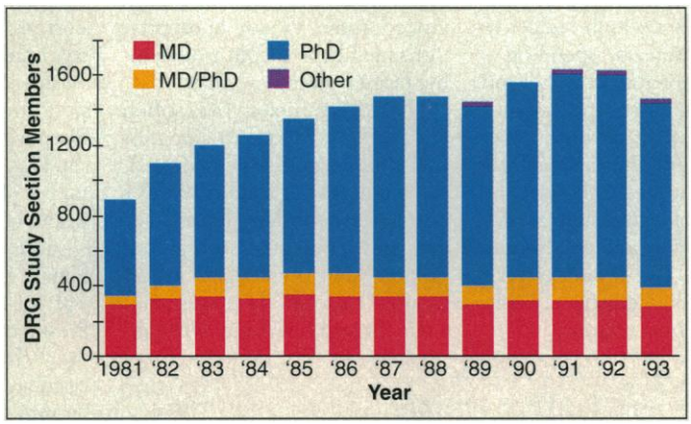
Does NIH Shortchange Clinicians?

Clinical researchers have been peppering NIH head Harold Varmus with letters of complaint; NIH is now looking to see if there is bias in its peer reviews

Soon after being installed as director of the National Institutes of Health (NIH) last fall, Harold Varmus was put on notice that he would have to contend with yet another grassroots biomedical lobbying group. This group was different, though. It wasn't led by patients, and it wasn't seeking more money for a specific illness such as AIDS or breast cancer. Instead, it was calling for a bigger share of the pie for an entire class of biomedical science: basic clinical research. Clinical researchers peppered Varmus last fall and early this year with letters complaining that NIH had turned its back on "patient-oriented" research in favor of molecular biology.

The complaint echoed a concern raised more than a decade ago by then–NIH director James Wyngaarden, who described physicians who fill the double role of doctor and researcher as "an endangered species." Wyngaarden noted that the ranks of physician-scientists were on the wane, apparently being replaced by Ph.D.s who had almost no experience in treating patients. Now, M.D.-researchers say, this shift has led to the devaluation of clinical research and a skewing of the way NIH distributes research funds.



Peer pressure. The fraction of study section members with M.D.s has been declining; clinicians say their proposals get short shrift.

Varmus and other top NIH officials are taking the clinicians' lament seriously. This summer, Jerome Green, head of the division of research grants and overseer of extramural peer review, will be working with a special advisory committee trying to determine whether there's any evidence that the system is in fact biased against clinicians seeking funds for small, self-initiated projects known as RO1 grants. And, in a related move that could have a bearing on clinical researchers' chances of winning grants in the increasingly stiff competition for funds, Varmus has asked NIH staff to undertake sweeping reviews of NIH's management of clinical studies and its training of young clinical researchers. The first of those reviews is being organized by Wendy Baldwin, NIH associate director for extramural research, who has mobilized "eight or nine working groups" to examine the quality of information provided to patients, the use of safety monitoring boards, audits, and other indices of quality control. And the new director of NIH's clinical center, John Gallin, is surveying intramural training programs to identify new strategies for training. He plans to develop a "generic core curriculum" for the 100-plus young M.D. clinical associates who arrive at NIH's campus each year for a 3-year tour.

The chairman of the ad hoc advisory group examining R01 grants—Gordon Williams, an endocrinologist at Harvard University's Brigham & Women's Hospital in Boston—says he has become aware of "an increasing groundswell of complaints from around the country." Indeed, when Williams sought comments this spring, he received "an incredible response" from more than 300 clinical researchers, including many department chairs. This is just the "tip of the iceberg," Williams believes. Williams' panel has met three times and is scheduled to hold a final public session on 1 September before issuing a report this fall.

This groundswell of concern is based more on anecdote than statistics, however. NIH has tried to evaluate the clinicians' case in the past, but the data it collected were weak: NIH classified as "clinical" any grant for which the applicant checked a box indicating human subjects were involved. Under this loose definition, which includes epidemiology and laboratory studies of human cells and tissues, about 30% of NIH RO1 grants go to clinical researchers. However, a more detailed review of grant abstracts by Edward Ahrens Jr., professor at Rockefeller University and champion of clinical research, found that only 7.4% of the RO1s funded by NIH in 1987 were patient oriented, and the percentage seemed to be on the decline. Another survey—conducted this year by an Institute of Medicine (IOM) panel that plans to release a report on clinical research next month—yields an even smaller estimate. The IOM panel found that 15% to 17% of 14,535 NIH grants awarded in 1990–1991 were for clinical research, broadly defined, and only 4.5% were for basic human research.

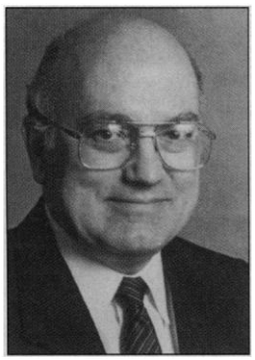
Staffers at NIH working with the Williams panel are just now beginning to collect new data about possible bias against clinical research, which the Williams panel defines as studies in which the researcher "directly interacts with human subjects in either an outpatient or inpatient setting." In June, the NIH staff surveyed all members of study sections to see whether they do this kind of research themselves, and the staff has been analyzing 1994 grant scores to see how clinical proposals fared.

According to Green, preliminary results suggested at first that clinical proposals were reviewed more harshly because they did poorly compared to basic laboratory studies. But when NIH staffers examined proposals that had been revised after an initial rejection, they found that clinical and basic studies scored about the same. To Green, this suggests that the initial submissions may have been poorly prepared. If so, he says, more training in biostatistics and grant writing might make the clinicians more competitive.

Many believe the problems run deeper than this, however. Ahrens points out that there are no M.D.s among the NIH staffers who supervise the study sections; all are Ph.D.s. And relatively few M.D.s serve as reviewers. This has created a "self-perpetuating" syndrome, Ahrens says, in which Ph.D. administrators turn to like-minded friends and colleagues to conduct reviews, and these reviewers tend to favor basic science proposals. The consequence: Study sections are less and less interested in clinical research. Physicians, for their part, "have gotten discouraged with the process," Ahrens says. Many young physicians don't even bother to apply for funding any longer, he adds.

But Belinda Seto, a former virology sec-

tion chief at NIH now helping with the Williams panel inquiry, points out that physicians themselves are partly responsible for this situation. She says that M.D.s don't pursue jobs at NIH, because physicians with experience comparable to NIH section chiefs can earn twice as much elsewhere. Busy physicians rarely serve as reviewers.



Reviewing peer review. Gordon Williams.

Roy Silverstein, president of the American Federation for Clinical Research, agrees that physicians share the blame for their absence from study sections. In a talk before the Williams panel on 10 June, Silverstein offered a solution: NIH should adopt a new mandatory service rule akin to jury duty. He said NIH should require all investigators who receive NIH funding to accept invitations to serve on a study section at least once every 8 years. The goal would be to "increase the number of reviewers who are knowledgeable about clinical research." Silverstein also urged NIH to set up a special study section to give special attention to clinical proposals that fall just below the payline. This group, according to Silverstein, could "recommend a specified number of these clinical research projects to be supported by a contingency fund, possibly in the director's office."

Baldwin isn't enthusiastic about the request for a new study section. Probably "20 different groups" have come up with this solution for problems in their fields, she says. Besides, clinical research is a broad category; Baldwin thinks it would be hard to create a panel that could handle everything under that heading. Finally, Baldwin says it's not clear that clinical proposals are being treated unfairly. She's withholding judgment until she sees the final report of the Williams committee, which will include a detailed analysis of how reviewers treated proposals this year.

As for Williams, he strongly suspects that the final report "is going to say we have a very substantial problem," although he isn't ready to say what changes it may recommend. At the same time, he recognizes that "we wouldn't be having this discussion" if NIH were able to fund more grants. The budget crunch, Williams concedes, is "driving the whole problem."

–Eliot Marshall

CHEMISTRY

Underhanded 'Breakthrough' Revealed

It was "just too good to be true," chemist Tony Barrett of London's Imperial College told *Science* 6 weeks ago about a startling new discovery by German chemists (*Science*, 13 May, p. 908). Barrett's circumspection about the discovery, which seemed to represent a breakthrough in the mystery of the "handedness" of such biomolecules as protein and DNA, has proved well-founded. Last week, the head of the team that carried out the work, Eberhard Breitmaier of the University of Bonn, retracted the results in a letter to the journal that published the original paper. One of the members of his team, he explained, had manipulated the experiments.

To many chemists, the announcement comes as a relief as well as a shock. Although they initially hailed the result, which appeared to have major implications for the pharmaceutical industry as well as for understanding of the origins of life, their doubts had been growing. As word had spread about the paper, which was published in the German journal *Angewandte Chemie* in February, many groups had tried and failed to repeat the experiment and had spotted inconsistencies in the data. If the Bonn team had stood by the results, it "could have become organic chemistry's version of cold fusion," says organic chemist T.V. RajanBabu of Dupont's Central Research and Development department in Wilmington, Delaware.

According to the paper, a static magnetic field can force chemical reactions that ordinarily produce equal amounts of two mirror-image molecules, or enantiomers, to favor one form. Although chemists were hard-pressed to understand how a magnetic field could skew the reactions Breitmaier and his colleagues studied, they pointed out that Earth's magnetic field could have had the same effect on the first biological molecules. That might explain why, for example, DNA in nature is almost always a right-handed helix. The discovery also seemed to offer a ready way to make single-enantiomer drugs —important because the two mirror-image forms of some drugs have very different effects in the body.

But warning signs in the paper made some researchers wary. RajanBabu, for example, says that he was skeptical from the start. The Bonn group had used nuclear magnetic resonance (NMR) spectroscopy to detect the relative quantities of the two enantiomers, but "the NMR spectra in the paper were clearly wrong," says RajanBabu. "It was a dead giveaway." Despite repeated attempts, he and his colleagues Chris Roe and Gary Halliday could not replicate the German results, even when they applied a magnetic field three times as strong as the Bonn group used. RajanBabu then asked Al Meyers of Colorado State University to attempt the experiments. Meyers' team was just completing the experiments as *Science* went to press, and it too drew a blank. Meyers says he isn't surprised. The magnetic field simply doesn't have enough energy to bias the reaction, he says. "On a theoretical level, there is just no way in hell that it could be true."

In all, says Peter Gölitz, editor of *Angewandte Chemie*, at least 20 groups were working on the problem, and many were getting negative results. But when several groups sent researchers to Breitmaier's lab to try the experiment there, the magnetic field seemed to work as advertised, which led to suspicions that something about the apparatus or starting materials was affecting the outcome. According to his letter, Breitmaier himself then instructed three experienced co-workers, none of whom had worked on the original paper, to carry out the most important of the reactions without the participation of Guido Zadel, the postdoc on whose thesis the original work was based.

This time the magnetic field had no effect. These researchers also found that starting materials prepared by Zadel for the experiments contained significant amounts of a single-enantiomer additive. Breitmaier and his colleagues believe the additive biased the reaction, deceiving other members of the team into thinking that the applied magnetic field was responsible.

In his letter, Breitmaier says that Zadel has now admitted this deception and two other manipulations of the scientific data in front of witnesses. Breitmaier and the two remaining co-authors, Catja Eisenbraun and Gerd-Joachim Wolff, have now disassociated themselves from all the experimental results in the paper. Breitmaier told *Science* this week that he was "very shocked" by the whole affair but would not elaborate until the university has completed an investigation.

Other chemists, meanwhile, are taking the episode as a reminder that the more important a finding seems, the more caution it demands. As Barrett of Imperial College puts it, "You should never rush to publish a fantastic new finding—get a trusted colleague to check it for you first." Meyers sees a lesson for would-be frauds, as well. "If you are going to cheat, cheat on something so unimportant that no one will repeat it."

–Daniel Clery and David Bradley

David Bradley is a science writer in Cambridge, U.K.