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A Medical Researcher Pays For Doubting Industry Claim

By CYNTHIA CROSSEN
Staff Reporter of THE WALL STREET JOURNAL

PITTSBURGH -- When Erdem Cantekin declared a war of ethics on the University of Pittsburgh Medical Center, he was an ambitious 42-year-old biomedical engineer with a future full of promise. He was a tenured professor, he and his wife, who was pregnant, were preparing to buy their first house, and he was director of research at a respected institute at the university.

Fifteen years later, Dr. Cantekin is broke, his career is in shambles, and he is widely known in his field as a "troublemaking whistle-blower," as he puts it. He is deep in debt to his lawyers and unable to afford a car, let alone the house he and his wife had once chosen for themselves. When he walks around the Pittsburgh campus, people who recognize him avert their eyes.

Erdem Cantekin

"I don't have any life left in this town," Dr. Cantekin says. "I am in the gulag.

Dr. Cantekin might have been nothing more than a brief sideshow in the annals of medical research, except that he is self-righteously persistent, and more important, his cause is at the center of a $3 billion-a-year industry: antibiotics for children's ear infections. Dr. Cantekin believes that in 1986, a fellow researcher at Pittsburgh, Charles Bluestone, manipulated the results of a study on children's antibiotics to benefit drug companies whose grants and honoraria he had accepted.

"It was a fraudulent study," says Dr. Cantekin, who was Dr. Bluestone's co-investigator on the project. "This isn't a question of scientific interpretation. They made certain changes to make the drugs look better." Partly as a result of this compromised research, he argues, millions of children have been taking antibiotics unnecessarily, spawning a population of antibiotic-resistant "superbugs" that threaten everyone.

Dr. Bluestone, a widely respected pediatric ear specialist, believed antibiotics were useful for the condition called otitis media with effusion, which is an accumulation of fluid in the middle ear. Lawyers for Dr. Bluestone and officials of the University of Pittsburgh, citing continuing litigation, declined to comment for this article. But in legal documents, they have repeatedly denied any impropriety in the research. At the time, there were no university or government regulations regarding private funding for research. Dr. Bluestone's paper on his research was peer-reviewed and accepted for publication by the New England Journal of Medicine. Dr. Cantekin, university officials have

maintained, was making his allegations out of "malice" because his point of view on the study had been overridden.

In the years since the two doctors split over their research, Dr. Cantekin's allegations against Dr. Bluestone have been weighed by three University of Pittsburgh committees, three panels of the National Institutes of Health, a congressional subcommittee, a federal district court and the U.S. Court of Appeals. The government, the university and Dr. Cantekin have spent thousands of hours and millions of dollars trying to sort out what happened in that Pittsburgh medical laboratory in the mid-1980s. And it isn't over yet: Dr. Cantekin has brought a whistle-blower lawsuit against his adversaries, and a trial looms.

Deadly Consequences

But as the dispute has moved slowly through these tribunals, medical science has gradually come to its own conclusions about antibiotics and ear infections -- and they are in line with Dr. Cantekin's. Although more antibiotics are prescribed today for children's ear infections -- and for longer periods of time -- in the U.S. than anywhere in the world, several recent, independently financed studies have found that for the vast majority of ear infections, antibiotics are little more effective than no treatment at all. Worse, physicians are now seeing in their own practices the potentially deadly consequences of too many children taking too many antibiotics -- drug-resistant strains of bacteria. In the past few years, some pediatricians have begun to prescribe shorter courses of antibiotics, or even to take a different tack entirely: so-called watchful waiting. If the infection doesn't clear up in a few days, then antibiotics are used.

This approach would have been anathema to the pediatricians of the 1960s and '70s, for whom antibiotics were a miracle drug. In the 1940s and '50s, it was unusual for a child to see a doctor for a simple earache -- there was little that could be done for them, and they usually cleared up anyway. But the consequences of untreated ear infections were well-known and occasionally dire. Some children suffered mastoiditis, meningitis, hearing loss and even death. Doctors and researchers suspected that antibiotics could help prevent some of these catastrophes, but there was no scientific proof.

That was the issue Dr. Cantekin and his then-mentor, Dr. Bluestone, decided to tackle in the early 1980s. The two men had met in Boston several years earlier. Dr. Bluestone, a graduate of the University of Pittsburgh and its medical school, was fast making a name for himself in pediatric otolaryngology. He has written more than 300 articles on the subject, as well as serving on government advisory boards. Dr. Cantekin, who was born and raised in Turkey, where his father was a middle-class public servant, had come to the U.S. to study at the Carnegie Institute of Technology in Pittsburgh, where he received a doctorate in biomedical engineering. In 1973, he was introduced to Dr. Bluestone, who was then working at Boston City Hospital. Dr. Bluestone hired Dr. Cantekin to help design and carry out research on children's ear infections.

In 1976, Dr. Bluestone invited Dr. Cantekin to come to Pittsburgh with him to set up the new Otitis Media Research Center. A few years later, the two men designed a large, randomized, double-blinded clinical trial -- the gold standard of biomedical research. Over five years, they would compare antibiotic treatment -- specifically, a generic drug called amoxicillin -- with no treatment at all on ear infections. Their research received a hefty $17.4 million in grants from the National Institutes of Health.

The first sign of trouble between the two investigators came in 1984, about halfway through the trial. The Otitis Media Research Center, of which Dr. Bluestone was the overall director, was then grappling with an accumulated deficit of about $300,000. Dr. Bluestone wrote letters to three pharmaceutical companies that made antibiotics for children, asking if they were interested in having their products tested alongside amoxicillin.

Eventually, several companies, including **Eli Lilly** & Co., Ross Laboratories (now part of **Abbott Laboratories**) and Beecham Group (now part of **GlaxoSmithKline** PLC), contributed about $3.4 million to support trials of antibiotics for ear infections. "If we didn't have the support of non-NIH funding, such as from pharmaceutical companies, we would not be able to complete our clinical trials," Dr. Bluestone said later in a letter to the NIH. In addition, between 1983 and 1988, Dr. Bluestone received $262,000 in honoraria and travel expenses from pharmaceutical companies whose drugs he was testing.

After adding new sponsors, Dr. Bluestone made some changes to the original study design. Looking at interim data, he concluded that amoxicillin was effective, compared with a placebo, and he created new arms of the study to compare two "boutique" antibiotics, Lilly's Ceclor and Ross's Pediazole, to amoxicillin. The newer antibiotics can cost between $30 and $70 for a course of treatment, compared with about $6 for amoxicillin.

Points of Disagreement

Dr. Bluestone's changes disturbed Dr. Cantekin, who wasn't convinced that amoxicillin had been proven superior to a placebo. The two disagreed on several items, including the study's primary end point -- the time at which the drug's effect is assessed. Dr. Bluestone thought it should be four weeks Dr. Cantekin, arguing that ear infections often recur, decided on eight. The data showed that after four weeks, a small percentage of children taking antibiotics had healthier ears than those on a placebo. But at eight weeks, the two groups had equal numbers of cures. In terms of scientific protocol, both researchers' choices were justifiable. Indeed, a panel of experts that reviewed Dr. Bluestone's research for the federal Office of Scientific Integrity found "no substantial evidence indicating willful misrepresentation or a serious deviation from commonly accepted practices."

Dr. Cantekin, however, believed that amoxicillin's efficacy was still open to question, and that the new arms of the study were therefore useless. "Every new drug has been compared with amoxicillin,' he says. "If the benchmark is only as good as a placebo, the whole thing is a house of cards." Although he himself had accepted funding from drug companies in the past, Dr. Cantekin decided to stop. He told the chairman of his department that he no longer wished to work on privately funded research.

Even then, Dr. Cantekin was one of only a handful of biomedical researchers who shunned industry funds. Since the early 1980s, connections in biomedicine between academics and drug companies have become so pervasive that a recent footnote to an article on antidepressants in the New England Journal of Medicine disclosed more than 350 financial ties between the authors of the article and pharmaceutical companies that sell antidepressants.

Many members of the medical establishment say cooperation between universities and industry is crucial, given rising research costs and the desire to attack disease swiftly and systematically. "Not to have a [public-private partnership] to study and bring to market new drugs would be a terrible thing,"

says Steve Berman, president of the American Academy of Pediatrics. "The industry budget far outweighs the government budget for some kinds of research. It's absolutely essential that industry be involved."

But such connections may have other, less visible consequences. The interlocking interests tend to protect the status quo by suppressing dissent and give the false impression that there is no doubt, disagreement or error in biomedical research. "In an environment where there seems to be a lot of uncertainty, you may not get the level of funding you want," says Edward Dangel of the Boston law firm of Dangel & Fine, one of Dr. Cantekin's lawyers. "You don't want to look disorganized."

At Pittsburgh, as at most other research universities, industry money has helped to step up the pace and rewards of innovation. For the fiscal year ended June 30, 1999, Pittsburgh received more than $36.3 million in corporate grants, about 11% of overall research funding.

While Pittsburgh was encouraging private industry to fund biomedical research, the National Institutes of Health was also unfazed by researchers commingling government and industry money. In the early 1980s, neither the NIH nor most research universities had formal conflict-of-interest guidelines. Scientists were assumed to be impervious to financial temptations, and while disclosure of private funding was required on grant applications, it wasn't considered relevant to a project's merit.

"It was common knowledge that [Dr. Bluestone] was partially supported by drug company money," said Ralph Naunton, a former official of the National Institute on Deafness and Other Communication Disorders, in a deposition. "We had Dr. Bluestone's verbal assurance that there was no conflict." (Dr. Naunton has since retired and couldn't be reached for comment.)

In 1985, with their data complete, Dr. Cantekin and Dr. Bluestone found themselves in an unusual position: Using the same statistics, Dr. Bluestone judged antibiotics useful for ear infections, while Dr. Cantekin declared the opposite. Dr. Cantekin tried to persuade other members of the research team that he was right and Dr. Bluestone wrong. Dr. Cantekin "was rigid," Dr. Bluestone told the Office of Scientific Integrity in 1989. "He only wanted it presented his way. He did not listen to anybody else. His co-authors had other opinions, and I felt their opinion was the best." So Dr. Bluestone, the study's senior investigator, wrote the official paper, and in the summer of 1986 submitted it to the New England Journal of Medicine.

Academia has conventions for scientific disagreements, but Dr. Cantekin, whose grandfathers were revolutionaries who helped overthrow the Ottoman empire, isn't a conventional man. Rather than writing a dissenting letter to the editor, he took the step that would destroy his career: He drafted a separate report of the study with his own conclusions and submitted it to the New England Journal of Medicine. Now holding two reports on the same study, the medical journal asked officials at Pittsburgh to choose one paper for publication. University officials responded by saying that only Dr. Bluestone was authorized to publish the data.

For the next five years, Dr. Cantekin's accusations were considered -- and mostly rejected -- by several panels. All three university committees exonerated Dr. Bluestone. One NIH inquiry found that while Dr. Bluestone should have been more forthright about his acceptance of private-sector funds when applying for NIH grants, his conduct was excusable. Another NIH report, however, recommended that Dr. Bluestone be placed on five years of administrative oversight for "having analyzed the data from NIH-funded research in a manner biased toward the effectiveness of the

antibiotics he had evaluated with public monies

Meanwhile, in 1989, the NIH issued its first draft of conflict-of-interest guidelines for researchers, which would have been voluntary. The proposal resulted in a storm of protest from universities and industry. Officials predicted that the requirement for scientists to divulge their financial holdings and divest themselves of stock in companies whose products they tested would cause "the U.S. biomedical industry to languish in a second-rate position," as one chief executive of a biotech company wrote to the NIH. It took six more years before the NIH produced a final draft.

In 1990, the congressional subcommittee on Human Resources and Intergovernmental Relations, which was holding hearings on misconduct in scientific research that posed public risks, excoriated both the university and the NIH for their handling of Dr. Cantekin's claims. Most troubling, the subcommittee reported, was that Dr. Cantekin's dissenting report had been, for all practical purposes, censored. "Evidence of the ineffectiveness of antibiotics would have been available to physicians and the public several years ago, if the medical school had not prevented Dr. Cantekin from publishing them," the panel noted.

But not even a congressional endorsement could rescue Dr. Cantekin from his exile in Pittsburgh, where he was still officially a member of the faculty, though his salary remained frozen at its 1986 level. He had no research projects, and he hasn't spoken to an official of the medical school for 15 years. Five times since 1986, Dr. Cantekin has arrived at his office to find a note on his door saying that his belongings had been moved somewhere else. Now he doesn't even bother to unpack his few boxes of books and papers. Nor will he turn on his office computer, which appeared mysteriously on his desk several months ago, in case his activities are being monitored. He brings his frustration home to his wife, a psychologist, and daughter, who has come to hate hearing her father talk about earaches. "My potential has been stolen from me," Dr. Cantekin says. "No one's going to hire me unless there's a revolution in the medical profession."

In April 1991, five years after the war had begun, two big events in the long-running dispute coincided. One was the publication by Dr. Bluestone's research team of another paper based on data collected during the clinical trials of 1981 to 1985. Again the team concluded that children with ear infections -- in this case, acute otitis media, or painful and inflamed ears -- "should routinely be treated with amoxicillin (or an equivalent antimicrobial drug)." A close reading of the data showed that children who hadn't received medication had a cure rate of 92.5%, compared with 96% of those who were treated.

Published in the journal of the American Academy of Pediatrics, the study became one piece of evidence for a federal panel then drawing up recommendations for the treatment of otitis media. The panel's Clinical Practice Guideline for parents stated that antibiotics "may increase chance (by about 14%) and speed of middle ear fluid going away." The panel cited the Bluestone group's study in six of eight footnotes to a chart illustrating the efficacy of antibiotic treatment. "If a government agency advises you that antibiotics are good for children's ear infections, you don't think, 'Drug companies are behind that.' But in this case, they were," says Danielle Brian, executive director of the Project on Government Oversight in Washington, D.C.

The second big event of April 1991 was that Dr. Cantekin filed a lawsuit against Dr. Bluestone and Pittsburgh in U.S. District Court in Pittsburgh. Until then, Dr. Cantekin had avoided the legal system or any consideration of a financial settlement with the university. "The first thing Pittsburgh did when they found out [Dr. Cantekin] had retained me was to dispatch a lawyer to my office with a

checkbook," says Robert Potter, a partner in the Pittsburgh law firm of Strassburger, McKenna, Gutnick & Potter in Pittsburgh. "The lawyer closed the door and asked, 'What does he want?' But for [Dr. Cantekin], it wasn't a question of money. You couldn't settle with him because you couldn't settle the scientific issue."

As his cause began to fade from public view, and antibiotic prescriptions continued to rise, Dr. Cantekin invoked the federal False Claims Act, which allows an individual to sue on the government's behalf for damages caused by another person's false claims. Enacted in 1863, the law has been used almost exclusively against defense contractors. But recently, it has also become an appeals court for academicians alleging scientific fraud against universities and scientists. If the whistle-blower's case is proved, he or she may collect as much as three times the amount of research grants that involved fraudulent claims. In his suit, Dr. Cantekin charged that Dr. Bluestone had fraudulently not disclosed his private financing in grant applications to the NIH. If the NIH had known of this drug company money, Dr. Cantekin asserted, Dr. Bluestone wouldn't have received his federal funding.

Dr. Bluestone and the university won the first legal round in 1998, when the district court issued a summary judgment in their favor. The judge, Donald E. Ziegler, noted that in June 1987, Dr. Bluestone had sent a letter to the NIH disclosing his private funding -- "a cost-sharing arrangement was implemented," Dr. Bluestone had written, adding, "but it was not explained fully." That letter nullified the claim that Dr. Bluestone hadn't told the government about his private funding, the court said. Even if Dr. Bluestone had notified the NIH on his grant applications, as he was supposed to do, there was no evidence that his NIH funding would have been jeopardized, the judge decided.

Dr. Cantekin appealed to the United States Court of Appeals for the Third Circuit, and in September 1999, he won his first major victory in the long war. "One can easily infer," the appeals court said, that Dr. Bluestone's letter, which was sent after Dr. Cantekin had lodged his complaint to the NIH, "was not an expression of an honest oversight, but an attempt to cover up prior misconduct and limit its damage."

'Material and Negative

Furthermore, two of the five members of the NIH panel that had approved Dr. Bluestone's grants said in affidavits that they hadn't known about his private funding. That information would have had a "material and negative" impact on their funding decisions, both said. Finally, the appellate court found it unlikely that Dr. Bluestone may simply have misread the instructions on the application, which asked for a list of "all research support." The court noted that for a scientist, the best of both worlds is to enjoy the munificence of private industry and a government imprimatur on their studies. "In investigating treatments that have a disputed efficacy and a high aggregate cost," the court said, "[Dr.] Bluestone can be reasonably expected to know of the government's heightened interest in avoiding bias." The appellate sent the suit back to the district court for trial, which hasn't been scheduled yet.

Conflicts of interest remain a contentious issue in biomedical research, particularly after the 1999 death of a young man undergoing gene therapy at an academic center whose director had a financial stake in the outcome of the procedure. But no one suggests that private industry, academia and the government should, or even could, disentangle themselves. As the saying goes, the only people without conflicts of interest are those who know nothing at all about the subject.

Erdem Cantekin wouldn't agree. But 15 years after having blown the whistle on what he believed was biased medical research, he has the whistle-blower's greatest regret. "If I had known the consequences would be so abrupt and severe," he says, "I wouldn't have done it."

Write to Cynthia Crossen at cynthia.crossen@wsj.com[1]

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