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BIOETHICS

NIMH to Screen Studies for Science and Human Risks

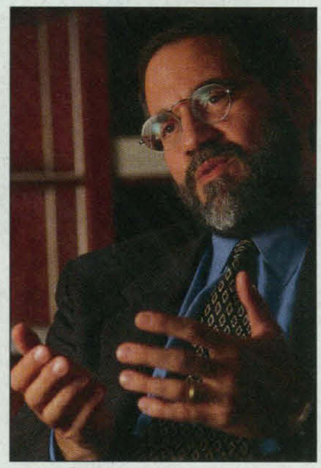
For more than a year, patient activists and ethicists have been calling for a revolution in the way clinical studies in psychiatry are monitored. They argue that studies of psychiatric disorders, especially trials that exacerbate symptoms or withdraw medication, expose subjects to needless risks. And they have been demanding a more critical, independent review of protocols. These ideas have circulated widely in the press and dominated the work of a national bioethics commission in 1998. Now, a surprising new voice has joined the chorus of reformers: Steven Hyman, director of the National Institute of Mental Health (NIMH), the nation's largest funder of clinical research in psychiatry.

At the NIMH advisory council meeting on 5 February, Hyman plans to seek approval of a new review panel that would screen "high risk" human studies before NIMH agrees to fund them. The goal, he says, is to reinforce the rule of "beneficence": NIMH needs to remind everyone that "we have the privilege of doing clinical studies only when the outcome is good and important." In addition, he would like to pare away some of the repetitious "me-too" studies now in the portfolio. Hyman has already been applying such criteria to NIMH's intramural research, conducted in the institute's labs in Bethesda, Maryland. On 5 January, he stunned many NIMH lab chiefs when he and NIMH scientific director Robert Desimone suspended enrollment in 29 of 108 clinical protocols and asked that more than 50 be rewritten to clarify scientific objectives or human subjects protections.

The intramural shake-out and the plan for a top-level review of new research—which is sparking concern among some NIMH grantees—are "separate," according to Hyman. But they are connected, he says, by a desire to make sure that the science in NIMH studies is good enough to justify the use of human subjects. Protocols that rely on human volunteers should be designed with "questions that are crisp enough to give a result. … You should have a real question that you want to answer, set it up well, and you don't have to keep replicating it."

In an interview with *Science*, Hyman said the proposed new panel—which would review both intramural projects and extramural grants—would include ethicists and other outsiders. Constituted as a subcommittee of his advisory council, it would review and approve the funding of clinical trials after a local institutional board has vetted them for safety, and shortly after an NIMH study section has ranked them for merit. This final check would focus on human studies that seem risky—a term that remains undefined but clearly would include the kind of work that got negative publicity in 1998: studies that halt mental patients' ongoing medication, replace it with a placebo, or "challenge" them by exposing them to chemicals that intensify their symptoms. It would balance scientific objectives with human risks.

> **"We have the privilege of doing clinical studies only when the outcome is good and important."**
>
> —Steven Hyman



As for the intramural shake-up, Hyman says he and Desimone made these "rather dramatic" decisions after reading the comments of an ad hoc panel that met at NIMH on 8 to 9 December to assess "every active intramural protocol." Hyman says he convened the top-level review—the most sweeping ever done by NIMH—because the institute is under orders to bring its own protocols into line with standards applied to extramural research. The 20-member group of outsiders, co-chaired by psychiatric researchers Dennis Charney of Yale and Jeffrey Lieberman of the University of North Carolina, Chapel Hill, examined scientific summaries and clinical descriptions for every protocol submitted to the NIMH institutional review board.

"No one had been doing anything that would harm [patients]," Hyman says. But "in many cases, [the summaries] weren't written in such a way that you could either clearly state the scientific hypothesis or understand exactly what was going to happen to the human subjects." In the past, investigators wrote in a "flexible" way to take advantage of new ideas as they appeared. Now investigators are being asked to redraft summaries to make their methods and goals clearer. But a few protocols, Hyman observes, "have not aged gracefully," and these are not likely to be continued. These will not resume. Desimone expects most of the others will be back on track by spring.

Hyman concedes that part of the reason for this intense scrutiny of intramural and extramural NIMH studies is that "there is currently a lack of public trust in how things are happening." Indeed, calls for increased scrutiny of psychiatric research began at least a decade ago, when relatives began complaining that research protocols were taking precedence over the needs of patients. For example, filmmaker Robert Aller sued the University of California, Los Angeles (UCLA) in 1992, alleging that a decision to end medication for his son, who was in a clinical trial, made the son's schizophrenia worse. UCLA denied the allegations, and Aller lost in court. But a federal inquiry ordered procedural changes at UCLA. And later, the media and an independent federal panel, the President's National Bioethics Advisory Commission (NBAC), looked into appeals for outside monitoring of such research and found many justified.

On the East Coast, an advocacy group led by Vera Hassner Sharav, Citizens for Responsible Care in Psychiatry and Research of New York City, launched a similar campaign.

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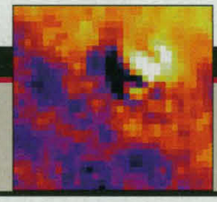

Hassner Sharav steered patient-critics to NBAC in September 1997, where they presented claims that clinical researchers were needlessly distressing patients in challenge trials. Later she asked NBAC to look into the use of ketamine, an anesthetic that has been given in small doses to hundreds of mental patients to provoke psychotic symptoms. Ketamine has short-lived effects like the hallucinogen PCP, causing weird auditory and visual disturbances. Based on its own review, NBAC recommended new protections for mental patients (*Science*, 27 November 1998, p. 1617).

Clinicians say the heaviest blow, however, came in late November, when the *Boston Globe* ran a devastating four-part series full of research horror stories. It concluded with an editorial asking the Justice Department to conduct a criminal investigation into challenge and drug-withdrawal studies. Research leaders were shaken. Within weeks, Hyman spoke publicly about the need for a new scientific panel to approve risky research.

Researchers doing the kind of work that has been criticized tend to see Hyman's move as a surrender to critics, and they don't like it. "I think it would be foolhardy," says William Carpenter, director of the Maryland Psychiatric Research Center at the University of Maryland, Baltimore. Carpenter's colleagues were among those criticized for conducting ketamine studies. Singling out clinical psychiatry for an extra review would be wrong, Carpenter says, because it stigmatizes that area of biomedicine. "It will discourage the best young investigators," he thinks, for "why would you go into a field that has a politicized review process, when others don't?" Like his peers, he insists that other medical researchers use probes that are at least as risky as those used in psychiatry.

Carpenter worries that once created, the new safety panel will slip out of NIMH's control. Critics "will see an innate conflict of interest" in allowing NIMH to watch over its own studies, he warns, and will take it over and "politicize" it. As a warning, he points to the attack on ketamine studies, which he defends as an important way of learning about the efficacy of schizophrenia drugs. He claims that through ketamine trials, people are finding that widely used antipsychotic drugs don't block the underlying pathological brain activity. As for side effects, "ketamine doesn't seem to cause much anxiety or distress," he says. At a 1 December meeting at NIMH, Carpenter reported that data from about 60 patients in ketamine trials at NIMH, Yale, and Maryland reveal few signs of distress. The effects in the worst cases lasted no more than 2 days, he said, and most effects were over within 90 to 180 minutes. However, two patients were distressed enough that they dropped out of the research.

Donald Klein, a professor at Columbia University and a psychiatrist at the New York State Psychiatric Institute, also feels that a national safety review panel for psychiatry could stifle research. His own work for the past 2 decades has involved inducing panic in people with panic disorder by injecting them with sodium lactate. It has led him to a theory that many cases of panic disorder arise from an innate derangement of the suffocation alarm, a hypersensitivity to carbon dioxide. This research could never have been done, Klein says, without challenge studies, and he wonders whether it would have been permitted by a national safety panel.

Although a few senior clinicians like these are hostile to Hyman's proposal, others are keeping their powder dry. The president of the American College of Neuropharmacology, David Kupfer, chief of psychiatry at the University of Pittsburgh, says he's pleased that NIMH is trying to be "proactive," but doubts that a national safety panel can do better than existing, local ones.

Hyman is aware of resistance within his community. But he believes NIMH must move ahead with the reforms. Given the attention being focused on the ethics of mental health research, he said at a meeting last December, the community needs "to get our house in order." –ELIOT MARSHALL

BIOMEDICAL RESEARCH

Ruling May Free NIH to Fund Stem Cell Studies

Scientists eager to begin studies on two new types of human stem cells got some good news this week: The National Institutes of Health (NIH) announced that, contrary to what many had feared, U.S. law does not bar federal support for this burgeoning field. Grant money could be approved as early as this fall, according to NIH staffers. Researchers hope to use the cells for studies ranging from basic research on early human development to the development of new technologies for tissue transplantation.

NIH director Harold Varmus announced on 19 January that, in the Administration's reading, "current law permits federal funds to be used for research using human pluripotent stem cells"—cells that have the potential to develop into a wide variety of human tissues. During a talk at a meeting of the National Bioethics Advisory Commission (NBAC) in Washington, D.C., Varmus released a memo on stem cell research by Harriet Rabb, general counsel of the Department of Health and Human Services. Rabb makes it clear that there is no legal reason why funding of stem cell research cannot begin now.

No legal barrier. Varmus hopes to move ahead later this year.

Rabb's ruling sets aside some of the concerns that arose in November, when researchers first announced that they had derived stem cell lines from human embryo and fetal tissue (*Science*, 6 November 1998, p. 1014). NIH officials were concerned that congressionally imposed rules on some types of embryo and fetal tissue research might restrict the use of the new stem cells to private labs. For example, a clause added to the 1999 NIH appropriations bill makes it unlawful to spend federal funds on the creation of embryos "for research purposes," and it blocks support of research in which embryos are "destroyed, discarded or knowingly subjected to risk of injury or death. ..." An earlier statute also restricts interstate transfer and the therapeutic use of fetal tissue.

In her memo, Rabb makes a distinction between federal support for the development and the use of stem cell lines. The congressional language would prohibit the development of cell lines from embryos but not necessarily from fetal tissue, she wrote. (Both stem cell lines announced in November were developed with private funds.) But the law doesn't apply to the use of stem cells from either source, she said. The law focuses on making a human "embryo" or "organism" for research, she notes, but stem cells are not organisms—or even precursor organisms, in her view—for they cannot develop into an embryo even if implanted in a woman's uterus.

Varmus discussed these detailed legal issues at the first of six meetings NBAC is planning for an ethics review of stem cell research. NBAC hopes to have a draft report by