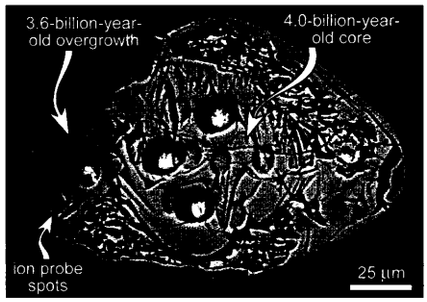
plates to form. They also argue that the hot surface layer would have been too buoyant to sink in subduction zones, and without sinking plates, the whole plate-tectonic cycle grinds to a halt. And they've questioned whether geochemistry alone can say anything certain about how rocks were formed. "It's groupthink, with a bunch of people who don't know what they're comparing [Archean geology] to," says Hamilton of the Colorado School of Mines, who helped formulate the theory of plate tectonics in the 1960s and 1970s but has become an outspoken opponent of the idea that it operated in the Archean.

Believers in ancient plate tectonics will find little comfort in the new results. Bleeker says the oldest parts of the Slave province seem to lack key signatures of plate tectonics, such as the long, narrow belts of accreted and deformed rocks. The mapping has even eliminated some supposed relics of ancient plate tectonics. Bleeker and his co-workers say, however, that they aren't coming down against plate tectonics, only calling it into question. "Plate tectonics is an attractive paradigm, because we understand it well," says Bleeker. "But that doesn't necessarily mean it is the best model for the early Archean."



Time capsule. An Acasta zircon, pitted where material was blasted away for dating. Spots at center yielded an age of 4.055 billion years.

Exactly what process might have been at work to build the ancient continent remains a matter of speculation. "That's where things get much more tenuous," admits Hamilton. In the nucleus of the old continent, rocks differing in age by a billion years or more are sometimes juxtaposed. That's not what geologists expect from the gradual accretion of crust at plate boundaries, but it could be the handiwork of episodic volcanic outbursts, fed by broad plumes of rock that rose periodically from deep in the mantle. "We need some stretching or cracking, and then it comes bubbling up," says Hamilton. These lava flows would have gradually built up the continental nuclei. Eventually the planet cooled enough for plate tectonics to take over. Bleeker speculates that the breakup of the continental nucleus his team has documented at 2.8 billion to 2.7 billion years ago might represent the dawn of plate tectonics.

Paul Hoffman of Harvard University cautions that looking only at a small area like the Slave won't be able to resolve the debate. "I hate to be negative, but ... a fragment of crust the size of the Slave Province is simply too small to ever work out the governing tectonic boundary conditions." Hoffman accepts the ancient geography that Bleeker and his colleagues have mapped, but he says that geologists will need to compare its distinctive stratigraphy with what they find on other fragments of ancient crust to conclude anything about ancient tectonic processes.

Bleeker agrees: "It's critical to try and find matching pieces scattered around the globe." But he adds that Earth's oldest crust is a good place to start. "The Slave Province is a wonderful laboratory for all these questions."

–CARL ZIMMER

Carl Zimmer is the author of *At the Water's Edge*.

BIOMEDICINE

Does Cancer Therapy Trigger Cell Suicide?

The notion that drugs and radiation kill cancer cells by causing them to self-destruct has guided drug searches. But some cancer experts aren't convinced

In the dark trenches of the war against cancer, a ray of light seemed to shine through a few years ago: a simple notion about what makes cancers susceptible to radiation or chemotherapy. The key, many cancer researchers came to believe, was the presence or absence of the *p53* tumor suppressor gene, which produces a protein that cells need in order to commit suicide when they are damaged or stressed. As long as *p53* remained functional, the theory went, cancer cells damaged by radiation or chemotherapy would self-destruct. But if the cascade of genetic changes that led to the cancer also inactivated the *p53* gene—which happens in about 50% of all human malignancies—the cells can shrug off the worst that oncologists can throw at them and continue to multiply. As a result, many researchers are looking for ways to restore cancer cells' ability to undergo apoptosis, as cell suicide is more technically called, in order to make them sensitive to cancer therapies.

But some specialists—among them many oncologists who treat tumors with radiation—don't buy this picture, at least not for solid tumors such as cancers of the lung, breast, prostate, and colon. They say that the kinds of test tube assays that point to apoptosis, and p53 in particular, as critical to cancer therapy may not accurately reflect what happens in cancers that have developed naturally in the body. What's more, they argue, using assays based on apoptosis to screen for cancer drugs might cause researchers to miss drugs that kill by other means. "People have become enamored with apoptosis—everything begins and ends with apoptosis—and that's not right," says radiation oncologist Martin Brown of Stanford University School of Medicine.

Recently, the radiation oncologists have been finding support for their position in a variety of studies showing that *p53* gene status does not correlate with a cancer cell's susceptibility to therapy. Not only may cells having a functional *p53* gene fail to respond, but those lacking one may be killed easily. But these findings are not easy to interpret, because other genetic factors can also determine whether cells will undergo apoptosis. This makes it difficult to tell whether apoptosis is in fact key to cancer therapy response.

"As with everything in biology and cancer, the situation is much more complicated than we would like," says cancer gene expert Bert Vogelstein of The Johns Hopkins University School of Medicine. Still, it's critical to learn just what determines whether radiation and drugs will kill cancer cells. As Vogelstein notes, "In the long term, understanding these complexities is likely to enhance our ability to develop better therapies and tailor such therapies to the specific characteristics of individual tumors."

Apoptosis is a rapid and tidy form of suicide that cells may opt for when their DNA is damaged by radiation or toxic drugs. A great deal of evidence has shown that the decision to self-destruct is controlled by a gene circuit, with the p53 protein serving as the key damage sensor that tells the circuit when to kick in. Over the years several lines of evidence have pointed to the importance of p53-induced apoptosis in determining whether blood cell tumors will respond to treatment.

Pediatric oncologist David Fisher of the Dana-Farber Cancer Institute in Boston cites acute lymphoblastic leukemia, a blood cell cancer that usually afflicts children, as an example. These tumors typically carry an intact *p53* gene when they are first diag-

CREDIT: R. STERN AND W. BLEEKER

nosed and virtually melt away when treated with chemotherapy, Fisher says. Recurrences occur in 20% to 40% of cases, however, and when the tumors come back, half of them carry a defective *p53* gene and are now resistant to further therapy.

No solid evidence

But although the evidence is convincing for the blood cell tumors, a definitive answer about how p53 influences the response of solid tumors to therapy has been much harder to come by. Simply collecting data from patients doesn't settle the issue, in part because it can be hard to determine whether a cancer has a working p53 protein. Even looking at biopsy samples from primary tumors that are shrinking after treatment to see whether the cells are dying by apoptosis hasn't provided conclusive results because apoptosis is rapid and leaves no traces.

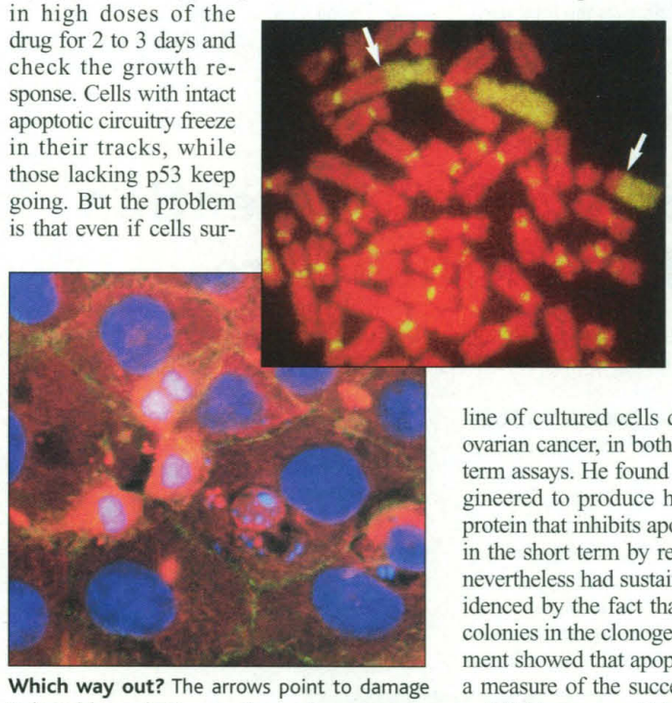
So in 1994 Scott Lowe, then at the Massachusetts Institute of Technology, and colleagues studied experimental tumors in mice. They transplanted cancer cells in which the *p53* gene had been inactivated into the animals. The resulting tumors were resistant to both radiation treatments and the chemotherapeutic drug Adriamycin. But tumors formed by cells with an intact *p53* gene were sensitive to both types of therapy (*Science*, 4 November 1994, p. 807). Furthermore, the cells in the shrinking tumors showed such hallmarks of apoptosis as having their DNA chopped into regularly sized bits.

Work on cultured cancer cell lines echoed these findings. Take the National Cancer Institute's (NCI's) drug-screening program, which since 1990 has tested 60,000 potential drugs against a panel of 60 human cancer cell lines. The screening indicated that many current cancer drugs work most effectively in cells with an intact *p53* gene, while cells with inactivating *p53* mutations tend to resist the compounds (*Science*, 17 January 1997, p. 343). So entrenched did the idea become that cell biologist Michael Strauss of the Max Delbrück Center for Molecular Medicine in Berlin told the German magazine *Der Stern* in a 1996 interview that patients whose tumors bear inactivating *p53* mutations would not benefit from radiation or drug therapy. Indeed, the interview bore the headline "*Jede zweite Therapie ist überflüssig*"—that is, "Every second treatment is superfluous."

Radiation oncologists think that's far too sweeping a conclusion, at least for solid tumors. "We don't worry about doctors," because they treat patients regardless of their *p53* status, says one such clinician, Lester Peters of the Peter McCallum Institute for Cancer Research in Melbourne, Australia. But he adds, "We do worry about patients who might look up the information and decide treatment is futile."

Stanford's Brown argues that the assays on which Strauss's conclusion was based are flawed. Lowe's transplanted cancer cells were highly artificial, having been made cancerous in the culture dish by the introduction of two oncogenes, *E1A* and *RAS*. Many studies, including some by Lowe himself, have shown that these oncogenes raise p53 levels, making cells totter on a knife edge of survival. Thus, Brown says, the cells are poor models for solid tumors because they would never withstand the insults encountered on the way to forming the tumor. Lowe concedes that the model he used was not ideal, but says that finding a model that accurately reflects what happens in natural tumors is a major challenge. "This is the question I've been struggling with for years," he says.

Brown says that short-term assays like those carried out in the NCI screen to test cancer drugs are also misleading. In those assays, researchers typically bathe cancer cells in high doses of the drug for 2 to 3 days and check the growth response. Cells with intact apoptotic circuitry freeze in their tracks, while those lacking p53 keep going. But the problem is that even if cells survive 48 hours, that doesn't mean they can survive and proliferate in the long term. "*p53* [status] tells you how a cell dies but not whether it dies," Brown maintains.



Which way out? The arrows point to damage induced by radiation in these chromosomes from lung cancer cells (upper right). But does such damage kill by interfering with cell division or by throwing cells into apoptosis, such as that seen in the center cell (above)?

More than one way to die

He and other radiation oncologists favor a nonapoptotic mechanism, partly because of their clinical experience. The behavior of tumors, they say, seems to indicate that rather than self-destructing, cancer cells die when they try to divide. "Most solid cancers take several weeks to respond [to treatment] because [their cells] have to undergo mitosis," Peters explains. In fact, he says, one can use a tumor's growth rate to predict how long it will take for a response to become apparent—within weeks for fast growing tumors, whereas slow-growing tumors, such as pituitary adenomas, take years to go away.

More direct evidence for that point of view comes from the so-called clonogenic assays that radiation biologists traditionally use to study the effects of radiation on cancer cells. In these assays, cells are exposed to radiation or drug therapy, seeded onto a culture plate, and then followed for about 12 days, long enough for six or seven divisions. In these assays, cells from solid tumors typically don't die until they divide, at which time the daughter chromosomes break when they try to separate. In other words, death appears to be a consequence of mechanical damage rather than a rapid self-destruct signal.

What's more, these assays don't show a consistent link between cells' ability to undergo apoptosis and their susceptibility to anticancer therapies. In 1995, for example, cell biologist Robert Schimke of Stanford University tested HeLa cells, a line of cultured cells derived from a human ovarian cancer, in both clonogenic and short-term assays. He found that although cells engineered to produce high levels of Bcl-2, a protein that inhibits apoptosis, survived drugs in the short term by resisting apoptosis, they nevertheless had sustained a fatal blow, as evidenced by the fact that they could not form colonies in the clonogenic assay. "Our experiment showed that apoptosis is not necessarily a measure of the success or failure of therapy," Schimke says. Schimke's experiment has since been followed by a host of others using clonogenic assays, which have come to similar conclusions.

Brown and his colleagues think solid cancers are unlikely even to retain the capacity to undergo apoptosis because of the way they develop. As these tumors grow, they outstrip their blood supply, at least temporarily, leaving their cells deprived of food and oxygen—stresses guaranteed to drive most cells to press the self-destruct button. So only those cells that have disabled their apoptosis circuitry are likely to make it to the point of forming solid tumors. If so, radiation and drugs that shrink solid tumors must therefore

CREDITS (TOP TO BOTTOM): FROM M. S. KOVACS *ET AL.*, *CANCER RES.* **57**, 672 (1997); NANCY KEDERSHA/IMMUNOGEN/SCIENCE PHOTO LIBRARY

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**

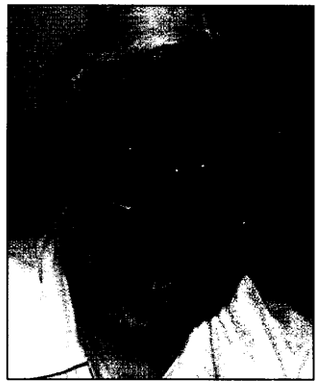
Elizabeth Finkel writes from Melbourne, Australia.

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.

CREDIT: SIO PHOTOGRAPHY

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.