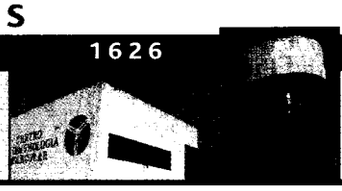


RESEARCH ETHICS

Panel Tightens Rules On Mental Disorders

A presidential panel's call for stronger protection of mental patients who take part in research is drawing fire from clinical psychiatrists and some advocacy groups. The clinicians say that the report, a final draft of which was approved on 12 November by the National Bioethics Advisory Commission (NBAC), would impose too many constraints on research and would further stigmatize an already vulnerable population by singling out people with mental disorders for competency tests. Some patient advocates, on the other hand, complain that the new rules would still permit some research to go ahead without a patient's approval.

The commission, which took up the issue 15 months ago on its own initiative, proposes 20 measures to protect people with mental disorders from exposure to risk in clinical trials. The panel—composed of ethicists, biologists, physicians, and patient advocates (but no psychiatrists)—says in its report that it isn't responding to a crisis. But with clinical studies of brain disorders such as schizophrenia and depression increasing, NBAC sought to "clarify the ethical framework" for such research. "I do not believe this will have any adverse effect on the research agenda," says commission chair Harold Shapiro, president of Princeton University. He predicts that the "public will be much more supportive" of research knowing that stronger safeguards are in place.

Clinical researchers, however, are alarmed at some of NBAC's recommendations, especially one that would require an "independent, qualified professional" to evaluate the competence of a subject in any study posing greater than minimal risk (see diagram). In general, says NBAC, only people judged capable of making a decision to enroll in such studies should be allowed to do so. Current guidelines, NBAC says, are murky and "inadequate." NBAC would also like to see the government create a standing committee to set guidelines and review protocols for "exceptionally important" research, for which the consent requirements might be loosened.

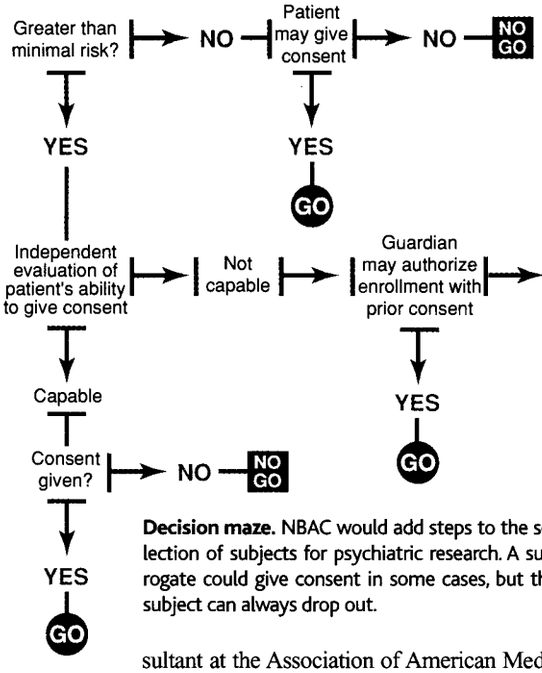
But this and many of NBAC's other proposals, if implemented, would constitute "a tragedy" for mental health research, says psychiatrist Roger Meyer, former vice president for medical affairs at George Washington University in Washington, D.C. Meyer, a consultant at the Association of American Medical Colleges, says the additional procedures would be a roadblock to recruiting subjects. Even noninvasive brain studies using PET or MRI scans would become "untenable" in many cases, he says, because under NBAC's scheme, these probably would be classified as posing more than minimal risk, making them off limits to many patients. Meyer also finds it "very scary" that a presidential commission has singled out this area of biomedicine for controls. He thinks NBAC members seemed "overtly hostile" to psychiatrists who testified publicly about the harm that might come from additional restrictions.

The report "sets us back 20 years," says Herbert Pardes, medical dean of Columbia University's College of Physicians and Surgeons. Pardes and federal research administrators met last month with NBAC members to argue that the focus not be restricted to people with mental disorders. They also suggested that the commission define a moderate-risk category of research that would permit brain scans and other routine procedures without a full competency review of each subject, an approach also suggested by the National Institutes of Health (*Science*, 30 October, p. 857). Both were rejected.

Constance Lieber, president of a nonprofit advocacy group, National Alliance for Research on Schizophrenia and Depression, also thinks NBAC's plan would hinder research without benefiting patients. She says the new procedures may "drive up costs" and "discourage young investigators." However, Lieber is pleased with NBAC's recommendations that local institutional review boards involve patients and their advocates more directly in vetting research protocols.

NBAC is getting some criticism from the opposite flank, too. Vera Hassner Sharav, head of the New York City group Citizens for Responsible Care & Research, calls NBAC's recommendations "outrageous" because they "legitimize nonconsensual, nontherapeutic research." NBAC's proposal to allow exceptional research to go forward—even when patients are not competent to give consent—violates the basic ethical principles medical researchers have followed since World War II, she says.

NBAC's report now goes to the interagency National Science and Technology Council and then on to the 17 federal departments that could be called upon to implement the changes. **–ELIOT MARSHALL**



Decision maze. NBAC would add steps to the selection of subjects for psychiatric research. A surrogate could give consent in some cases, but the subject can always drop out.

SOURCE: NBAC

DEVELOPMENTAL BIOLOGY

Hairy Mice Offer Hope For Baldness Remedy

Hairbrained as it may sound, a better understanding of cancer could lead to a cure for baldness. Recently, researchers have linked overactivity in one of the cell's major biochemical routes for relaying developmental messages to the nucleus, the Wnt signaling pathway, to colon and other cancers (*Science*, 4 September, pp. 1438 and 1509). Now, researchers at the University of Chicago have shown that a key player in that pathway, a protein called β-catenin, can stimulate the growth of new hair follicles in mice.

In work reported in the 25 November issue of *Cell*, Elaine Fuchs and her team have found that mice engineered so that their skin makes extra β-catenin grow more hair than

their normal counterparts. "It's really a striking result," says Matthew Scott, a developmental biologist at Stanford University School of Medicine in Palo Alto, California.

Fuchs and her university, which has applied for a patent on the work, see the finding as a possible first step toward harnessing β-catenin or the Wnt pathway to help some

No cue balls here. Mice with extra β-catenin grow thick coats.

30 million balding men in the United States grow new hair. That's not a sure thing, however, especially because the researchers will have to be very careful that such tinkering doesn't trigger tumors—as happened with the Fuchs team's hirsute mice.

Fuchs has long been fascinated by hair because it grows out of a structure, the follicle, that forms and regresses periodically, creating cycles of hair growth and loss. "It's one of the most complex forms of differentiation," she says. She suspected that β-catenin might play a role because of an observation her group made about another protein, Lef1/Tcf, in the skin of early mouse embryos. The researchers found that the protein appears in a dot pattern reminiscent of that displayed by the progenitor cells that produce hair follicles. And because Lef1/Tcf is thought to link with β-catenin to control gene expression, the finding suggested that these two molecules, and the Wnt pathway, might help regulate hair follicle development. That idea was buttressed by what Rudolf Grosschedl's group at the University of California, San Francisco, found when they knocked out the *Lef1* gene in mice: The animals had far fewer hair follicles than the controls.

To test the idea that β-catenin is also involved in hair follicle development, Uri Gat in Fuchs's lab created a new strain of mice carrying extra copies of the β-catenin gene. Before introducing the gene into the animals, Gat had linked it to a regulatory sequence that would cause it to be expressed only in skin cells. He also removed part of the gene so that β-catenin protein could not link up with proteins that would cause it to break down.

Animals carrying this gene not only were hairy critters, but they also got new hair follicles even as adults. Typically, an individual's full complement of hair follicles is set during embryonic development, but in these mice, new ones began to appear within a month after birth. They filled in the spaces between existing hair follicles, but did not form on areas, such as the foot pads, where no hair existed before. Apparently, only the cells in haired skin still had "properties that would allow them to be primed for new hair follicle [growth]," says Fuchs; these properties remain a mystery. The new hairs stuck out in many different directions, however.

The additional β-catenin had darker effects as well. As adults, the mice had hind paws three times the normal size and thickened skin, as well as ridges around the ears, eyelids, and nose. And the mice tended to develop benign tumors in the hair follicles. Humans can develop very similar tumors. Their genetic basis is not known, but the mouse results suggest that β-catenin might be involved; Fuchs is looking for signs of excess β-catenin in the human tumors.

Other goals would be to find the genes that β-catenin turns on to trigger hair follicle development in hopes that they could be activated specifically without causing tumors. Fuchs also wants to determine how β-catenin activation differs in embryonic versus tumor cells. The question is, "can we separate tumorigenesis from hair follicle morphogenesis," she says. If they can, then perhaps her ideas about manipulating the Wnt–β-catenin pathway to cure baldness won't be so hair-raising after all. **–ELIZABETH PENNISI**

BIOTECHNOLOGY

Improving Gene Transfer Into Livestock

About 10 years before they startled the world by cloning Dolly the sheep, scientists at The Roslin Institute south of Edinburgh had rocked the scientific community by producing the first healthy sheep carrying a human gene. Since then, a few research groups have used similar gene transfer techniques to build herds of sheep, cattle, goats, and pigs that make human proteins, often with the goal of milking them for valuable drugs. Now, a new method developed by a team of researchers in Wisconsin and California promises to make production of such transgenic livestock much easier than it is today.

Current gene transfer procedures for large animals are time-consuming and expensive, mainly because their efficiency is low: Only 1% to 10% of the animals that develop from eggs inoculated with a foreign gene carry it, and many of those who do can't transmit it to their progeny because

ScienceScope

UN TO MOVE ON GENE RESOLUTION

The United Nations (UN) is nearing approval of a resolution calling for restrictions on human gene research and respect for genetic diversity.

Last week, a UN committee approved the Resolution on the Human Genome and Human Rights, which calls for vigilance against discrimination based on a person's genes and recommends restrictions on human cloning and germline gene therapies, which risk introducing new genes into a population. The resolution also argues that use of human DNA "should not give rise to financial gain"—a controversial issue as companies race for lucrative gene patents.

Observers say the panel's endorsement virtually ensures that the measure will pass a 10 December General Assembly vote. But whether nations will adhere to the guidelines is uncertain. Germany and Australia, which are still working on their own policies, have expressed reservations. And the United States pressed to soften the guidelines before endorsing them. Georgetown University bioethicist LeRoy Walters says Americans generally have "less hesitancy" than others about genetic manipulations.

FENCING OVER SWORDFISH

The United States is threatening to retaliate against nations if they violate international swordfish catch quotas. But fisheries experts say the saber rattling won't help stocks—which have declined by 70% since the 1960s—unless quotas are reduced to reflect current science.

At a fisheries summit in Spain last week, U.S. officials warned the 21 other signers of a swordfish and tuna treaty that they may impose trade sanctions against nations that violate the limits, which were set in 1996 and cut the yearly kill in half. But conservationists are pushing the nations to close a loophole that allows undersized swordfish to be discarded and not counted in the catch. "Compliance with insufficient regulations is not going to solve the problem," says Lisa Speer of the Natural Resources Defense Council. Whether the treaty signers buy that argument won't be known until later this year.