But others say Fleming's position sidesteps the reality of AIDS drug development today. "It's allowing people to get sick," says Schooley. "A lot of times people sanitize things. It's more acceptable to say that they're doing things for humanity. It's the licensing gap, and you could drive a truck through it," says Schooley.

Richman thinks opponents of surrogates often fail to appreciate the magnitude of the changes seen in viral load and CD4 levels with today's treatments. "All this talk of HIV and CD4 being surrogate markers, that has always bothered me," says Richman. "They are not surrogate markers. They are the measurement of the disease."

Some researchers have strong faith in the virologic marker, but worry about relying on it too heavily. "At the ACTG, we have a number of very important studies with virologic end points," says the University of Alabama's Saag. "All of them will end in 24 to 48 weeks. What are we going to have when that's all over? Highly active regimens that lead to undetectable virus in 90% of patients. What do we do with that in practice? How do we know strategically when to employ one over the other?"

Saag suggests that it would be more useful to do a clinical end-point trial that mirrors the way people take drugs in real life. "In my ideal scenario, it doesn't matter what regimens they are getting," says Saag. His idea, which he calls "Strategic Timing of Antiretroviral Therapy," or START, is to offer patients a menu of treatment options, and to switch to a different regimen whenever the viral load increases above a certain cutoff—a strategy he acknowledges could lead to one very long trial.

As yet, Saag has won few converts, though. Lange, for instance, counters that it matters greatly how you drive HIV down: As soon as your viral load goes up, you have developed resistance to at least some of the drugs on that regimen, he says. Consequently, he says hitting HIV as hard as possible right away will prolong the use of all of the drugs in a given regimen. Many ACTG leaders share Lange's view, and Saag's START idea was rejected at an ACTG meeting last month. They instead hope to analyze the clinical outcome of all of their trials collectively in a giant matrix.

Harvard biostatistician Victor de Gruttola, who collaborated with Saag on the START idea and is working with colleagues to develop a computer model that can analyze anti-HIV drug options in different patient populations, is disappointed by the ACTG's decision, but allows that the matrix idea might yield useful results. "The whole thing is just in chaos right now, but hopefully it's creative chaos," says de Gruttola.

–Jon Cohen

SCIENCE AND COMMERCE

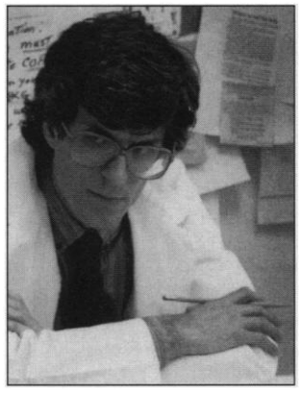
Publishing Sensitive Data: Who Calls the Shots?

A rash of events in the past few days has thrown a spotlight on the tensions that can arise between science's tradition of open publication and industry's penchant for secrecy. The following articles detail two cases of alleged suppression of unfavorable research findings, a survey indicating that a substantial fraction of researchers in the life sciences have delayed publication or withheld results and materials from colleagues, and a dispute among the top medical journals over rules to guard against conflict of interest in medical publications. But a story on page 527 suggests that not all university-industry interactions are so fraught with problems.

Secrecy Dispute Pits Brown Researcher Against Company

Faculty members at Brown University are in an uproar over what appears to be a classic industry-academic research conflict. At the center of the furor is David Kern, an occupational health physician who claims that his research on an outbreak of lung disease at a local textile plant is being suppressed by a Brown-affiliated hospital and the plant's owner—and that his clinic was closed in retaliation.

Kern, who is employed by the Memorial Hospital of Rhode Island in Pawtucket and is an associate professor at Brown's School of Medicine, conducted the research as a consultant to the textile company. (The parties involved would not reveal the company's identity, but *Science* has learned that it is Microfibres Inc., of Pawtucket, Rhode Island.) Company officials insist that the research is too premature to publish, and Memorial Hospital officials—who deny that they closed Kern's clinic in retaliation—say Kern cannot make his findings public because he is bound by a confidentiality agreement that he signed with the company. Now, the medical school too has been drawn into the dispute: Last week, some of Kern's colleagues both inside and outside the university urged administrators to stand behind Kern over what they see as an issue of academic freedom, and the school has launched an inquiry.



Center of the storm. Memorial Hospital's David Kern.

This tangled saga began last spring when Kern—then Memorial's chief of general internal medicine and head of its Occupational and Environmental Health Service since 1986—examined a young man from the plant. Both the man and another plant employee Kern had examined a year earlier had symptoms of interstitial lung disease (ILD), an inflammation of the alveoli that can lead to permanent scarring and reduced breathing capacity.

When Kern learned that a similar outbreak had occurred at the company's Ontario plant in 1990, he alerted the National Institute for Occupational Safety and Health (NIOSH) and offered to probe the outbreak as a paid consultant to the company. Microfibres agreed and asked Kern to sign a confidentiality agreement to protect the company's "trade secrets." Kern says he found six more employees at the 150-employee plant with what he considers work-related ILD—a far higher incidence than expected, he says, as the disease's incidence in the general population is one in 40,000. But he was unable to link these cases to any specific chemical or airborne material at the plant.

Last October, when Kern showed company officials a draft abstract on the outbreak, prepared for the May 1997 meeting of the American Thoracic Society, he says the company threatened to sue him for breaking the secrecy agreement if he submitted the abstract. Kern then broke off the consultancy agreement—and went ahead and submitted the abstract anyway, because, he says, it does not identify the company and includes no proprietary information. Moreover, a brief report on the outbreak itself, co-authored by Kern and staffers at NIOSH—which also does not identify the company by name—is currently under review in the *Morbidity and Mortality Weekly Report*, published by the Centers for Disease Control and Prevention, NIOSH officials say.

Kern insists that company officials knew he planned to publish his research when his consultancy began and only balked when he turned up additional cases of ILD. But offi-

cials at Memorial Hospital and the Brown medical school apparently also considered Kern's abstract to contain confidential information. Peter Shank, associate dean for research at the medical school, last November advised Kern to withdraw the abstract for that reason, says Dean of Medicine Donald Marsh. And in a 23 December memorandum obtained by *Science*, hospital president Francis R. Dietz ordered Kern to do so, saying its publication "could seriously jeopardize or compromise legal obligations you have and the Hospital has under the [confidentiality] Agreements." Dietz also wrote in the same memo that Kern's Division of Occupational Health was terminated "effective immediately," and that "Memorial Hospital does not wish to remain in the environmental and occupational health business in the future."

This memo "clearly indicates the hospital's position" today, says Memorial's Rick Dietz, head of marketing and development and son of hospital president Francis Dietz. Noting that Kern's sole staff member in the clinic, an industrial hygienist, resigned last December (for unrelated reasons), Dietz told *Science* that the decision to close the clinic "had nothing to do with any conditions with our clients," but was based on "staffing issues" and the quality of the program.

Microfibres officials acknowledge in a written statement to *Science* that there are "several cases of associates at Microfibres' Pawtucket, RI, plant experiencing shortness of breath and cough." But the statement says company officials have "a point of professional disagreement with Dr. Kern." It says: "To date, no definitive cause for the cases at the Pawtucket plant has been confirmed. Microfibres believes it is premature to release the information."

Kern is still planning to present his work at the 16 to 21 May meeting in San Francisco. His employment contract with Memorial lasts 3 more years, but he says he hopes to rebuild his clinic—the only facility where Brown medical students could train in occupational medicine—at another Rhode Island hospital.

Many Brown faculty members call Kern's predicament a stark case of the tension between the tradition of openness in research and industry's desire for secrecy. "It's a fairly clear infringement of [Kern's] academic freedom," says Harold Ward, a professor of chemistry and environmental studies at Brown and one of several faculty members who met last week with Brown administrators. "And the result of that infringement has been an attempt to suppress information on what appears to be a significant occupational health risk."

The furor has prompted Marsh to appoint a special committee of inquiry made up of faculty members and administrators. It is expected to recommend this week how the school should respond to Kern's case.

–Wade Roush

Conflict over conflict. *The Lancet*, and *Epidemiology*, don't see eye to eye with *NEJM*.

Journals Joust Over Conflict-of-Interest Rules

A peppery exchange of letters and editorials in the world's top medical journals this week reveals that the editors of these elite publications disagree sharply about how to handle their authors' conflicts of interest. On one side is Boston's venerable *New England Journal of Medicine* (*NEJM*), upholding a tough policy that requires full disclosure of authors' financial interests and bans editorials by anyone with a financial stake in the subject being discussed. On the other side are *Epidemiology* of Newton, Massachusetts, and *The Lancet* of London, both of which argue that it is wrong to screen authors based on financial interest, and that modest requirements for self-disclosure are adequate.

The jousting over conflict-of-interest policy has been going on for years, mostly behind the scenes. But it burst into view this week with the publication of a letter to *The Lancet* (19 April) signed by Marcia Angell, *NEJM*'s executive editor. Angell writes that "*The Lancet* was sleeping on the job when it neglected to inform readers" of what she regards as a "conflict of interest" involving authors of an article in the 15 February *Lancet*. She lights into the article itself, which described the use of markers for autoimmune disease to monitor women who have had breast implants, claiming it suffered numerous technical flaws. Angell goes on to note that the authors, Scott Tenenbaum of Duke University and a colleague at Tulane, Robert Garry, share in royalties earned by Tulane every time the test they devised is used.

The authors respond in the same issue that Angell's attack "serves no scientific purpose," and note that they gave *The Lancet*'s editor, Richard Horton, a detailed financial disclosure statement long before their article was published. *The Lancet* did not publish the disclosure initially, but added it to Tenenbaum's response this week. Similar disclosures follow each of six other comments on the Tenenbaum study, including Angell's. She is identified as the author of a book, *Science on Trial*. It is a razor-sharp attack on those (like Tenenbaum) who support the notion that breast implants may have caused systemic autoimmune disease.

Horton also takes up the pen himself in the same issue to defend *The Lancet*'s policy. He writes that some people "have worked themselves up into something of a frenzy about conflicts of interest," and suggests that the *NEJM*'s editors are among those who have gone too far. It is easy to run afoul of rules that are too rigid, he suggests. In a swipe at Angell, Horton writes that "Even editors can inadvertently run into danger." Horton says that Dow Chemical Co., a maker of silicone breast implants, cited Angell's criticism of Tenenbaum and exploited "the authority of the *NEJM*'s name" in a company press release on 12 March. "The only way to minimize bias," Horton concludes, "is to allow maximum dialog from all parties, irrespective of their interests."

Horton denounces what he calls the move toward "censorship" in denying authors editorial space because of potential conflicts of interest, and he argues instead for voluntary disclosure of conflicts. For support, he points favorably to a discussion appearing in the May issue of *Epidemiology*. Harvard endocrinologist JoAnn Manson describes how she was subjected to "an emotionally distressing ordeal" in the media after editors at *NEJM* identified her and another author as having violated *NEJM*'s conflict rules last year. She had written an editorial in *NEJM* favoring a weight-loss drug even though she had briefly served as a consultant to a manufacturer of the drug.

Manson insists that she fully disclosed her consultancy to *NEJM*'s editors in advance, but that they misinterpreted what she told them. The result, writes Kenneth Rothman, *Epidemiology*'s editor, was that Manson was "pilloried" in a kind of "editorial police action" by *NEJM*. If this policy were widely adopted, Rothman writes, it would encourage ad hominem evaluations of research and stifle free expression of ideas. He advocates a "non-policy regarding conflict of interest."

Neither Angell nor *NEJM* Editor-in-Chief Jerome Kassirer was available to comment. But in written statements, they have endorsed an uncompromising policy: "Because editorials involve interpretation and opinion," they wrote last October, "we require that authors be free of financial associations ... with a company that stands to gain from the use of a product (or its competitor) discussed in the editorial."

–Eliot Marshall

Secretiveness Found Widespread in Life Sciences

Some scientists have long griped that commercialism and competition are destroying the once-congenial atmosphere of U.S. academic labs. Such complaints are usually based on anecdotal information about data hoarding and publication delays that occur while researchers secure their intellectual-property rights. It has been hard to know just how widespread such behavior is. Now, a survey published in the 16 April issue of *The Journal of the American Medical Association* (JAMA) may help define the scope of the problem. It suggests that secretiveness is indeed intruding in the life sciences, particularly where competition is hot—as it is in the field of genetics.

The survey, conducted by a health-policy group led by David Blumenthal at the Massachusetts General Hospital, found that almost 20% of the 2167 academic life scientists who responded to a questionnaire said they had delayed publication of data by more than 6 months. Their reasons were often linked to commercial stakes: 46% said they needed time to prepare patent applications, 33% said they had to protect intellectual property in some other way, 31% were trying to keep ahead of competitors, and 28% reported they had to "slow dissemination of undesired results." When the survey writers drafted this last question, Blumenthal says, "we had in mind something like the thyroid-study event," in which a company sought to block the release of data (see next story). But the question was left vague to cover self-censorship as well as sponsor-imposed delays.

Geneticists, Blumenthal found, were more likely than others to delay publication of data. Among a group of 595 researchers identified as being in the field of genetics, 22% reported that they had delayed publication of results for more than 6 months, as compared to 19% of other respondents. And 14% of the geneticists (compared to 6% of others) said they had refused to share research results with a colleague. Blumenthal zeroed in on genetics, he says, because his study was funded by the National Human Genome Research Institute (NHGRI), a leader in studying ethical issues in genetics research. "We didn't want to single genetics out for criticism," Blumenthal says. "It's just that genetics [and NHGRI] may be out in front in identifying the problem."

NHGRI's director, Francis Collins, told *Science* that he found one aspect of the study "troubling." The summary in *JAMA* seemed to imply that people funded by the genome project were likelier to withhold information than others were. That's not so, claims Collins. In fact, "Early release of data has become the cultural norm for NHGRI grantees," Collins says, "and we like to think that we are setting a standard here." NHGRI is unlike other agencies in the National Institutes of Health in that it requires grantees to publish data within 6 months of completing the research. And it goes even further for recipients of large DNA-sequencing grants: They must release DNA information to the public within days of generating it.

Blumenthal says the study may point to the need for even stronger action to get NHGRI's message across. "We may need to alert universities and departments of genetics," says Blumenthal, "that they should set a tone that encourages data sharing rather than data withholding."

–Eliot Marshall

WHY RESEARCHERS ARE SECRETIVE

Reasons for delaying publication	Percent
Allow time for patent application	46
Protect the proprietary or financial value of the results (other than by patent applications)	33
Protect the investigator's scientific lead	31
Delay the dissemination of undesired results	28
Allow time for license agreement	26
Resolve dispute over the ownership of intellectual property	17

Reasons for withholding data and materials from academics	Percent
Protect scientific lead	46
Too expensive or scarce	27
Informal agreement with a company	18
Protect the financial interest of the university	6
Formal agreement with a company	4
Protect my own financial interest	2
Other	45

SOURCE: D. BLUMENTHAL *ET AL.*, *JAMA*

Holding back. Of 2167 life scientists surveyed, 410 said they had delayed publication and 181 admitted not sharing data or materials. Their reasons (some gave more than one) varied.

Long-Suppressed Study Finally Sees Light of Day

Last week, a paper claiming that generic thyroid drugs are as effective as their brand-name counterparts finally appeared in *The Journal of the American Medical Association* (JAMA)—almost 7 years after a drug company that sponsored the research first raised objections to the findings and later tried to suppress their publication. The authors claim that 8 million Americans could save as much as $365 million a year by switching to the cheaper generic versions of the drug. Beyond the findings, experts say, the paper's tortuous route to publication reflects the potential pitfalls of commercially sponsored research for researchers, universities, and the companies themselves.

The study explored whether different brands of the thyroid drug levothyroxine, a synthetic version of the hormone thyroxin, affected patients differently. Boots Pharmaceuticals of Lincolnshire, Illinois, the maker of Synthroid, the oldest and most prescribed synthetic version of the drug, agreed to finance a study by University of California, San Francisco (UCSF), pharmacy professor Betty Dong to test Synthroid against a rival brand called Levoxine (now called Levoxyl) and two generic brands. Twenty-two women whose thyroids were damaged or had been removed received each drug for 6 weeks at a time in random order, and the researchers measured blood levels of thyroid hormones throughout the treatment. Dong and her team found that although hormone values fluctuated, there were no discernible differences among the four preparations. They concluded that for most patients, the generic drugs were just as effective as Synthroid.

When Dong shared the results with Boots officials in 1990, she says they charged that the study was seriously flawed, and complained to the university's chancellor, vice chancellors, and several department heads. But UCSF investigators found only minor, easily correctable problems, says Leslie Benet, a pharmacokineticist and chair of the biopharmaceutical sciences department at UCSF who helped mediate the dispute between Boots and Dong. At least two separate teams of university investigators found no reason not to publish, he says, and so the researchers submitted their manuscript to *JAMA*. Five referees—some with ties to Boots—found the paper acceptable, says *JAMA* Deputy Editor Drummond Rennie, and after what Rennie terms minor revisions, the *Journal* scheduled the paper for publication on 25 January 1995.

Less than 2 weeks before publication, however, the UCSF lawyers asked Dong to withdraw the manuscript, says Benet. The contract Dong had signed with Boots at the beginning of the study stated that the data could be published only with the company's permission. Dong admits it was naïve of her to sign such a contract, but she says she expressed her concerns to a now-retired UCSF lawyer and he told her the university could probably argue around the clause. But by 1995, the university had a new lawyer who said the contract was binding and that UCSF would not defend the authors if they were sued.

Benet says it would not have been in the company's best interests to sue, but when the university refused to back the researchers, they had little choice but to withdraw the paper. The university "fell down on its responsibility" to its faculty and to the public, says Benet.

Meanwhile, scientists at Boots published

their own analysis of the study data in a new journal called *American Journal of Therapeutics*, where senior author Gilbert Mayor was an associate editor. The paper, entitled "Limitations of Levothyroxine Bioequivalence Evaluation: Analysis of an Attempted Study," did not acknowledge any of the UCSF researchers. Boots representatives told *Science* they offered to include Dong and her colleagues as coauthors, but the researchers declined. Dong says she does not recall such an offer.

Benet says he was still trying to persuade Dong to publish her original paper when *The Wall Street Journal* ran a front-page article last April detailing the saga (*Science*, 26 July 1996, p. 411; and 27 September 1996, p. 1783). After the ensuing media storm, Knoll Pharmaceuticals of Mount Olive, New Jersey, which bought Boots in 1995, agreed to let *JAMA* publish the paper. Company spokesperson Linda Mayer says although the company still claims the study is flawed, "when the *Wall Street Journal* article came out a year ago, it took on a life of its own." She says Knoll is "pleased that the study is now published, so it can be thoroughly evaluated."

Experts say the study is unlikely to be the final word on treatment. "This is an additional study," says endocrinologist E. Chester Ridgeway of the University of Colorado Medical Center, "that is now in a list of publications, some in favor and some against."

But the lessons for researchers involved in industry-supported research are more clear-cut, says Dong. "I'm more cautious in negotiations with anybody," she says. "We've learned that these things really can happen." *JAMA*'s Rennie, who wrote an editorial accompanying the paper, agrees. "When industry gets in bed with academia," he says, "their agendas and their backgrounds are so different that you'd better be damn careful that you don't end up with suppression of unfavorable results or—worse—dangerous results."

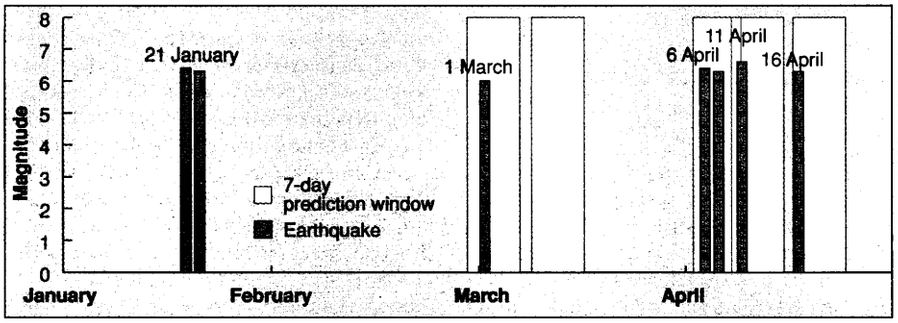
–Gretchen Vogel

EARTHQUAKE PREDICTION

Warnings Precede Chinese Temblors

BEIJING—It doesn't rain much in parts of far northwestern China, but when it comes to earthquakes there, it can pour. During the past 3 months, seven magnitude-6-plus quakes have rocked Jiashi County in China's Xinjiang Uyghur Autonomous Region. But while spates of earthquakes are nothing unusual in that part of China, what's new is that Chinese scientists made four predictions of time and magnitude, and three were apparent successes. Their insights prompted wholesale evacuations as little as hours before the earthquakes and protected thousands of lives.

China has spent the past 30 years trying to identify reliable precursors of impending earthquakes. A new test of these prediction skills began on 21 January, when two quakes struck Jiashi 1 minute apart, registering at magnitude 6.4 and 6.3, according to Chinese seismologists. (Magnitudes calculated by the USGS National Earthquake Information Center in Golden, Colorado, from distantly recorded seismic waves run about 0.5 units lower.) Neither quake was predicted. When another magnitude 6 hit on 1 March, it was obvious that a swarm of quakes could be under way like the one that shook an area 90 kilometers to the west in April 1961, notes Zhang Guomin, deputy director of the Center for Analysis and Prediction of the State Seismological Bureau (SSB) in Beijing. That seismic record, the recent quakes, and the public's heightened awareness of the threat emboldened scientists at the Xinjiang Seismological Bureau in Ürümqi to begin making "imminent predictions," explains Zhu Lingren, director of the Xinjiang bureau.



Mixed record. Chinese seismologists made "imminent predictions" before some earthquakes in a swarm, but they missed the start and cried wolf once.

Western researchers are intrigued but puzzled by these reported successes. "It's wonderful that they were able to evacuate and save lives," says Lucile Jones of the U.S. Geological Survey (USGS) in Pasadena, California, "but there isn't enough information to say whether they have a better understanding of the potential for earthquake prediction than what we already have." U.S. seismologists have not yet successfully made an official prediction (*Science*, 19 February 1993, p. 1120), and the technique the Chinese relied on—extrapolating from ongoing seismic activity—has yielded few consistently reliable results in the West. Still, Jones is eager to learn more. "We hadn't heard anything about Chinese earthquake prediction since China opened up."

Predicting the next quakes boiled down to deciphering the pattern of ongoing seismicity. For example, following three magnitude-4 quakes between 1 and 4 April, Xinjiang seismologists took the ensuing quietude as a sign that stress was still building up and would soon be released in a larger quake. So, late on 5 April, they predicted that an earthquake between magnitudes 5 and 6 would strike within a week. During the night, authorities evacuated 150,000 people to shacks and canvas shelters. Early the next morning, a magnitude-6.4 quake occurred, and at noon a magnitude 6.3 struck. Together, they destroyed 2000 houses and severely damaged 1500 more, but no one was killed. Similarly based predictions preceded a magnitude-6.6 quake on 11 April and a magnitude 6.3 on 16 April.

An independent prediction was made 3 days before the twin 6 April quakes by seismologists working with a Beijing-based United Nations program linking public administration and disaster science. Zhang says their predictions were based on crustal stress and "alternative methods." This one got the time and location right but called for a single quake in the range of magnitude 7.0 to 7.5, 10 times more powerful than any of the quakes that struck.

Chinese researchers are modest about their prediction accomplishments. "We are still at our initial stage of scientific approaches," says Zhu. "Currently, our ability to make imminent predictions is very low." Xinjiang scientists did have a false alarm in March, and Zhang and Zhu note that this swarm has lasted far longer than the 1961 example, so they can't say when the shaking will stop.

Of course, says seismologist Max Wyss of the University of Alaska, predicting the next quake in a swarm is hardly as challenging as predicting a quake in isolation. "Nevertheless, if 150,000 people in the epicentral area were evacuated and lives were saved," he says, "I would say it came close enough to a correct prediction to be useful." Both Wyss and Jones would like to know more, and they may soon get the chance. Zhang says that, next year, the SSB will hold an international symposium on earthquake prediction so that foreign scientists can examine the data for themselves.

–Li Hui and Richard A. Kerr

Li Hui is a reporter for China Features.