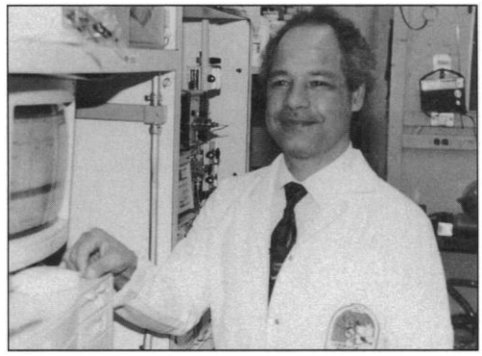
CLINICAL RESEARCH

NIH Adds an Extra Layer of Review for Sensitive Grants

Last June, officials at the National Institutes of Health (NIH) were caught badly off guard—not for the first time—by biotech critic Jeremy Rifkin. They were unprepared for the fuss over Rifkin's attempt to halt a clinical trial in which human growth hormone (hGH) was being tested as a treatment to make healthy, short children taller. Rifkin accused NIH of straying from its traditional role of studying diseases into the ethically murky realm of manipulating traits, and the press jumped on the theme. At the time, the principal investigator of the hGH trial—which had been under way for 8 years—was on vacation and unreachable, and most other NIH officials knew too little to comment knowledgeably. According to one NIH scientist involved in the trials, "After a week of being villainized, we were told to stop talking to the press." NIH Director Bernadine Healy, scientists and officials at NIH recall, was furious about NIH's stumbling response and the fact that she'd not been informed of the protocol's potential for controversy. "Had we been better prepared for Mr. Rifkin's concerns, it would have been better for everybody," laments Alan Sandler, director of NIH's Office of Human Subjects Research.

Rifkin's petition didn't succeed in halting the trials but it did help insert a new layer in NIH's review procedures—one that some researchers fear might cause headaches in the future. The new policy was put in place last fall, when Lance Liotta, deputy director for intramural research, asked each NIH institute to form a panel to re-examine every clinical research protocol proposed by NIH researchers after it has gone through peer review and been cleared for funding. Known as protocol implementation review committees (PIRCs), the new panels are supposed to flag anything that might spell trouble for NIH. If a PIRC finds a "hot" protocol, it kicks it over to Liotta, who in turn alerts Healy and decides whether to convene yet another panel to review the research further.



Point man. New committees report to intramural research chief Lance Liotta.

Although many NIH researchers seem to be unaware of the new system, as word of it spreads around the campus it is generating some unease. NIH is bending over backwards in an effort to please everybody, some scientists say, and a few grumble that the review amounts to a test of political correctness, calling the PIRCs "P.C. panels." Says one top researcher: "This has the potential to become a Big Brother issue."

Such concerns are "ridiculous," scoffs Healy. In an interview with *Science*, Healy said she set up the PIRCs simply to ensure that a collection of NIH committees called institutional review boards (IRBs) are functioning properly as "patient advocates." The IRBs, which consist of clinical researchers and consulting bioethicists, re-

Eyeing a Project's Ethics

On 6 September 1991, an unusual panel met at the National Institutes of Health (NIH) to review a plan by researchers at the National Institute of Neurological Disorders and Stroke (NINDS) to test a device that might lead to a visual prosthesis for the blind. The procedure could provide a model for the kinds of reviews that may now be required for sensitive clinical research protocols (see main story).

A research team led by NINDS neurologist Conrad Kufta had proposed electrically stimulating the brain of a 42-year-old blind woman. The plan was to trigger phosphenes—sensations of light induced by electrical or magnetic stimulation of the visual cortex—with an array of microelectrodes inserted 2 millimeters into the patient's visual cortex. The experiment was an early step toward the possible development of a visual prosthesis in which microelectrodes connected to a miniature camera create a phosphene map of the outside world. But the blind volunteer in this experiment was told to expect no personal benefits from the device.

The proposed experiment raised some eyebrows at the National Eye Institute (NEI). In a 30 August 1991 memo to NEI director Carl Kupfer, Robert Wurtz, chief of NEI's sensorimotor research lab, suggested more work on animals before the procedure is carried out on humans. Kupfer, who at the time was acting deputy director for intramural research, recommended to NIH Director Bernadine Healy that she convene a special panel to review the protocol further. Healy agreed. "Most of the time our research has a glimmer of a chance of helping a patient," she says. But in this case, she says, the woman "was literally going to be used as an experimental subject."

The NINDS researchers were surprised to hear that their plan was going to get another review. Their protocol already had passed peer review as well as safety and ethical reviews by the NINDS Institutional Review Board and the Food and Drug Administration. "We felt kind of singled out in a way, rather unfairly," says NINDS neurologist F. Terry Hambrecht, neuroprosthesis program chief.

The 10-member review panel, consisting of four NIH scientists, five outside scientists, and a Washington, D.C.-based minister, reviewed the protocol, heard presentations from Kufta, Hambrecht, and other NINDS researchers, and deliberated in a private session before voting 8 to 2 to let the experiment proceed. In a report, the panel called the protocol "excellent" and "carefully prepared," but the two members who voted against it—neurobiologist Torston Wiesel, now president of Rockefeller University, and Johns Hopkins medical researcher Vernon Mountcastle Jr.—issued a separate statement calling for more experiments on nonhuman primates before NIH permits research on humans.

Soon after the panel approved the protocol, the NINDS researchers installed the electrodes and last fall they presented their results at the Society for Neuroscience annual meeting. They reported that 34 of 38 microelectrodes stimulated phosphenes, and that the volunteer reported "seeing" the letter "I" when a vertical row of microelectrodes was fired. NIH officials say they are pleased with the process. "This was a landmark protocol, so we had to know if it got the broad review it deserved," says Saul Rosen, director of NIH's clinical center.

–R.S.

view clinical research protocols to make sure they conform to ethical guidelines governing research on human subjects. They have the authority to require changes in protocols or veto them if they don't pass muster.

Healy is not alone in wanting to beef up the IRB system. "The IRBs aren't nearly as sensitive to the changing morals of society as they should be," asserts Walter Rogan, an epidemiologist at the National Institute of Environmental Health Sciences and chair of its IRB. In particular, Rogan argues that some IRBs are only now beginning to realize how important it is to include women and minorities in study populations. Because of these perceived shortcomings, the director of NIH's Clinical Center, other institute directors, and NIH's bioethics office in the past have kept an eye out for potentially troublesome protocols. In fact, in the fall of 1991, then deputy director for intramural research Carl Kupfer singled out one project—an experiment that may one day lead to a visual prosthesis for the blind—for an extra review that could serve as a model for the sort of additional scrutiny the PIRCs will recommend (see box on p. 1820).

Liotta formalized this ad hoc screening in an August 1992 memo to the institutes' scientific directors, asking them to set up a PIRC in each institute. Liotta said the PIRCs (each composed of the institute's scientific director, clinical director, and a third scientist, preferably an official in NIH's extramural program) should double check the IRB minutes and pay close attention to research that involves "potentially vulnerable" subjects such as children, pregnant women, and prisoners. They should ensure that any collaborative research ventures are "fully documented and are deemed to be free of conflict of interest." And, finally, Liotta gave the panels a broad directive that some researchers find troublesome: The PIRCs should check that each protocol is "consistent with [the institute's] research objectives and is likely to yield knowledge of importance to the mission of NIH." Says one IRB chair: "That's vague...there's great concern in the scientific community over what that means."

Liotta said that the panels should direct specific problems with protocols to the IRB chairs, but protocols "of special interest" should be sent to him. Liotta would then decide whether to convene a "special review committee," including NIH policy experts and a couple of ad hoc members with relevant scientific backgrounds, to take a closer look. Sandler, who played a key role in designing the new system, says the committee has the authority to turn down protocols if necessary.

Most NIH officials contacted by *Science* are reserving judgment until the system has been in operation for some time. (Since the PIRCs were established last fall, they have flagged six protocols, all of which Liotta has approved without further review.) But there's some unease about the power of the Special Review Committee, says David Goldman, a geneticist at the National Institute on Alcohol Abuse and Alcoholism and chair of that institute's IRB. Says another IRB chair: "We didn't want [this extra layer of review]; it's a potentially dangerous layer of administrative coverage."

Investigators themselves also seem to have mixed feelings about the new system. "It's all pretty reasonable," says Frank Balis, a cancer researcher at the National Cancer Institute and previously a longtime IRB chair. "In a sense it's not the committee that's making those protocols political, it's the studies themselves," he says. But one investigator who's been through an extra review commissioned prior to this system—Conrad Kufta, principal investigator of the visual prosthesis protocol—feels differently. "There's a lot of controversy at the principal investigator level," he asserts. "We don't want to go through another layer of bureaucracy to get things done."

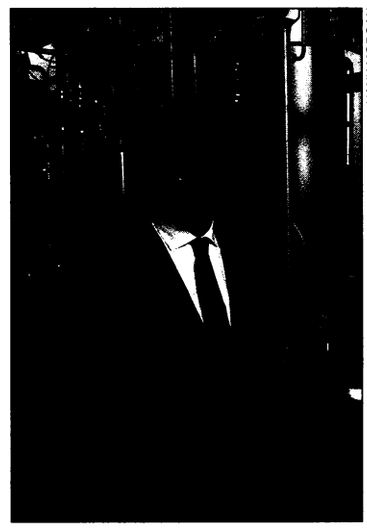
Some IRB chairs welcome the new system, however. "On the surface there's an air of political correctness," says Phillip Fox, a dental researcher who chairs the IRB for the National Institute on Aging. But, he says, "it doesn't hurt to have more people look at a protocol. In the climate of society today, the more examination the better."

–Richard Stone

AIDS VACCINES

MicroGeneSys Withdraws From Trial

MicroGeneSys Inc., the controversial biotech firm that enraged AIDS researchers last fall when it successfully lobbied Congress for $20 million to test its therapeutic AIDS vaccine, once again has the scientific community up in arms. Ironically, this time the Meriden, Connecticut, company is being assailed for the opposite behavior: refusing, at the last minute, to allow its vaccine—VaxSyn—to be used in a long-planned, government-sponsored trial of therapeutic AIDS vaccines.



HANK MORGAN

Pulling out. MicroGeneSys president Franklin Volvovitz.

Why would the company take such different stances only a few months apart? MicroGeneSys president Franklin Volvovitz did not respond to repeated requests for an interview by *Science*, but the small biotech firm's corporate partner, Wyeth-Ayerst Research, said in a letter to the organizers of the planned trial that the protocol "does not address any specific issues directly relevant to the Clinical Plan for VaxSyn development and licensure," and cited "scientific considerations" as reasons for the withdrawal, including the timing of vaccine shots in the trial and the trial's clinical endpoints. Some angry researchers, however, don't think that's the whole story. They point out that the trial MicroGeneSys pulled out of would have involved a comparison of VaxSyn with vaccines made by two other companies: Chiron and Genentech. The trial the company lobbied for last fall, in contrast, would focus solely on the MicroGeneSys product.

Therapeutic AIDS vaccines aim to expand immune responses in already infected people, delaying or preventing the onset of disease. A half-dozen such vaccines are now being tested in human beings, and though it is not clear that any of them can delay the onset of AIDS, they appear to be safe—and some show hints of clinical promise.

The comparative trial MicroGeneSys bowed out of is being planned by the National Institute of Allergy and Infectious Diseases (NIAID) to find out which preparation is most likely to fulfill that promise. Though the MicroGeneSys, Chiron, and Genentech vaccines all contain genetically engineered versions of a protein that studs HIV's surface, the vaccines differ in the size of the protein they contain, the strains of HIV they rely on, and the way they are prepared. These differences might mean that one of them works better—or worse—than the rest.

John Moore, a researcher at New York's Aaron Diamond AIDS Research Center, contended in a letter published in the 11 February *Nature* that MicroGeneSys, unlike Chiron and Genentech, has engineered a protein that does not mimic the native HIV protein closely enough and thus has a "severely limited" ability to induce a "relevant" antibody response. "It's unfolded and has a shape nothing like the natural molecule," says Moore. "Some people would think that's a virtue. Most people would think of that as a crippling handicap." In the past, MicroGeneSys has argued that no one knows precisely what the relevant antibody