all correct," he later testified. "I didn't feel I had a challenge." Sams, then 64, retired from the university.

Sams now lives on a farm near Charlottesville, Va. Friends say he was devastated by the FDA's action and has been snubbed by former colleagues. He declined to be interviewed for this article.

"I do not wish to relive" the BioCryst scandal, he wrote in an e-mail. "I hope you understand."

After he left the university, Sams wrote an article for the Journal of the American Academy of Dermatology. While he did not mention BioCryst, Sams warned that "the very soul of medicine is corroding and eroding at an unprecedented pace." He lamented the medical profession's "convenient and sometimes excessively cozy relationship to ... industry."

How did medicine go wrong?

"We let it happen. It happened slowly, by a sort of progressive creep," he wrote. "We succumbed to the siren songs of scientific advances, political power and, worst of all, financial success."