Fraud Strikes Top Genome Lab

Francis Collins, head of NIH's Human Genome Project, has informed colleagues that a junior researcher in his lab faked data in five papers Collins co-authored

It is every scientist's nightmare: An editor calls saying he needs to talk urgently about a paper you've submitted. A reviewer thinks there's something weird in the data. It can't be too bad, you tell yourself, because you've read the manuscript a dozen times, and the smart people in your lab have been plowing this ground for 2 years. But when you start checking the reviewer's questions, you get a queasy feeling. You dig through the freezer, bring out clones, repeat experiments. Soon there's no denying it: The evidence says you have been the unwitting co-author of a fraud. Now what do you do?

RICK KOZAK

Quick response. Francis Collins is correcting the literature.

This scenario, or one like it, has been played out many times in top scientific laboratories and universities. It has affected departmental chairs, basic scientists, clinicians, the best and the brightest—and it has now claimed another victim: Francis Collins, one of the country's top genetics researchers. Collins says he discovered that a junior scientist in his lab, a trainee without a Ph.D., fabricated data in a paper that went out for publication under Collins's name. Now this paper and five others in the literature must be corrected or withdrawn (see box).

As director of the National Center for Human Genome Research (NCHGR) at the National Institutes of Health (NIH), Collins pilots the $189 million juggernaut of the human genome project, but he also guides a $44 million intramural research program, an $11 million bioethics program, and a genetics research lab of his own. A witty speaker and impassioned defender of research funding, Collins casts a big shadow in biomedicine. So his response to an apparent fraud in his own lab—discovered in August and made public last week by the *Chicago Tribune*—was bound to make news, no matter how he handled it. Many of his peers think he handled it well, confronting the alleged wrongdoer swiftly and informing the world of problems in the data. But the incident has led some to question whether Collins—and other top scientists who run huge enterprises—can pay enough attention to the details of the research they co-author to ensure that the work is valid in the first place.

Once Collins was sure that fraud had occurred, he says, he notified the authorities and obtained from the student a confession that some data in papers he co-authored with Collins on the effect of leukemia genes were fraudulent. Collins mailed letters to colleagues on 1 October outlining the tainted areas of research. But he did not make a public announcement, he says, because government lawyers forbade him from doing so. When the news broke last week, Collins began speaking openly about the scientific and emotional impact of the case. As he told *Science*, it is the kind of calamity most scientists don't prepare for because they don't think it will happen to them: "It's like walking down a street on a sunny day," says Collins. "You don't think you're going to get mugged. You can't think about it too long because it's not something you want to imagine could happen to yourself or somebody you know. And now it's happened to me."

Collins declines to identify the student, but one of the tainted papers includes only one other co-author: Amitav Hajra, a graduate student at the University of Michigan (UM), Ann Arbor. (*The New York Times* also identified Hajra as the suspect last week.) Collins was Hajra's mentor when both were in Ann Arbor, before Collins left in 1993 to take over NCHGR. Hajra followed Collins to NCHGR to complete his dissertation. *Science* was unable to reach Hajra, and messages left with his attorney were not answered. Hajra's father, a UM biology professor, said in a phone interview that his son would not comment until an official UM investigation is completed.

Now that the damage is being repaired, Collins has begun reflecting on questions about the general problem of fraud in science: Is there anything a scientist can do to prevent a tragedy like this? Is there anything Collins might have done himself to nip this one in the bud? "That," says Collins, "is the hardest question" of all, one which "I have wracked my brain" to answer. But so far, Collins hasn't come up with any ideas, other than to create a kind of "police state" in the laboratory that would double-check everyone's work. He rejects that solution.

The telltale blot

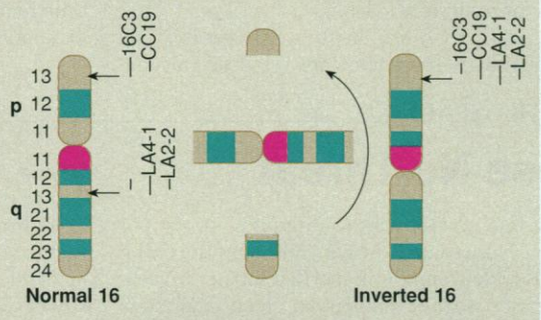
The trouble came to light in August, says John Jenkins, editor of the British journal *Oncogene*, through the work of a meticulous reviewer. The reviewer spotted something odd in a paper about aberrant proteins created by rearranged genes on chromosome 16—the latest in a series of papers on genes associated with leukemia co-authored by Collins and several others at NCHGR over the last 2 years. Neither Jenkins nor Collins is ready to release the paper, saying it is still a confidential manuscript. But Collins described what caught the reviewer's eye.

In a figure showing various proteins in columns or "lanes" of a Western blot assay, the reviewer had noticed a strange repetition of "little telltale glitches," Collins says, the kinds of artifacts that are usually ignored. The reviewer—who remains anonymous—noticed that lanes for two different proteins had the same visual flaws. Collins explains: "There is a lane in the upper left, which if you cut it about halfway down, and then took the lower half and turned it 180 degrees so that the bottom is now the top, you end up with something that looks like a lane in the lower right." An apparent cut-and-paste job. Not easy to spot, but "absolutely unequivocal once you look" at it, says Collins.

After the call from *Oncogene*, Collins and a researcher in his lab, P. Paul Liu, spent 2 weeks looking through the freezer, sequencing clones, and checking every detail of the work that had been done by their junior colleague. As their inquiry proceeded, Collins says, he realized "day by day that the enormity of what was done here was quite profound." They discovered, for example, that the student apparently had had trouble creating a control cell line for tests to find out whether a gene on chromosome 16 would trigger cancer in mouse tissue cells. Frustrated, the student allegedly made up data for the control. He apparently did the same in another study in which a different gene was supposedly transfected into mouse cells. In another instance, Collins says, stretches of human DNA sequence were made up, using mouse DNA as a guide. The "astounding

Doubts Cast on Leukemia Papers

The discovery that a grad student had apparently faked some data in papers co-authored by Francis Collins, director of the National Center for Human Genome Research (NCHGR), dramatized the conflict between trust and vigilance in science (see main text). It also cast doubt on a line of research concerned with a chromosomal aberration and leukemia. Collins's lab at NCHGR—and before that at the University of Michigan, Ann Arbor, where Collins worked until 1993—has been studying an oddity in which the center of chromosome 16 is rotated 180 degrees with respect to the ends. Inverted 16, as it's known, has been linked to 15% of acute myeloid leukemia cases.



Inverted 16. Rearrangement of chromosome 16 creates a "fusion gene" linked to some cases of leukemia. Some work extending this finding is now in doubt.

In 1993, before the grad student—who has been identified as Amitav Hajra—became deeply involved in this project, another colleague of Collins's, P. Paul Liu, identified a "fusion" gene on the long arm of 16 formed by the inversion. It consists of two normally distant pieces: one gene involved in DNA transcription, called core-binding factor beta, and another that produces a smooth muscle protein. The link to leukemia, the gene cloning, and data on the protein it creates—all reported in a paper with Hajra as a co-author (*Science*, 20 August 1993, p. 1041)—are "absolutely, unequivocally right," says Collins: "None of that is in question, not even the slightest bit."

The bad data, according to Collins, are found in subsequent reports on the detailed structure and function of the abnormal gene. Much of that work, published in 1995 and 1996, has been discarded and will be redone.* Most disturbing, perhaps, the student's data showing that the gene causes cancerous growth when expressed in mouse fibroblast cells are now in question. This important result must be reconfirmed.

Collins and Liu say they believe the fraud was caught early enough to avoid repercussions outside their own lab. But at least two other researchers who have been studying chromosome 16—David Claxton at the M. D. Anderson Cancer Center in Houston, and Alan Friedman at Johns Hopkins University—were affected, according to Claxton. Friedman says only that "I agree with Francis [Collins] that there's been little impact." But Claxton says his attempts to get the fusion gene to trigger cancerous growth in test assays—including blood cells—have not worked. He adds that, "I just found myself kind of frustrated" over many months as he tried to get the results reported by Collins's lab.

A new paper authored by Liu, in press at *Cell*, may dispel some of the uncertainty about the fusion gene's function. Liu declines to discuss it, citing *Cell*'s strict embargo policy. But Claxton and others who have seen the data say that Liu's paper shows that the fusion gene, when put into a knock-in mouse and expressed at a high level, doesn't make blood cells cancerous; it kills them. It may, perhaps, cause cancer when expressed at low levels. What is clear, says Claxton, is that "this is a very significant finding," which will reinvigorate studies of chromosome 16. **–E.M.**

*The retracted papers appeared in *Genomics* **26**, 571 (1995) and *Molecular and Cellular Biology* **15**, 4980 (1995). Those for which some data are being withdrawn appeared in *Proceedings of the National Academy of Sciences (PNAS)* **92**, 1926 (14 March 1995), *PNAS* **93**, 1630 (20 February 1996), and *Genes, Chromosomes & Cancer* **16**, 77 (1996).

thing," says Collins, is that someone sophisticated enough to concoct such a fraud didn't realize it would be discovered.

Collins shared his suspicions with UM officials and the Office of Research Integrity at the Department of Health and Human Services, which investigates and rules on scientific misconduct cases involving NIH grantees. Then, with evidence in hand, Collins flew to Ann Arbor in September to confront the student.

It was, says Collins, "one of those days you'll never forget." Collins presented the young man with the collected file of evidence on data fabrication, and at the end of three-and-a-half hours, Collins says the student confessed. His attitude was not so much remorseful as resigned, says Collins—a sense that, "I guess you caught me." Collins today gives the student credit for keeping his word and writing out a three-page description of all that he had made up, and for not backtracking on that confession.

Making a clean breast

After consulting with colleagues, Collins decided to write a quasi-public letter outlining what had happened. Says NIH Director Harold Varmus: "Francis had shown me the whole story some time ago, and I suggested that he write that letter" to clear the air. Collins felt it was important to warn people in the field quickly that there were false reports in the literature. NIH lawyers put up "some resistance," says Collins, but agreed to a "generic letter," omitting mention of UM and the student and sticking to technical details. The letter, dated 1 October, went out to 100 researchers on a "need-to-know" basis, according to Collins. Remarkably, it did not reach the press until 4 weeks later.

Collins's letter expresses "a profound sense of regret" about the discovery of "a serious case of fabrication and falsification of data." It retracts two papers entirely and corrects parts of three more. It exonerates many other co-authors by name. And Collins raises the question of whether "I as the research mentor was paying sufficient attention to this individual." His answer: "I had no evidence, in frequent interactions with the individual over the course of 3 years, to question his honesty. Even in retrospect, I am not sure how these deceptions could have been uncovered sooner."

Some scientists, however, worry that a busy schedule may have prevented Collins from monitoring his trainee as closely as he should have. And one former NIH institute director, speaking on condition of anonymity, says he believes it is a mistake for institute chiefs to try to run basic science labs while managing complex organizations. Doing so creates tension and jealousies, inevitably shortchanging either the lab or the institute, says this ex-director. Another research leader argues that significant results should always be double-checked by other members of the lab, as was his practice when he ran a lab at Harvard.

But most researchers *Science* contacted agree with Collins: There is no need to isolate research managers from bench science, and no way to prevent them from being taken in by a talented, dedicated fraud. "A committed liar is going to get you every time," says C. K. Gunsalus, associate provost of the University of Illinois, Urbana-Champaign, who has handled many miscon-

duct cases and is an advocate of tackling such problems aggressively. She adds: "You just can't afford to write rules in a cooperative community—where the foundation must be trust—for the bad actors."

Varmus—who runs his own lab while heading NIH—says he would "take issue" with the idea that an institute chief is at greater risk of getting snared in a fraud case than the head of a large academic center or department, or any other person leading a large scientific project. Like Gunsalus, Varmus thinks it is hard to guard against "someone who's very smart and very determined, and who builds a house of cards from which they can't escape." It would be "wrong," Varmus believes, to conclude from this case that "you have to mistrust everything" or require duplication of every significant result in the lab.

As for Collins, he, too, believes it would be "naive" to try to create a "fail-safe mechanism" to prevent fraud. It may be, he says, that deceit and betrayal are part of the price we must pay for a free system. "If [research] is going to be open, if it's going to be creative, if you're going to allow people with talent to explore the unknown," Collins says, "there are going to be people who take advantage" of that freedom and abuse it. He thinks the only remedy may be "to do science with our eyes more open."

–Eliot Marshall

POWER LINES AND HEALTH

Panel Finds EMFs Pose No Threat

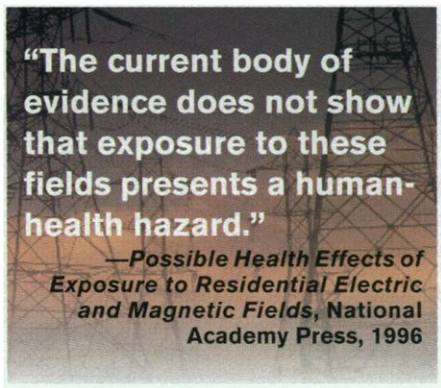
Last week, the National Research Council (NRC) seemed to deal a mortal blow to one of the most polarized and long-running environmental controversies—whether electromagnetic fields (EMFs) from power lines or household appliances pose a threat to human health. After an exhaustive, 3-year study, a 16-member panel said there is "no conclusive and consistent evidence" that ordinary exposure to EMFs causes cancer, neurobehavioral problems, or reproductive and developmental disorders. But this is a debate that won't die easily. And ironically, three panel members may help to keep it alive: In a separate press statement, they said that it's still an open question whether EMFs threaten health.

Public concerns about possible health hazards from EMFs first arose in 1979, when researchers reported that children living close to high-voltage power lines in Denver had elevated rates of leukemia. A blizzard of studies ensued (*Science*, 11 December 1992, p. 1724). Many found no health risks from ordinary EMF exposure, but others linked EMFs to a range of maladies, from miscarriages to breast cancer. To address burgeoning public fears and help decide whether protective regulations were in order, the Department of Energy (DOE) in 1993, at Congress's request, commissioned the NRC report.

After reviewing more than 500 studies, the panel concurred that at very high doses, EMFs can have biological effects. These include disruption of chemical signaling between cells in cultures, and inhibition of melatonin production and promotion of bone healing in animals. But the panel found no adverse effects on cells or animals at the low levels measured in residences.

The committee also found epidemiological studies linking ordinary EMF exposure to adult cancer and other health problems unpersuasive "in the aggregate." For example, a few studies have suggested that EMFs from electric blankets and video display terminals can harm the developing fetus, and research on workers in electrical jobs has found elevated rates of brain, breast, and other cancers. But the panel said the results are inconsistent and difficult to interpret.

Nonetheless the panel thought the childhood leukemia link merited further investigation, so the members did a meta-analysis of 12 studies from the United States and Europe. While they found a 1.5-fold increase in the cancer rates in homes with a high "wire code"—an estimate of household EMFs based in part on the distance to high-voltage power lines—they also found that wire code values are not a good indicator of actual fields in the home. Moreover, the panel noted that researchers have failed to find a correlation between actual EMF measurements in the home and childhood leukemia.



The panel suggested that the leukemia link may be due to some other factor, air pollution, for example, since high wire code homes tend to be on heavily trafficked streets. The panel's chair, Charles Stevens of the Salk Institute in La Jolla, California, says more research is needed to pinpoint what—if not EMFs—may be causing the elevated rates of leukemia. But overall, the report concludes, "The current body of evidence does not show that exposure to these fields presents a human-health hazard." The report is "an enormous step forward," says Robert Park of the American Physical Society, which issued a report last year that also concluded EMFs do not threaten health.

Though all NRC panel members signed the report, three took the unusual step of releasing a separate statement saying that the debate over health effects was far from over. "People may interpret the report [to mean] the matter is settled, but we don't think it is," says epidemiologist Richard Luben of the University of California, Riverside, who was one of the signers. According to the release, issued by the Bioelectromagnetics Society, a scientific organization of 700 EMFs researchers, the panel's most important finding is "a reliable, though low, statistical association between power lines and at least one form of cancer." The release also highlights a statement within the report that says effects from environmental EMFs "cannot be totally discounted" and underscores the panel's call for more research.

JASMINE/PNI

Some other EMFs researchers also find the report's tone too dismissive. Neurologist Ross Adey of the Veterans Administration Medical Center in Loma Linda, California, says the summary "does not adequately reflect the body of biological and biomedical knowledge" about EMFs. Adey heads a working group conducting an EMFs study for the National Council on Radiation Protection and Measurements (NCRP), a congressionally chartered advisory group. An earlier, unreviewed draft, which caused a furor when it was leaked to the press last year, concluded that EMFs pose a sufficient threat to warrant regulatory measures. It is now being reviewed by the NCRP council.

Two other groups are also studying the issue. The Environmental Protection Agency (EPA) was leaning toward recommending regulatory measures in a long-delayed report which EPA's Robert McGaughy says was shelved last year, in part for "budgetary reasons." And the National Institute of Environmental Health Sciences, which together with DOE conducts a $65 million EMFs research program, is scheduled to deliver a report to Congress in mid-1988.

But even this string of studies may not lay the controversy to rest. As Dimitrios Trichopoulos, chair of epidemiology at the Harvard School of Public Health, points out, "It's one thing to say, 'Not guilty,' and another to say, 'Innocent.'" For that reason, he predicts, the issue of residential EMFs "will never go away."

–Jocelyn Kaiser