be acting by other mechanisms.

Yet the issue is far from settled. Many biologists say the clonogenic assays are as unnatural as the short-term tests that pick up apoptosis. Cells individually seeded onto a plate to test their growth are a far cry from cells growing in a tissue, where their fate may be influenced by contact with neighboring cells or the extracellular matrix. For instance, Caroline Dive and John Hickman of the University of Manchester in the United Kingdom found that lymphoma cells made resistant to apoptosis by an extra copy of the *bcl-2* gene had no long-term survival advantage in a standard clonogenic assay. But when the culture dishes were made to resemble tissue by coating them with the extracellular matrix protein laminin and adding the growth factor IL-4, apoptosis-resistant cells had a survival edge.

Further complicating efforts to untangle the situation is the fact that cells' responses to therapy may vary depending on the drug used. One recent example comes from the Vogelstein team at Johns Hopkins. In experiments reported in the August issue of the *Journal of Clinical Investigation*, the researchers specifically inactivated the *p53* gene in a line of cultured colon cancer cells. Although the mutants did become resistant to 5-fluorouracil, a drug widely used to treat colon cancer, they became more sensitive to another cancer drug, Adriamycin, and to gamma radiation.

In addition, *p53* status by itself is not enough to indicate whether cells are capable of apoptosis. Other components of the apoptosis circuit can determine the final outcome. For example, mutations that activate the oncogenic potential of Bcl-2 and its relatives are well-known derailers of apoptosis. And recent work shows that the second most common mutation in solid cancers—disruption of the chromosome locus that includes the *p19* tumor suppressor gene—also results in the failure of apoptosis.

In work reported in the 15 October issue of *Genes and Development*, Lowe, now at Cold Spring Harbor Laboratory on Long Island, Clemens Schmitt (also of Cold Spring Harbor), and their colleagues inactivated the *p19* gene in a strain of mice already prone to B cell lymphomas because the animals carry an active *myc* oncogene. The researchers found that the resulting animals developed an aggressive lymphoma that closely resembles the cancers seen in animals with inactivating *p53* mutations; among other things, they were highly resistant to chemotherapy. These results mean that researchers wanting to establish whether apoptosis is important in how cancer cells die will have to determine exactly which genes are defective in resistant cells, an effort already going on under the aegis of the NCI in Bethesda, Maryland.

"Brown is right in saying the answer's not known yet; we have to bite the bullet and get into these experiments," says Dive. The hope is that order will soon emerge from the chaos, says Vogelstein: "Whether the models we have now are correct is not as important as the fact that cancer researchers are for the first time getting some real insights into why drugs fail, and more importantly, why they work at all." **–ELIZABETH FINKEL**

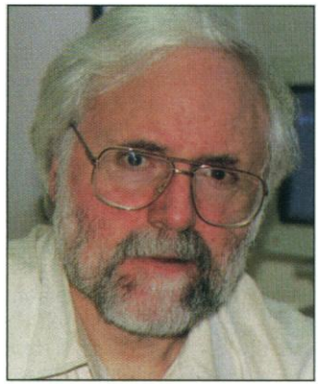
Elizabeth Finkel writes from Melbourne, Australia.

SCIENTIFIC MISCONDUCT

Europe Stresses Prevention Rather Than Cure

European research managers have woken up to the issue of fraud. But rather than policing it, they aim to nip it in the bud

RINGBERG, BAVARIA, AND EDINBURGH, SCOTLAND—Drummond Rennie, deputy editor of *The Journal of the American Medical Association*, says he had a strong sense of déjà vu when he attended a recent conference on scientific misconduct in British biomedical research at Edinburgh's venerable Royal College of Physicians. "The U.K. is almost exactly 20 years behind the U.S. [in dealing with scientific misconduct]," says Rennie, who estimates he has accumulated some 250,000 travel miles to attend meetings on scientific misconduct. "It's really striking—it's all the same questions and arguments that used to come up" in the United States in the late 1970s and early 1980s.



Long haul. *JAMA* Deputy Editor Drummond Rennie.

European researchers would likely agree that, until recently, institutions on this side of the Atlantic maintained a concerted head-in-the-sand policy toward fraud and other forms of research misconduct. "A lot of [U.K. researchers] thought that this only happens in other countries," says Stephen Lock, former editor of the *British Medical Journal* (*BMJ*). Povl Riis, one of the founders of the Danish Committee on Scientific Dishonesty, encountered the same attitude in Denmark in the early 1990s. "Many researchers think that a high IQ goes hand in hand with high moral values —which is, of course, absolute nonsense."

But a rising tide of retracted papers and some high-profile fraud cases are finally stirring research officials into action. Ethics committees and working groups are now hard at work in the United Kingdom, Germany, and other countries churning out new guidelines and procedures for good lab practice and publication. And at two recent conferences,* one in the U.K. and one in Germany, scientists from both countries engaged in some serious navel gazing. The focus was on prevention rather than cure. "The main goal was to find out what circumstances would favor scientific misconduct and to try and create an environment that would prevent it from happening in the first place," says Rüdiger Wolfrum of the Max Planck Institute for Comparative Public Law and International Law in Heidelberg, organizer of the German gathering. This view is shared on the other side of the English Channel. "There is little value in lengthy discussions about a definition of scientific misconduct as done in the U.S. A better approach seems to me an emphasis on implementing good research practice guidelines," says Graeme Catto, vice principal of the University of Aberdeen, who helped organize the Edinburgh conference.

Although Britain took an early lead in Europe in tackling the issue—with a 1991 report on scientific fraud in medical research from the Royal College of Physicians—it took a while to capitalize on that head start. "That's where matters stopped. The report hasn't even been publicized widely and certainly not implemented," says Lock. A case in point, says George Alberti, president of the Royal College of Physicians in London, was a recent investigation of British medical schools, which revealed that "local mechanisms [for dealing with misconduct] were in chaos or nonexistent."

One reason for the slow progress in Britain is the wide variety of funding sources:

* Ringberg Conference on Ethics in Research, 20 to 23 October, and Joint Consensus Conference on Misconduct in Biomedical Research, Edinburgh, 28 to 29 October.

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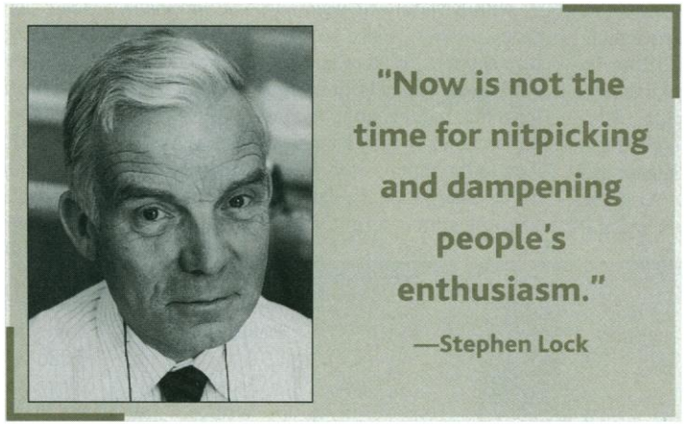
two separate research councils; the health and agriculture ministries; and numerous charities, which provide the largest slice of the pie. This contrasts sharply with the situation in Denmark, the first European country to take firm action against scientific fraud, where "90% of the funds are paid for by the government, which makes it easier to have a government-regulated framework," Lock says. Britain's Medical Research Council (MRC) did finally adopt procedures to investigate scientific misconduct in 1997. It followed those up last year with guidelines for good clinical practice and is currently working on a booklet defining good research practice. But few other bodies have made any efforts, Lock says.

Germany was thrown more precipitously into self-analysis over misconduct by a major scandal in the mid-1990s involving allegations of manipulated or falsified data that might affect more than 50 publications by two biomedical researchers (*Science*, 15 August 1997, p. 894). This served as a late wake-up call for the scientific establishment by revealing that German science was ill prepared to deal with scientific misconduct. In the wake of the scandal, Germany's main granting agency, the DFG, which funded the suspect research, and the Max Planck Society embarked on a mission to combat fraud, and both have now developed procedures for investigating and sanctioning scientific misconduct. Many smaller grant-giving institutions as well as German universities—which have to adopt similar procedures to receive DFG money—are now following suit.

The October meeting, which took place at the Max Planck–owned Ringberg castle in the Bavarian Alps, is part of the next, preventive stage in Germany's crusade against scientific misconduct. In June 1998 Max Planck president Hubert Markl asked an interdisciplinary working group of Max Planck scholars to come up with a code of conduct for scientists that would ensure good research practice, akin to the ones already drawn up by the U.S. National Academy of Sciences in 1992 and the DFG in 1997. A report is due early next year and is likely to incorporate many of the points discussed at the meeting, says the chair of the working group, Wolfgang Edelstein of the Max Planck Institute for Human Development in Berlin. Both the Ringberg and the Edinburgh meetings, held just 1 week later, came to similar diagnoses:



The main ingredients for an effective anti-misconduct recipe are the proper training and education of scientists at all levels on what constitutes acceptable ethical behavior, some cultural changes to diminish the steep hierarchy in certain research institutions and to encourage open scientific discussions, and—especially at the German meeting—an emphasis on good publication practice.

"There's no appropriate scientific education for medical doctors in Germany, although they're expected to do basic research" in order to become professors, says Ulrike Beisiegel of the University Hospital Eppendorf in Hamburg. Even standard procedures such as keeping comprehensive lab journals and notebooks are often lacking, says Gordon Duff of the University of Sheffield: "Record keeping is little short of disgraceful in most [U.K.] universities." The consequences of a loose collection of unnumbered sheets of hieroglyphic scribbles with no dates can be dire: "The Imanishi-Kari case [which cast a shadow over U.S. research in the late 1980s and early 1990s, before charges were dismissed by an appeals board in 1996] wouldn't have taken 10 years if she'd kept proper records," says MRC chief executive George Radda.

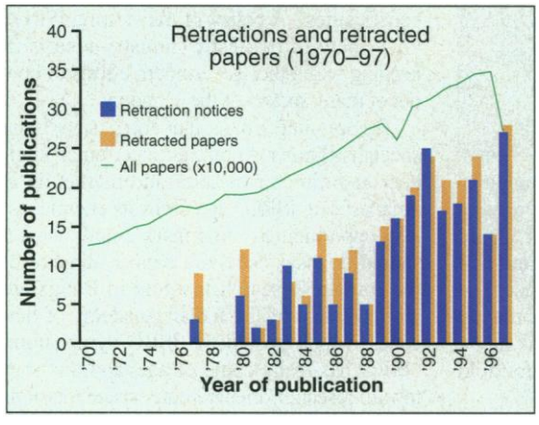
Many of those who met in Edinburgh and Ringberg argued that education in research ethics should be an obligatory part of an advanced degree such as a Ph.D. But even that may not be a panacea. "One shouldn't expect too much from formal [ethics] courses; there are tons of lawyers who finish their formal legal training and still go work for the Mob," cautions Markl. Whatever the merits of ethics classes, there was little dispute about the best way of fostering ethical and responsible behavior in the lab: "You have to teach it by example; the young scientists have to see it day in, day out. It's about a culture, a climate," says Lord Kilpatrick of Kincraig, former president of Britain's General Medical Council and chair of the panel that drew up the Edinburgh meeting's closing statement.

Some delegates also suggested that the very structure of research institutions might be creating an environment that encourages research misconduct. Extremely hierarchical structures, such as those in most medical institutions but also in many Max Planck Institutes where an almost almighty director sits atop a pyramid of researchers, may put pressure on younger staff members. Often it takes some courage for junior group members to come up with ideas that go against the group leader's school of thought. "It's important to take away the fear of talking openly from students and to develop a culture of criticism and open discussions," says Marinus Lamers of the Max Planck Institute for Immune Biology in Freiburg.

If institutions are reluctant to adopt guidelines or don't comply with given procedures, Rennie has a simple remedy: "Cut the funds." The Edinburgh meeting's closing statement also reflects this attitude. It recommends withholding grants unless institutions have in place a proper system for dealing with scientific misconduct and guidelines for good research practice.

Delegates were generally enthusiastic about the progress made at the two meetings. Lock thinks the Edinburgh consensus statement is "very encouraging. Now is not the time for nitpicking and dampening people's enthusiasm. Let's see how it evolves," he says. From his vantage point, Rennie, the traveling salesman of scientific misconduct, keeps his fingers crossed that European colleagues can keep the ball rolling. He says he is mildly surprised, however, "that they invent the wheel all over again instead of looking at the experiences in other countries." But then again, he says "maybe you've got to do this. You have to carry the community along and get them involved. People here wouldn't believe in a system simply copied from the U.S."

—MICHAEL HAGMANN



Errata. Retractions in MEDLINE are on the rise.

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