Dispute Splits Schizophrenia Study

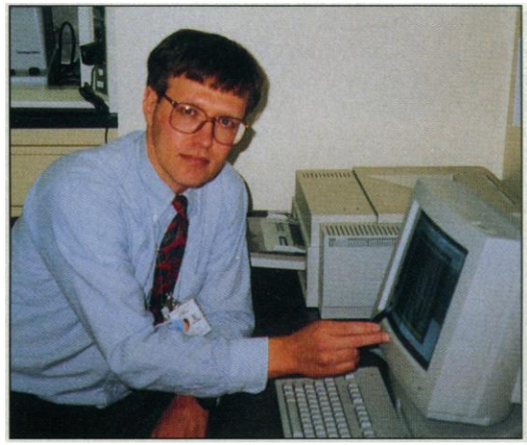
A report that a schizophrenia susceptibility gene may reside on chromosome 6 may say as much about problems of scientific collaboration as about the biology of the disease

When a U.S. biologist published a paper last week on inherited schizophrenia in Ireland, no one was more surprised than Tony O'Neill. A psychiatrist at the Queens University of Belfast, O'Neill says that many of the people who donated DNA for this study were his own patients. But he never agreed to let their diagnoses be used in last week's paper. Between 1987 and 1992, O'Neill and his colleague, Dermot Walsh, a senior psychiatrist at St. Loman's Hospital in Dublin, sent hundreds of blood samples and diagnoses to a team of U.S. geneticists based at the Medical College of Virginia (MCV) in Richmond. The fruits of their labor appeared in print without the consent of either Walsh or O'Neill after members of the MCV team had had a falling-out and one of them—molecular geneticist Scott Diehl—decided to publish the data on his own.*

Diehl, now a staffer at the U.S. National Institute of Dental Research (NIDR), argues that he had good reason for going solo. Diehl says he was "locked out of [his] lab" at MCV following a dispute with the study director, psychiatrist Kenneth Kendler. MCV denied Diehl access to computer files, but Diehl says he made copies of key documents. Using these, he prepared a paper and invited his MCV and Irish colleagues to become coauthors, with himself as senior author. They declined. After a series of rebuffs, Diehl says, he was free to publish without their consent. He went ahead, and the resulting paper, providing evidence that a gene on chromosome 6 may confer risk of schizophrenia (see box on p. 793), made headlines.

What amazes the Irish clinicians is that Diehl's right to publish his former colleagues' data has been backed by the general counsel of the U.S. National Institutes of Health (NIH), Robert Lanman. Since 1993, Lanman has been trying to help Diehl get access to data at MCV. He has also sent MCV his written opinion that Diehl is entitled to publish the data—with or without MCV's agreement—because Diehl was one of the principal investigators on the project, and because some of the Irish clinical data have been cited in other publications. (Two such publications were written by a student of Diehl's, and one, a dissertation appendix containing diagnostic details, has been protested by the Irish.) Lanman and Diehl argue that these releases converted the Irish data to public property. Kendler disagrees and points out that much of the data was not included in these publications.

O'Neill says he only realized that Diehl had forged ahead with his plan to publish when Diehl's paper appeared in the May issue of *Nature Genetics*. He doesn't question the importance of the study. Indeed, O'Neill and Walsh are proud to have contributed to the research. But they aren't pleased to have received so little credit: They are listed in a short acknowledgment, along with 20 other names and some grant numbers, at the end of Diehl's paper. O'Neill says it was "really infuriating" and "frustrating" last week to read Diehl's paper, particularly its reference to the Irish patients as "our families."



Going it alone. When negotiations with his former colleagues broke down, Scott Diehl published without them.

Nature, the parent publication of *Nature Genetics*, noted the dispute in an editorial in last week's issue under the puzzling title "Good manners win out." The Irish psychiatrists certainly don't think good manners prevailed in this case. O'Neill and Walsh continue to work with Kendler and have taken his side in the dispute with Diehl, but O'Neill thinks the flap could renew an old stereotype of U.S. science, one in which Americans get the glory while others do the work. It also illustrates the fragility of big scientific collaborations, particularly those in which clinicians and laboratory researchers must trust one another over many years. Finally, the Irish study raises difficult questions about when it is right for outside authorities to step in and seize control of clinical data.

Founding father

No one doubts that Kendler is the father of the Irish project. He conceived it and in 1986 won a grant from the National Institute of Mental Health (NIMH) to conduct a genetic linkage analysis, known as the "Irish Study of High Density Schizophrenia Families." The goal was to search systematically for patients with well-defined mental illnesses, particularly among families in which more than one person was affected, in a setting where the diagnosis of schizophrenia would be relatively clear. He settled on Ireland because it has large families, little nonalcohol drug abuse, and a close-knit social fabric.

Beginning in 1987 Kendler and his Irish colleagues collected data on roughly 1700 individuals in 277 Irish families, creating what many consider the best database of its kind. Over a period of 5 years, clinicians met with subjects, diagnosed them, collected blood samples, and turned the samples over to molecular biologists. The lab workers extracted DNA and scanned the patients' genomes for identifiable bits of DNA ("markers") that might stand out as being more frequently associated with the disease. In this way, they hoped to locate a gene that makes carriers susceptible to schizophrenia.

Kendler's chief Irish partner, Walsh, a member of Ireland's Medical Research Board, had collaborated on an earlier study of schizophrenia in western Ireland. It was Walsh who made an unusual linkup with Northern Ireland, through Roy McClelland, a professor of mental health at the Queens University of Belfast. McClelland, in turn, tapped O'Neill to handle research in the North.

At first, the project leaders attempted to run DNA studies in Ireland. But, according to Diehl, it became painfully evident that a local molecular biology lab couldn't handle the task. Diehl says the cell lines died, and Kendler decided to reconstruct the lab in the United States. Kendler recruited Diehl from the University of Michigan in 1988 to rebuild the lab, and Diehl claims his contribution helped Kendler win a grant renewal.

* "Evidence for a susceptibility locus for schizophrenia on chromosome 6pter-p22," Shengbiao Wang, Cui-e Sun, Cynthia A. Walczak, Janet S. Ziegle, Barbara R. Kipps, Lynn R. Goldin & Scott Diehl, *Nature Genetics*, May 1995, pp. 41–46.

A Glimpse of an Elusive Quarry

Most researchers who study schizophrenia are convinced that there is a genetic component to the disease. Family studies, for example, consistently show that risk for schizophrenia, a disease that strikes roughly 1 in 100 people, is inherited. But, because the disease is complex, and because many causative factors are involved, the search for a schizophrenia susceptibility gene has been a frustrating quest. Over the past decade, genetic linkage analysis, in which researchers look for DNA markers that are consistently inherited along with the disease, has turned up at least half a dozen "hot spots"—areas of the genome that appear to harbor a candidate gene. None of these tentative sightings has held up, however.

Last week's announcement by Scott Diehl of the National Institute of Dental Research that another candidate hot spot has been found, this time on chromosome 6 (see main text), is the latest glimpse of this elusive quarry. Like the earlier reports, the evidence is far from clear-cut: The chance that the marker Diehl used to establish linkage is actually associated with the disease meets geneticists' standard measure of statistical significance by a small margin. But Diehl's report is causing a buzz in the community—and not just because of the dispute over who owns the data.

The finding is attracting interest because other groups are coming up with similar sightings. Among them are Diehl's former colleagues at the Medical College of Virginia (MCV) in Richmond. Led by psychiatrist Kenneth Kendler and molecular biologist Richard Straub, they have reanalyzed their data and have found additional evidence pointing to a schizophrenia gene in the same area. The MCV researchers say that geneticist Ann Pulver of Johns Hopkins University has also found a hint of linkage to chromosome 6. Pulver told *Science*, however, that she isn't ready to discuss the details yet. And, again according to the MCV group, Dieter Wildenauer and Wolfgang Maier of the University of Munich have also obtained evidence implicating chromosome 6 in a group of families they study. They hope to publish their results later this year.

If these tentative reports hold up, this discovery could be the most important for psychiatric genetics in more than a decade. On the other hand, there have been so many ups and downs in the past that few geneticists are ready to believe that a real quarry is in their sights. Kenneth Kidd of Yale University, who has seen many claims come and go, sums up the reaction of many of his colleagues: "I am underwhelmed by the so-called hot spots."

–E.M.

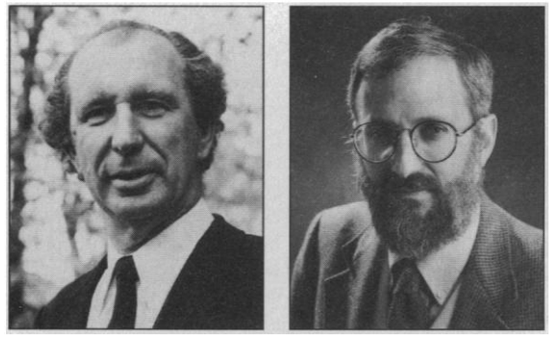
This account is "not accurate," according to Kendler, who downplays the problems with cell lines in Ireland. Kendler says he had planned to establish a molecular genetics lab at MCV long before recruiting Diehl.

Diehl and Kendler agree that Diehl was given considerable independence at MCV. He became an assistant professor in Kendler's program, taking charge of the molecular genetics effort and building up the lab and the computer database. Kendler says he agreed that Diehl should get a grant of his own as a principal investigator on the study, although "some of my colleagues advised against" yielding so much authority. In 1989, Diehl won a large NIMH grant to support his genetics lab work.

Kendler and Diehl both say their relationship went sour sometime during 1992. Kendler says he became dissatisfied with Diehl's rate of publication. Diehl agrees that he was slow to publish at first, but claims it was important in that period to focus on establishing data quality. The two also began to quarrel over the order in which their names should appear on papers arising from the research project and over rights to genetic data. By 1992, Diehl had learned that NIDR was interested in starting a molecular genetics lab, and he began negotiating to become its director.

In the same period, Diehl disclosed to his colleagues at MCV that his genotyping effort had found significant evidence linking a "hot spot" on chromosome 6 with cases of schizophrenia among the Irish families. Diehl meanwhile was making plans to leave MCV and gave notice in May 1993 that he would depart for NIDR that summer. He wanted permission from Kendler to publish his results after departing, but he wanted to be listed as senior (last) author. Kendler did not agree.

Shortly afterward, in early June 1993, the situation at MCV exploded. Kendler accused Diehl of scientific misconduct, alleging that Diehl had threatened in a private conversation with Kendler to make it impossible for anyone but Diehl to use the genetic database, perhaps by "encoding" the data. Charles MacLean, a statistician at MCV, also said that he heard Diehl say something like this, although in a joking tone. Diehl vigorously denied these allegations to university officials. He explained that he had only meant to suggest that, after he and his staff departed, no one at MCV would be competent to handle the molecular data. MCV convened a three-member panel of inquiry. Diehl hired a lawyer very experienced in scientific misconduct issues—Barbara Mishkin of Hogan & Hartson in Washington, D.C.—to represent him. In August 1993, the panel unanimously cleared Diehl, and he moved to NIDR. But MCV officials refused to let Diehl take with him any of the digital or diagnostic data he had worked on in the lab.



Left out. Psychiatrists Dermot Walsh *(left)* and Kenneth Kendler received only an acknowledgment.

Mishkin, hoping to "save Scott some money" on legal costs, helped persuade NIH counsel Lanman to take up Diehl's plea for access to the computer files. Since then, Lanman has written a series of increasingly forceful letters to David Ross and William Dewey, general counsel and chief of research, respectively, at MCV's parent organization, the Virginia Commonwealth University.

In October 1993, Lanman asked MCV to "give Dr. Diehl access to the research data and materials he was involved in producing as promptly as possible." In January 1994, Lanman again sought to gain access for Diehl, admonishing the university that it has an obligation to cooperate as a federal grantee. In March 1994, Lanman asked once again that Diehl be given copies of "the complete data tapes" from the Irish study, as they existed at Diehl's departure. The university wanted an agreement on authorship rights first, but Lanman wrote, "We see no reason for delay."

University officials stood firm. They met with NIH officials in September 1994, after which Lanman laid down a three-page "plan for settlement of authorship dispute." It stipulated that if the authors could not come to terms, either one could "publish a manu-

script based upon the research they have conducted."

Kendler says this was a "one-sided" plan in that it gave Diehl a green light to publish without the clinicians' consent. Neither he nor Dewey accepted it, arguing that the diagnostic data should remain under Kendler's control. The MCV team learned that Diehl was preparing a manuscript for publication, although they didn't understand how Diehl was able to analyze the results without all the data. (Diehl says he copied some data contributed by colleagues while at MCV, and that as a co-investigator, he was entitled to take such paper files with him.)

With Diehl gone, a new molecular biologist, Richard Straub, arrived at MCV in 1993. By the summer of 1994, Straub had completely redone the analysis of chromosome 6, confirming Diehl's earlier finding. "We felt we really couldn't sit on it," Kendler says. "It was too important. ... We wanted to get the science out." So on 23 August 1994, the MCV team and Walsh faxed an announcement to "20 leading groups" in psychiatric genetics. It reported that "we are following up unpublished linkage results observed by Dr. Scott Diehl (while at MCV in 1992–1993)." In three pages, it sought to cover all the ground, listing positive results for linkage to schizophrenia and several genetic markers in the region 6p22-25. The MCV group staked out this turf again in a presentation at the International Congress on Schizophrenia Research in April.

Meanwhile, Diehl's manuscript—with co-authors including statistical analyst Lynn Goldin, a geneticist at NIMH, and some of Diehl's former MCV staff who accompanied him to NIH, including biologist Shengbiao Wang (first author)—was submitted to *Nature Genetics*. Kevin Davies, editor of *Nature Genetics*, says he was unaware of the controversy swirling behind the scenes. Today, he adds, the "most constructive" way to solve the problem is to entertain manuscripts from others who feel aggrieved. (Kendler and Straub are submitting their manuscript this week.)

When Diehl's paper appeared, it contained a big surprise for his former colleagues. The genetic marker that Diehl highlighted (D6S260), which gave the strongest evidence of linkage between schizophrenia and chromosome 6, is one that no one at MCV had ever heard of. "It isn't in our database," says Kendler, who marvels that Diehl was able to study it at MCV without telling his colleagues about it. Kendler wonders whether Diehl removed some biological materials or digital information from the lab and analyzed them elsewhere. Diehl strongly denies this. The initial research with D6S260 was performed at MCV, Diehl says, but "that marker had never been input into our computer system" because he had to leave in such a hurry. "We never had time" to enter the data, Diehl says. He claims he left information in the lab, but that the MCV team "never figured out what they had in hand."

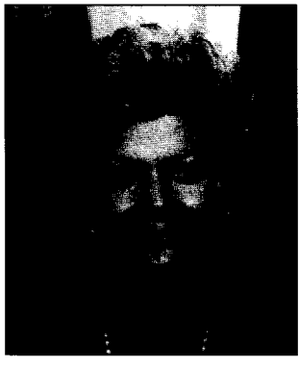
Although the struggle over chromosome 6 goes on, many feel that the worst of the battle is over. According to NIDR's acting director, Dushanka Kleinman, the government has undertaken two fence-mending efforts. Diehl and his colleagues are considering sending a note to *Nature Genetics* to "clarify the authorship" issues. And NIH's top brass, under the guidance of Michael Gottesman, associate director for intramural research, is putting together a special panel to see whether NIH handled this case in the best possible way and whether it needs to change any of its policies.

–Eliot Marshall

DEPARTMENT OF ENERGY

O'Leary Takes Swipe at Bureaucracy

Surrounded by huge charts and graphs, Energy Secretary Hazel O'Leary last week promised to cut more than $14 billion over the next 5 years from the Department of Energy's (DOE's) budget without jettisoning any research programs. O'Leary and a team of DOE officials want to slash the number of employees and sell off everything from DOE's power-marketing administrations to gold and highly enriched uranium. Almost 4000 jobs will be eliminated. In contrast, O'Leary singled out science and technology as favored missions: "We're cutting out the crap so we can do this work," she told reporters at a press briefing. The result will be a "dramatically different and rationalized DOE."



Chop shop. O'Leary would "cut out the crap" to save science.

O'Leary has little choice. In December, shortly after the Republicans won control of Congress on a promise to shrink government, the Clinton Administration floated the idea of eliminating DOE and several other agencies. To avert that fate, O'Leary promised the White House that she could make dramatic reductions. And while many of those Republicans still want to abolish DOE, O'Leary is betting that her plan is radical enough to quiet the critics.

Her proposal for the national labs incorporates many of the recommendations made in February by a panel led by Motorola Chairman Robert Galvin, although not Galvin's idea of privatizing them (*Science*, 10 February, p. 787). The plan is expected to save $1.4 billion, mostly by reducing personnel at the labs and at the DOE field offices that oversee them. O'Leary is also creating a lab management board to oversee the strategic direction of the labs, now set by individual lab directors. But the secretary reiterated her opposition to a recommendation by the Galvin panel to get Lawrence Livermore National Laboratory out of the business of designing nuclear weapons over the next 5 years. "I do not think it can be done" that fast, she said. "And we would need to do that very carefully."

O'Leary may gain support from an interagency panel of the National Science and Technology Council, chaired by DOE, which is looking at Livermore's future. Its report is due 31 October, but O'Leary says she would like it by September so that its advice can be worked into the 1997 budget request. One Administration official predicted its conclusion will bolster her preference for moving cautiously.

O'Leary's plan earned bipartisan praise last week from science advocates in Congress. Representative Robert Walker (R–PA), chair of the House Science Committee, called it "a vital and necessary step in reforming government and saving taxpayers' money." Representative George Brown (D–CA), the ranking minority member of the panel, said it was "a perfect example of how we can move to make responsible cuts without sacrificing more of our diminishing national science and technology capability."

But while the plan seems the epitome of fiscal austerity, congressional staffers and Energy Department officials say it will not relieve pressure to drop one or more of several proposed research facilities, including the National Ignition Facility at Livermore or the Tokamak Physics Experiment at Princeton University that are central to the U.S. fusion effort. The President's Committee of Advisors on Science and Technology hopes to complete a report this summer outlining fusion's future.

Congress still must hash out DOE's fate. Brown noted that O'Leary's plan "is not the last word from the department on savings," and Walker added that the secretary "has provided a useful first step, but reorganization is not the end of the walk." For DOE's research programs, that means waiting to see what lies around the next budget corner.

–Andrew Lawler