Conflict of Interest Eyed at Harvard

A clinical trial of an ophthalmic ointment, conducted by researchers who held stock in a company that was to market the product, is the focus of multiple investigations

THIS IS A STORY about a drug study at Harvard Medical School that went awry. Depending on one's point of view, it may turn out to be a tale of greed or one of naïvete, a morality play about what happens to researchers with stock options or a cautionary tale about the dangers of careless enthusiasm. Either way, the story takes place in an ethical no-man's land where the interests of academic science and business collide. It is the kind of case, says a congressional aide whose boss is planning to hold hearings on the affair, "that has everything."

The central character is Scheffer C. G. Tseng, an ophthalmologist who ran a clinical trial at the Harvard-affiliated Massachusetts Eye and Ear Infirmary in Boston, where Tseng tested an experimental ointment for the treatment of "dry eye" syndrome, a nasty condition caused by a diseased eye's inability to maintain a tear film.

The rub is that Tseng did his study at Harvard while owning 530,000 shares of stock in Spectra Pharmaceutical Services, Inc., a company that hoped to market the very same vitamin A–enriched jelly that Tseng was smearing onto the eyeballs of his patients. During the time that Tseng was a principal stockholder of Spectra, he published several reports on what seemed to be vitamin A's remarkable ability to reverse some of the causes of the syndrome.

Tseng's supervisor at Harvard Medical School, Kenneth Kenyon, also owned shares of Spectra and contributed to an early report on vitamin A's apparent efficacy.

To make matters more complicated and in truth more emotional, a figure whom Kenyon calls "my mentor, my father in ophthalmology" is the founder of Spectra. That man is A. Edward Maumenee, who is widely recognized as an aging giant in the field. A former director of the Wilmer Institute at Johns Hopkins, the 75-year-old emeritus professor trained both Kenyon and Tseng, and was responsible for launching Tseng on his study of vitamin A. With 1.5 million shares, Maumenee is also the largest stockholder in Spectra, as well as chairman of the board and chief executive officer.

The financial and scientific affairs of Tseng, Kenyon, and Maumenee are now the stuff of at least nine separate investigations. Indeed, ever since the *Boston Globe* broke the story in October, investigating the trio has been something of a growth industry. The story is still very much an emerging one. The investigators want to know if owning so much stock led Tseng to withhold negative data. They also want to confirm that no federal money was spent on the drug trials, and to understand how Tseng and his colleagues managed to exceed the boundaries of their approved protocol.

The Food and Drug Administration (FDA) is asking questions, as is the Massachusetts Securities and Exchange Commission. So are the University of Miami, where Tseng is now an assistant professor, and Johns Hopkins, where early studies of the ointment were run without approval from either the FDA or human studies panel at Johns Hopkins. In addition, the National Institutes of Health launched two of its own inquiries in recent weeks. In the meantime, NIH support for Tseng has been yanked and Kenyon's grant is "frozen" while the federal probes are under way. Kenyon has also taken a leave of absence from his administrative duties at the Harvard hospital, though he continues to see patients.

Daniel Tosteson: *Medical School dean expressed concern that procedures were bypassed to allow this "flawed study" to take place.*

Over the past 2 years, Harvard formally investigated Tseng and his colleagues twice. Both the faculty of Mass Eye and Ear and the university's standing committee on faculty conduct concluded that a conflict of interest had occurred after Tseng's study began. They found evidence that the researchers had deviated from the approved study design. The Harvard investigators also stated that "proper safeguards were not in place to protect the study from potential bias" and that "good scientific and accounting procedures had not been followed."

The investigators, however, also concluded that no patients were harmed. They found no evidence of scientific fraud. Nor did they see anything in the literature that begged for a retraction. Instead, they urged the prompt publication of the results of a large, multicenter, double-blind trial of vitamin A, a $2-million study paid for by Spectra but done by researchers with no ties to the company. This study, which appeared in the October issue of *Ophthalmology*, concluded that the vitamin is no more effective for most cases of dry eye than the placebo.

Supporters of Tseng say he was a young and inexperienced doctor struggling to develop a drug to help desperate patients. Tseng was proud of his ideas and did not see anything wrong with profiting from them, says Kenyon. Tseng himself is not talking to reporters, though his attorney, Robert Kasky of Hollywood, Florida, portrays his client as a "student" who followed orders. Tseng at the time had both an M.D. and a Ph.D. and was on a fellowship at Harvard.

For his part, Maumenee says: "I did nothing wrong." Maumenee has not sold any of his stock in Spectra and, in the end, may even lose some money on the deal.

Kenyon points out that he himself never made a penny. At the urging of his peers who investigated the case, Kenyon gave his stock away to the Eye Research Institute in Boston. This was a gesture that Tseng did not make. Tseng's attorney reports that his client sold most of his stock. Kasky would not say how much money Tseng made.

As for his once owning shares in Spectra, Kenyon asks: "Who doesn't own stock? Who isn't a consultant? Where's the beef?" Kenyon agrees that "mistakes were made," but believes he is being crucified for behavior that is rampant in academic medicine. "I think it is appropriate, at the moment of my academic death, for this to be an example of

how perverted and screwed up the academic system has become," says Kenyon.

The ethical no-man's land, it seems, is a place with many guidelines, but few rules. There is much confusion. Where are the lines to be drawn? How much stock is too much? "Three months ago, you might find a lot of people who had never heard of conflict of interest," says Walter Abelmann of the Harvard Medical School and a member of the university's faculty conduct committee.

Into this ethical vacuum comes Representative John Dingell (D–MI), chairman of the House subcommittee on oversight and investigations, which is interested in the story as a kind of case study on what happens when academia and industry meet. On hand to help the committee unravel the complicated story are Walter Stewart and Ned Feder, a couple of tenacious but controversial watchdogs of scientific conduct, who are on loan to the Dingell committee from NIH. Hearings are planned for February.

The case certainly has the makings of theater, even if the story revolves around tubes of mineral oil and petroleum jelly mixed with an analogue of vitamin A.

Maumenee says he had long been intrigued by the possibility that retinoic acid might restore normal epithelial differentiation in the eye, and thereby reverse the processes that kept the malfunctioning eye from secreting mucus, which is the foundation, so to speak, of the tear film. Maumenee says he encouraged Tseng in the research.

In 1983, while Tseng was doing his residency at Johns Hopkins, Maumenee tried vitamin A on a young boy from Guatemala with a severe eye disease called Stevens-Johnson's Syndrome. The physician noted dramatic improvement. In the months that followed, Maumenee, Tseng, and their colleagues at Johns Hopkins applied vitamin A to at least 20 more patients with severe cases of dry eye. Up at Mass Eye and Ear, Kenyon also administered the ointment to at least one of those early patients. Unfortunately, none of the physicians had permission to use the experimental ointment for the purposes of a study. According to Maumenee, neither the institutional review board at Johns Hopkins nor the FDA had approved the drug for use in that first group of patients.

In hindsight, Maumenee agrees with his critics that he should have sought approval, but he contends that "it is a technicality in my mind compared to letting patients suffer." Compared to the kinds of dramatic, and often irreversible, decisions that Maumenee says he and his associates make everyday in eye surgery, applying a dab of ointment seemed like a trivial exercise.

This kind of thinking was shared by Kenyon, who was responsible for supervising Tseng when he arrived at Mass Eye and Ear for a 2-year fellowship in the summer of 1984. Kenyon views vitamin A as an innocuous agent commonly used on the skin to treat everything from acne to bunions.

At Harvard, Tseng did apply to the eye infirmary's human studies committee for permission to test vitamin A in a group of patients with dry eye conditions. He also applied for approval from the FDA to begin tests of his investigational new drug.

But there were a number of problems with Tseng's clinical trial. Neither Kenyon nor Tseng had ever designed a human study before. Several sources, including Kenyon, contend the trial was a mess. First of all, Tseng was dealing with a mixed bag of patients, since "dry eye" can be caused by a number of ailments, some common, some quite rare. According to Kenyon, Tseng was having trouble sorting the patients out for the purposes of the study. The patients themselves, who were supposed to put vitamin A in one eye and a placebo in another, were confusing their symptoms.

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Tseng, too, kept changing the study design, which made it difficult to figure out whether or not vitamin A was effective. "We gained lots of experience, but not much substance," says Kenyon. This caused delays in publishing the results. "What was there to publish?" asks Kenyon. "We admit it was not a good study. So what? It was a pilot study. Why publish junk?"

The study dragged on as the number of patients grew. The protocol limited Tseng to 50 patients. During the 18-month course of the clinical trial, Tseng and his colleagues tested the ointment in at least 250 patients. Says Kenyon: "Patients started coming out of the woodwork."

It was during this time period that Tseng became deeply involved in the financial future of his ointment. In January 1985, at Maumenee's urging, Tseng asked the FDA to designate his vitamin A ointment as an orphan drug, a move which would give the drug's sponsor exclusive rights to market the product for 7 years. "It was as good, if not better, than a patent," says Maumenee.

In the middle of April 1985, the FDA ruled that Tseng's vitamin-enriched jelly was an orphan drug. A week later, Maumenee and four co-founders started Spectra with the goal of selling a line of generic ophthalmologic products, as well as the Tseng's eye ointment.

Two months later, in June 1985, a paper appeared in *Ophthalmology* by Tseng, Maumenee, Kenyon, and colleagues, detailing the early use of vitamin A in the 22 patients treated at Hopkins and Harvard. The paper gave an upbeat account of vitamin A.

The next month, in July 1985, Tseng sold the commercial rights to his ointment to Spectra for $310,000. Around this time, Kenyon and Tseng also purchased stock in Spectra at the insider's price, which works out to be about 2 cents a share, following a 530 to 1 split in stock in August 1985. Kenyon paid $1,000 for his shares, while Tseng bought in for $10,000. The following December, Spectra went public, selling its stock for $2 a share. The company quickly raised about $3 million. According to Maumenee, many of the buyers were themselves ophthalmologists.

Since then, the value of the small start-up company stock has roamed from a peak of about $8 a share, down to 50 cents a share, where it languishes now, largely a result of negative publicity and the emerging consensus that vitamin A is not much better than a placebo for most dry eye conditions.

After Kenyon and Tseng purchased their stock, they informed their department chairman Claes Dohlman. Dohlman recalls telling the two that he thought that owning stock and doing the vitamin A study posed a conflict of interest. "I urged them to divest," says Dohlman, who adds that the situation was a difficult one, for the researchers had already bought the stock when they came to see him, and that they could not legally sell their shares on the open market for 2 years because they had purchased them at insider's prices.

Dohlman says he was faced with a dilemma. If he had insisted that Tseng and Kenyon discontinue the study, the results of the vitamin A trial would not be published, and both the financial and ophthalmology community would have to wait for the results of the large, multicenter study.

In the following months, Dohlman says he became "doubly anxious" to get the clinical trial's results into press because it appeared that vitamin A was not all it was cracked up to be. Dohlman asked colleagues to review Tseng's data, which were "clean" says Dohlman, but suggested that vitamin A might be ineffective.

To "break the chain of conflict of interest" Dohlman brought in independent biostatisticans to interpret Tseng's raw data. Following a review of the study, Dohlman urged Spectra to tell the public about its discouraging results, which it did in a press

release in March 1987.

Tseng left for the University of Miami in the summer of 1986. Soon after, the medical board at Mass Eye and Ear decided it should look into Tseng's study, partly because of some irregularities in the clinical trial and partly because of "undercurrents of conflict of interest," says Dohlman.

What followed was a 9-month investigation by Mass Eye and Ear, followed by 7 months of scrutiny by the faculty conduct committee at Harvard. Details of the case, however, only appeared in public after the *Globe* got hold of the story in October.

In a November letter to the entire faculty of the Harvard Medical School, Dean Daniel Tosteson wrote: "There remains serious concerns about how the institutional policies and procedures could have been bypassed to allow this flawed clinical study and conflict of interest to proceed without existing safeguards falling into place."

When asked why safeguards did not fall into place, Tosteson says that part of the problem is the faculty's dim awareness of guidelines concerning conflicts of interest. And part "is taking them seriously."

"Harvard's conflict of interest policy was like the Magna Carta. . . . It was off in a glass box somewhere," says Kenyon.

Tseng's attorney points out that there was no conflict of interest policy in place at Mass Eye and Ear when Tseng arrived in Boston in the summer of 1984. But Harvard Medical School, where Tseng had an appointment, did have such a policy in place. Still, Dohlman admits that not many people at Mass Eye and Ear knew of its existence.

The whole affair is causing some institutions to reevaluate their policies regarding conflict of interest. Ephraim Friedman, president of Mass Eye and Ear, has recently formed a panel to consider beefing up the hosptial's policies. The University of Miami is planning its own introspection. Says Robert Rubin, vice provost for research in Miami: "I don't think we have a policy that we could point to and everybody could understand."

■ **WILLIAM BOOTH**

NIH Panel Finds No Fraud in *Cell* Paper but Cites Errors

Last June, three distinguished immunologists spent 2½ days in Boston investigating the accuracy of a paper Nobel laureate David Baltimore and colleagues had published in 1986 in *Cell*. Informal reports at the time suggested that the panel concluded that the paper contains errors but vindicated the authors of suggestions of fraud (*Science*, 15 July, p. 286).

Now, in a draft report the panel, which conducted its investigation for the National Institutes of Health, officially dismisses implications that flaws in the paper derived from fraudulent behavior. "In view of the fact that the panel found no evidence of fraud, misconduct, manipulation of data, or serious conceptual errors, the panel felt that no further action was required . . . ," according to the draft, which *Science* has obtained.

But further action there will be. For one, Representative John Dingell (D–MI), the powerful congressman who held hearings on the *Cell* paper last summer (*Science*, 1 July, p. 18) is likely to hold more hearings sometime in February. In addition, Baltimore and his coauthors do not accept all of the NIH panel's findings about inaccuracies in the paper and have written two rebuttals that run to some 30 pages. Thus, it is possible that the panel's report will be modified (or accompanied by a dissenting report) before it is officially released.

In the rebuttal, Baltimore and coauthors declare "Where the panel is critical, it has based its criticism mainly on the form of our presentation of the data. It is where the panel members would substitute their own judgment for our own that we take exception."

For example, the authors recently published a letter in *Cell* (*Science*, 2 December, p. 1240) in which they acknowledge various errors and misstatements in the original 1986 article. The NIH panel thinks they should have gone further, particularly with regard to errors in one of the paper's important tables—table 2. The panel said inaccuracies in table 2 are "sufficiently serious" to merit correction and that different data should have been presented. In their rebuttal, the authors say simply: "We disagree. It was our belief that table 2 was the best way to summarize a large amount of data in easily accessible form."

This is but one of the topics of continuing dispute. At present, the draft report and the *Cell* authors' replies are in the hands of the NIH committee which is comprised of Joseph M. Davie of Searle Pharmaceuticals, Hugh McDevitt of Stanford, and Ursula Storb of the University of Chicago. NIH officials still hope that the matter can be resolved before the end of the year. But, in any case, it looks as if the resolution may not be as clear cut as many people have hoped it would.

■ **BARBARA J. CULLITON**

"Fifth Force" Update: More Tests Needed

Physicists reviewing data from gravitational measurements taken in a hole in the Greenland ice sheet say more experiments will be needed to determine if Newtonian gravity needs modification. The comments came at last week's meeting of the American Geophysical Union in San Francisco.

Mark Ander of Los Alamos National Laboratory, team leader for the Greenland experiment, said analysis of the data shows "a strong non-Newtonian signal" that could be evidence for a deviation from Newtonian gravity. However, the data conceivably could be explained by unusual density distributions in the rock beneath the Greenland ice sheet, and members of the team differ on whether it is more reasonable to postulate such unusual distributions or to suggest that Newtonian gravity needs some fine tuning.

"Many of us [team members] feel it's stretching geology tremendously to get that distribution," Ander said, and they lean toward the likelihood of a new component of gravity, sometimes referred to as a "fifth force." Robert Parker of the Scripps Institution of Oceanography, who did new calculations to show what type of density distribution would be needed to explain the Greenland data, was the most cautious of the group. "I think the Greenland experiment is not a good candidate for evidence against Newton's Law," he said.

Richard Hughes, a theoretical physicist working with the group, said little has changed since the group announced results last summer. Analysis done since then has shown that the density distributions necessary to explain the data would be unusual but not impossible. "In my opinion, it is probably a new piece of gravity," but "all of us would say a better experiment needs to be done." A new experiment in the middle of the ocean is already under way.

Ander and Hughes were irritated by press reports they had backtracked on their earlier position. At the meeting, Hughes emphasized that deviations from Newtonian gravity are likely to be evidence of an additional component of gravity and not of a so-called "fifth force." Jokingly, he told his audience, "Read my lips: No new forces."

After an Associated Press story used that quote to indicate Hughes was recanting earlier statements on the need for a new component of gravity, he said he knew "how politicians must feel when they're quoted out of context."

"I'll never tell a joke in front of reporters again."

■ **ROBERT POOL**