Private investigations

The tortuous tale of a probe into charges of scientific misconduct levelled at a rising neuroscientist raises questions about the adequacy of US procedures to tackle the problem. Rex Dalton reports.

Four years ago, when Harvard University officials started to investigate allegations of scientific misconduct against neuroscientist Evan Dreyer, he quickly admitted fabricating some of his data. But despite this confession, the case only came to a close last November, when Dreyer agreed to an unusually heavy punishment: a 10-year debarment from receiving federal research funds.

During the investigations, Dreyer moved from Harvard to the University of Pennsylvania, and won a new federal grant. What's more, a clinical trial of a drug was initiated that relied, in part, on a further study conducted by Dreyer that was thrown into question as a result of the probe — for which government officials have never found the primary data.

Federal officials responsible for policing scientific misconduct are concerned that the case exposes serious flaws in current US procedures for investigating misconduct in biomedical research. "I think this whole event with Dreyer has opened a lot of eyes on a lot of issues," says Ron Geller, acting research integrity officer at the National Institutes of Health (NIH) in Bethesda, Maryland.

The making of a monster

Scientific misconduct has been a highly contentious issue in the United States ever since the late 1980s, when a congressional committee started to investigate allegations against scientists who had worked with such prominent figures as Nobel laureate David Baltimore, now president of the California Institute of Technology. In March 1989, the NIH created the Office of Scientific Integrity (OSI), which was given wide-ranging investigative powers.

But in the years that followed, many of the OSI's investigations failed to demonstrate misconduct — including the case in which Baltimore had become embroiled. Eventually, the federal government responded to complaints from scientists that the OSI had become an orwellian monster, and handed primary responsibility for investigating misconduct back to universities and medical centres. The revamped Office of Research Integrity (ORI), formed in May 1992 within the NIH's parent body, the Department of Health and Human Services, was limited to a supervisory role, reviewing the outcome of institutional probes and administering sanctions.

But an examination of the Dreyer case suggests that this decentralized system can leave many issues unresolved. If a researcher under investigation switches universities, for example, the new institution is likely to be kept in the dark. Investigations are also liable to drag on for years as the defendant uses a wide array of available defensive tactics. In the interim, questionable data can remain unchallenged, even as the investigation throws doubt on their veracity. And such data can continue to be used to support clinical trials on patients.

> The effectiveness of the current system ought to be the focus of concern.

The Dreyer case ended only after he had appealed against an ORI finding of misconduct. Although he finally agreed to the debarment, and conceded that the ORI could demonstrate misconduct, he refused to admit to all of the ORI's allegations regarding data fabrication, or to cooperate with the ORI's reviews of the data. Dreyer also declined to be interviewed for this article, issuing a statement claiming that "Harvard failed to conduct a good-faith investigation".

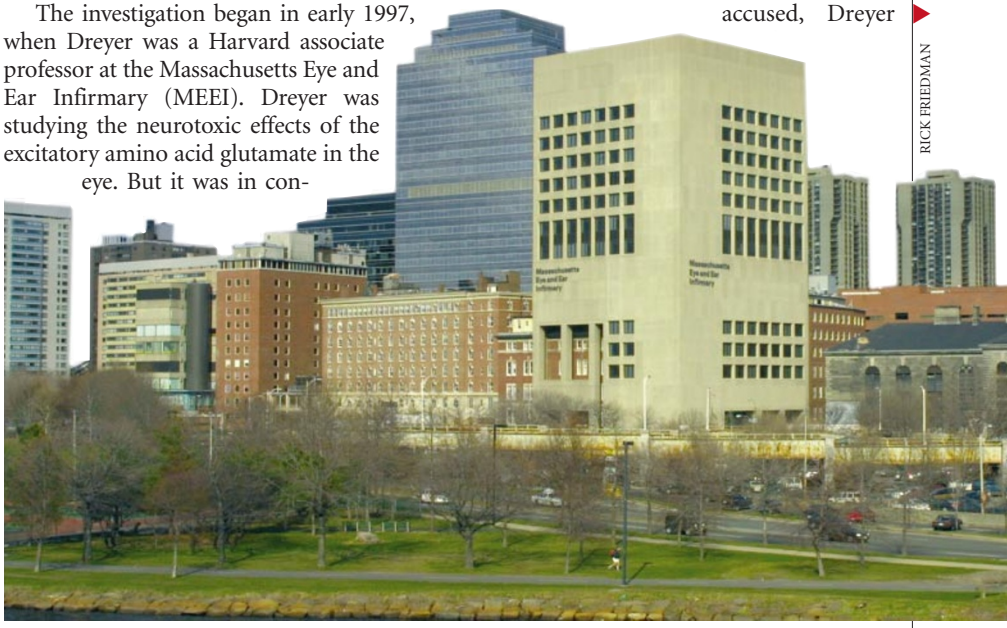
The investigation began in early 1997, when Dreyer was a Harvard associate professor at the Massachusetts Eye and Ear Infirmary (MEEI). Dreyer was studying the neurotoxic effects of the excitatory amino acid glutamate in the eye. But it was in connection with his studies of glutamate's effects in the ear that allegations of misconduct first arose. The study used guinea pigs as an animal model of Meniere's disease, a disorder of the inner ear in which a build-up of fluid causes dizziness, hearing loss and ringing in the ear.

Data discrepancies

When this study was first questioned by other MEEI faculty, Dreyer submitted a computer disk purporting to show high-performance liquid chromatography (HPLC) data for glutamate levels in guinea pigs. But analysis by other scientists at the MEEI determined that the data on the disk were probably fabricated. Shortly afterwards, Dreyer admitted to Harvard officials that he had faked the HPLC results.

University officials continued with a full investigation, following the trail of data in an unpublished manuscript, in an abstract for a meeting, and in applications for an NIH grant and an award for mentoring junior scientists. Dreyer then began an aggressive defence. Deviating from his original confession, he accused a co-worker of faking the HPLC data, and claimed that the investigation was in retaliation for his attempts to expose alleged fraud in billing for surgery by other MEEI faculty. Harvard officials found that both allegations were without merit.

Then, three months after being accused, Dreyer



RICK FRIEDMAN

Under scrutiny: the misconduct probe rocked Harvard's Massachusetts Eye and Ear Infirmary.

announced that he was leaving Harvard to assume an appointment as co-director of the glaucoma service at the University of Pennsylvania's renowned Scheie Eye Institute in Philadelphia. The confidentiality of Harvard's probe into Dreyer meant that Pennsylvania officials were not informed of the misconduct allegation when they hired him.

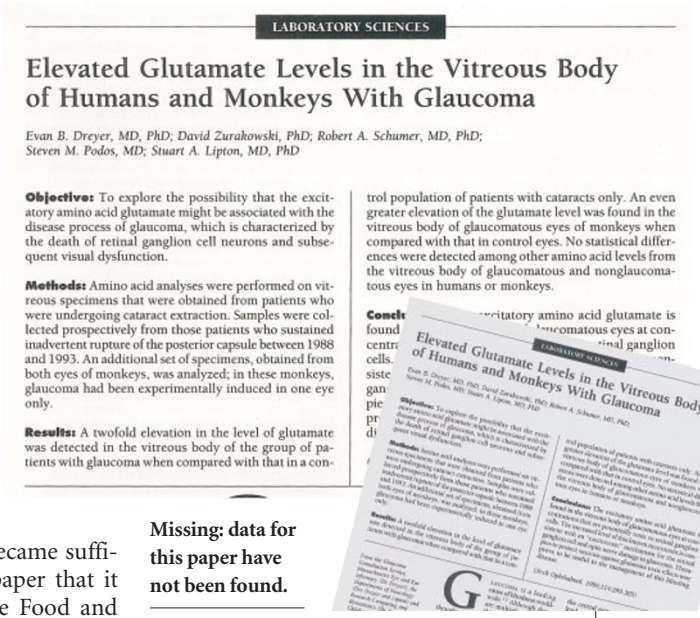
Highly recommended

Robert Barchi, provost of the University of Pennsylvania, says that its hiring procedures did not include questions that would have required Dreyer to reveal whether he was the subject of a misconduct investigation. Dreyer was given "extraordinarily positive" recommendations by eight neuroscientists nationally, Barchi told *Nature*, including two from Harvard.

In August 1998, just over a year after Dreyer had moved to Pennsylvania, Harvard completed its investigation and concluded that he had fabricated data. But Dreyer was uncooperative towards the subsequent ORI inquiry, which as a result took until April 2000 to complete, reaching the same conclusion. In the interim, Dreyer sued the MEEI over the alleged surgical billing fraud, only dropping the case at the final settlement of his appeal against the ORI ruling last November.

Two weeks before the April ORI ruling, Dreyer obtained a new NIH grant — a five-year award totalling more than $1.25 million — for research on the role of excitatory amino acids in glaucoma, in which a build up of fluid in the eye damages the optic nerve. According to the confidentiality rules under which the ORI operates, the NIH officials handling the grant application were not aware of the misconduct investigation. So when the ORI delivered its verdict, they were faced with awarding a grant to someone who had already been found guilty of misconduct by a leading research university. The officials then worked out a deal with the Pennsylvania authorities to shift the funds to another researcher, Alan Laties, on the understanding that he would check the data underlying the grant application before proceeding with the work.

This checking was deemed necessary because the Harvard investigation had also recommended an internal administrative review of other research data, which Dreyer and co-authors had used to publish an article on glutamate exacerbating glaucoma in humans and monkeys (*Arch. Ophthalmol.* **114,** 299–305; 1996). Primary HPLC data for this article have never been found, say federal officials familiar with the case.



LABORATORY SCIENCES

Elevated Glutamate Levels in the Vitreous Body of Humans and Monkeys With Glaucoma

Evan B. Dreyer, MD, PhD; David Zurakowski, PhD; Robert A. Schumer, MD, PhD; Steven M. Podos, MD; Stuart A. Lipton, MD, PhD

Objective: To explore the possibility that the excitatory amino acid glutamate might be associated with the disease process of glaucoma, which is characterized by the death of retinal ganglion cell neurons and subsequent visual dysfunction.

Methods: Amino acid analyses were performed on vitreous specimens that were obtained from patients who were undergoing cataract extraction. Samples were collected prospectively from those patients who sustained inadvertent rupture of the posterior capsule between 1988 and 1993. An additional set of specimens, obtained from both eyes of monkeys, was analyzed; in these monkeys, glaucoma had been experimentally induced in one eye only.

Results: A twofold elevation in the level of glutamate was detected in the vitreous body of the group of patients with glaucoma when compared with that in a control population of patients with cataracts only. An even greater elevation of the glutamate level was found in the vitreous body of glaucomatous eyes of monkeys when compared with that in control eyes. No statistical differences were detected among other amino acid levels from the vitreous body of glaucomatous and nonglaucomatous eyes in humans or monkeys.

Missing: data for this paper have not been found.

In January 2000, the ORI became sufficiently concerned about this paper that it notified both the NIH and the Food and Drug Administration (FDA). The FDA was informed because ORI officials believed that the paper had been used in support of a clinical trial of a drug called memantine being undertaken by Allergan of Irvine, California. Memantine appears to be protective against glutamate's neurotoxic effects, and has been used in Germany for some time to treat dementia.

With Dreyer gone from Harvard and being uncooperative, the university's administrative review never got off the ground. Laties says that he was not informed of Harvard's concerns regarding missing data for the glaucoma paper, either directly or through his superiors at the University of Pennsylvania. And although ORI and FDA officials did meet to discuss the matter, it remains unclear what happened as a result — commercial confidentiality means that FDA officials cannot discuss the issue.

In an interview with *Nature* in December, Larry Wheeler, Allergan's chief scientific officer, said that no one from the FDA had ever contacted him about the missing data. He referred inquiries to neuroscientist Stuart Lipton, senior author on the glaucoma paper. Lipton, formerly of Harvard but now at the Burnham Institute in La Jolla, California, is named with Dreyer as inventor on a patent for using memantine to treat glaucoma. Lipton says the questioned data are Dreyer's responsibility. Lipton told Harvard officials in October1998 that he did not have the primary data. But unless someone makes a specific allegation of scientific misconduct regarding data in the glutamate/glaucoma paper, Harvard's probe will go no further.

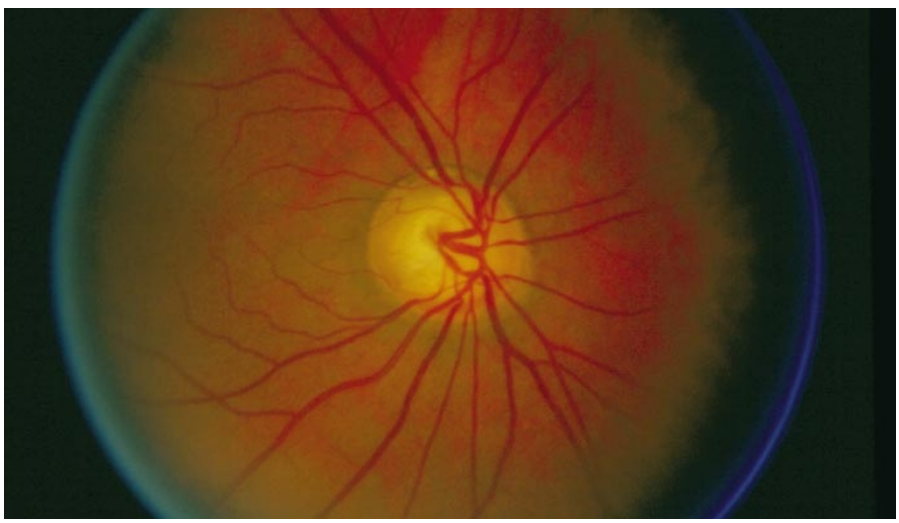
Wheeler says that the ongoing clinical trial is underpinned by several animal studies. But the paper co-authored by Dreyer and Lipton is regarded as the seminal publication linking glutamate with glaucoma in humans.

Wiley Chambers, an official at the FDA's eye-drug evaluation centre, says that the glutamate/glaucoma paper will be subjected to closer scrutiny if Allergan seeks approval to use memantine as a treatment for glaucoma after its trials are complete. Again, because of commercial confidentiality, the FDA will not discuss its decision to let the trial go ahead.

Scientists and some university administrators are now expressing concerns about the costs involved in conducting misconduct investigations, which they would like the government to share. When extensive reviews of data are required and the accused scientists are uncooperative, the costs can spiral.

To the federal officials who monitor misconduct cases, these complaints are frustrating — particularly as they are coming from many of the same people who previously lobbied against the centralized OSI system. Pointing to the loose ends left hanging by the Dreyer case, they argue that it is the effectiveness of the current system, rather than its cost, that ought to be the focus of concern. ■

Rex Dalton is *Nature*'s West Coast US correspondent.



STANFORD EYE CLINIC/SPL

One in the eye: glaucoma can be diagnosed by observing the retina.