MOLECULAR MEDICINE

One Less Hoop for Gene Therapy

The federal government quietly decided last week to relax its scrutiny of human gene therapy experiments. Harold Varmus, director of the National Institutes of Health (NIH), and David Kessler, commissioner of the Food and Drug Administration (FDA), both agreed to a change in the review process that should make it quicker and simpler to win approval for most gene-therapy protocols. The move, expected to be approved by NIH advisers this fall, suggests that human gene therapy has come of age after a stormy adolescence; now it will be treated much like any other human experimentation.

The change will remove a requirement that all gene-therapy protocols be subjected to public examination. At present, anyone planning to run a human gene therapy experiment must undergo two major reviews—a private evaluation at FDA and a public review before the Recombinant DNA Advisory Committee (RAC), a board that advises the NIH director. Originally created in 1974 to monitor all gene splicing, RAC has shed most responsibility for overseeing plant and animal experiments, and, since 1984, it has focused mainly on human gene therapy. According to the new plan, RAC will now stop working as a primary reviewer of human experiments as well. However, if FDA and RAC staffers see an important safety or policy issue—such as a plan to try a new gene transfer vector—they may ask researchers to appear before RAC.

The proposal to streamline the process came up and was quickly endorsed on 19 July during a meeting of a special task force on AIDS drug development, chaired by assistant secretary of health Philip Lee. Varmus and Kessler were present, as was panelist Dan Hoth, a former NIH research administrator now at Cell Genesys of Foster City, California. Hoth and another member of the special task force, Flossie Wong-Staal of the University of California, San Diego, had proposed cutting back on the use of RAC last spring. Lee brought their suggestion up last week, and Varmus and Kessler endorsed it. NIH and FDA staffers immediately set to work writing up an agreement, and RAC itself is expected to take a formal vote on the matter at its meeting on 12 September.

When gene therapy began in a blaze of publicity in the late 1980s, it was seen as a way to treat rare genetic disorders. But over the past few years, most protocols under review have aimed to treat terminal patients with common diseases such as cancer and AIDS. With the passage of time, some reviewers felt that the multilayer review process had become repetitive and increasingly trivial. So when Varmus and Kessler agreed to the change last week, there was little dissent—except from Andrew Kimbrell, attorney for Jeremy Rifkin, the well-known critic of bioengineering. Kimbrell says, "This is not the time for decreased reviews," arguing that the government should be doing more, not less, to follow up early experiments for possible late-developing hazards. Kimbrell says his employer, the Foundation for Economic Trends, is ready to sue to keep the review system on its present track.

Hoth says he suggested the change on behalf of researchers investigating gene therapy for AIDS because "we are now subjected to a four-layer review" by the government—a process which he claims can delay experiments for months and confuse applicants about whose advice they really must follow. Genetic experiments are now reviewed by a local ethics panel, a local biosafety panel, RAC, and FDA. Only the RAC proceedings are conducted in public, however, and only the RAC review would be eliminated. Hoth specifically objected to RAC's tendency to rehash issues in the informed consent documents approved earlier by local institutions.

While Hoth is no enemy of RAC—he says "we find it to be helpful" for airing broad concerns—others would be happy to see RAC disappear entirely. For example, former FDA official Henry Miller, a champion of the biotech industry and now a fellow at the Hoover Institution, a conservative think-tank in Palo Alto, California, would like to see RAC shut down and all of its actions filed away in the U.S. Archives, since he considers the whole process to be an anachronism. Miller says he tried to get Kessler to push for closure of RAC during the Bush Administration, but that he got nowhere. The current streamlining effort, Miller grumbles, is "purely cosmetic."

But RAC's executive director, Nelson Wivel, points out that the changes are far from trivial. From now on, gene therapists will be asked to fill out only one application. And they will learn within 15 working days after submitting it whether they will have to undergo a single FDA review or a dual FDA-RAC review. Wivel expects RAC will want to see only "the newest game in town...those cutting-edge experiments which haven't been done before." However, it may be a long time before RAC folds its tent, for Varmus says "we still need the RAC to provide public review of novel gene-therapy protocols" which are in an "early phase." He thinks "careful oversight" is needed, particularly as researchers start using new vectors to put genes into humans.

–Eliot Marshall

ENVIRONMENTAL PROTECTION AGENCY

Browner to Beef Up Outside Research

After 18 months of saying that the agency's decisions must be based on good science, Environmental Protection Agency (EPA) Administrator Carol Browner has unveiled a major overhaul of EPA science aimed at achieving that goal. Her plan would shift funds from applied to basic research, reduce the use of outside contractors, and reorganize the agency's in-house research laboratories.

Browner says the changes reflect her philosophy of "having the EPA move beyond tackling environmental problems crisis by crisis, incident by incident, and pollutant by pollutant." That approach, she says, has forced the agency to collect data in haste and then make split-second regulatory decisions. In an interview with *Science* early this week, Browner said, "There was a consensus across the agency that we needed to have a top-line, long-term research program in order to help us with the decisions we'll need to make 5 or 10 years down the line."

For extramural scientists, the changes will mean a better shot at funding. Over the next 2 to 3 years, Browner hopes to raise EPA's budget for extramural basic research from $20 million to $100 million, increasing from 35% to 50% the portion of the Office of Research and Development's (ORD's) budget committed to long-term research. The proposed changes "are long overdue," says toxicologist Bailus Walker, dean of the University of Oklahoma's Health Sciences Center. "One of the major gaps in the EPA's efforts has been its commitment to academic research," says Walker.

EPA is also wrestling with how best to award those dollars. It may try a system of soliciting grants from individual scientists similar to that used by the National Institutes of

RICK KOZAK

Moving ahead. Browner's plans for EPA are called "long overdue."

Health, coupled with a merit-review system devised with help from the National Science Foundation (*Science*, 22 July, p. 463). The overall effort will require "changing the culture of an entire organization," says Roger McClellan, director of the Chemical Industry Institute of Toxicology and co-chair of an EPA Science Advisory Board panel that favorably reviewed Browner's proposal.

One thing that's not in the cards is large-scale lab closures. That idea, floated in May by the Mitre Corporation as part of a congressionally mandated review of EPA's ORD, would have folded ORD's 12 research labs into four "mega-labs" and relocated staff (*Science*, 20 May, p. 1077). "In truth, we were never very comfortable with physical consolidation, but we felt we had the responsibility to bring the issue to the table," says Gary Foley, acting ORD director. "At least over the near term, consolidation will be costly, will disrupt ongoing research, and will damage employee morale," EPA officials wrote to Congress last week, and in a memo to employees Browner said the subject has been shelved "until at least June 1996." She later told *Science*, "You couldn't ask people to undergo these kinds of changes while they were worrying about where they might be working 6 months from now."

Although she's not closing EPA labs, Browner does intend to consolidate them administratively. She plans to create four mega-labs that will oversee and coordinate the work of other labs. One will focus on basic research on health and environmental effects, another will monitor exposures to potential hazards, a third will prepare risk assessments, and the fourth will develop pollution-prevention and remediation technologies. These labs will coordinate activity at 21 sites. "We're talking a sea change here" in reorganizing the labs around EPA's major activities rather than individual scientific disciplines, says Thomas Hadd, deputy director of ORD's office of research program management. ORD headquarters in Washington will also cede authority for research protocols and daily operations to the mega-labs, easing a paperwork burden that chews up about half of the average EPA scientist's time (*Science*, 29 October 1993, p. 647).

Implementing these changes will be high on the agenda of ORD's new research chief, chemist Robert Huggett, whose nomination will be considered next month by the Senate. And they will have to be done with a budget no larger than the current $533 million. The increase in extramural funds, says Foley, is likely to come from money being spent on private firms under contract to EPA for technical support underlying the issuance of regulations. The shift in focus "will have its impacts on other parts of the program," says Foley, who says that ORD will have to come up with ways to do the same amount of short-term research with less money. "We're taking a very bold step," he says.

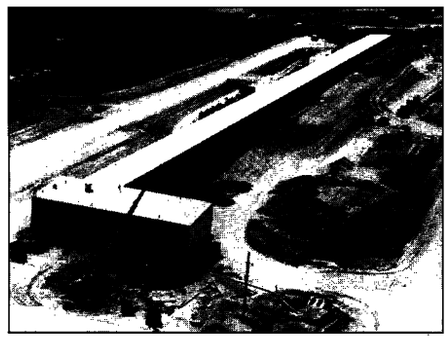
–Richard Stone

SUPERCONDUCTING SUPER COLLIDER

DOE and Texas Settle SSC Claims

It's been a long, strange trip, but the ill-fated Superconducting Super Collider (SSC) project, killed in midconstruction last October after receiving more than $2 billion of a planned $11-billion federal investment, is about to be laid to rest. Last week the Department of Energy (DOE) announced that it had reached an agreement with the state of Texas, which had pledged $1 billion toward building the 54-mile-long SSC at a prairie site an hour outside Dallas, that resolves the debates over whether Texas should be reimbursed for its contribution and the fate of facilities already built. DOE agreed to pay Texas $145 million in cash and contribute $65 million toward a project to convert one of the few nearly completed parts of the project—a proton-generating linear accelerator—into a cancer treatment center.

The agreement frees the government of the threat of a lawsuit and allows it to walk away from what was once envisioned as the world's premier high-energy physics laboratory. Since October, lawyers for the two parties have been in a Texas standoff over the state's demand that the federal government reimburse it totally for what it claims was an investment of $539 million in cash, land, labor, materials, and buildings. Negotiations were complicated by what DOE describes as an "unprecedented intermingling of federal and state funds...and the inadequacy of the [original] agreements to resolve matters in the event of project termination." Although DOE disputed Texas' claim that it should be reimbursed for the state's entire contribution, DOE lawyers concluded that Texas had grounds to go to court. Even if the state were eventually to lose, the prospect of having the SSC's existing computer and physics resources and large sums of DOE research funding held hostage to years of litigation was daunting enough to persuade DOE to seek a compromise. "We were really moving into paralysis," says Peter Didisheim, a special assistant to Energy Secretary Hazel O'Leary. "This was the best outcome we could get." An aide to the SSC's chief congressional opponent, Representative Sherwood Boehlert (R–NY), calls the settlement "generous but not unreasonable."



SSC

Healthy choice. DOE will give Texas $65 million to help convert the SSC's linear accelerator into a cancer treatment facility.

The compromise also ends the debate over the main "follow-on" project for the SSC. As part of a congressionally mandated effort to reclaim as much of the federal SSC investment as possible, DOE has been funding project definition studies on several proposed uses for the remaining SSC assets, including a regional computing center and a project to measure the index of refraction of light in a magnetic field (*Science*, 13 May, p. 898). But a Texas academic-industrial consortium has been pushing for a cancer treatment and radioisotope production facility using the linac, and Texas has asked for federal funding for the medical facility.

Although DOE says it will conduct an independent peer review of the medical and scientific feasibility of the project before awarding the $65-million grant, officials say privately that approval is a near certainty. (DOE will also continue funding the ongoing studies on the other proposals and turn the information over to Texas.) The linac proposal, however, has already failed to pass muster with a special panel convened by the National Research Council. In a 12 January report, the panel concluded after a brief examination of the proposal that the linac was not optimized for either proton radiotherapy or radioisotope production and was "too remote from established medical facilities to be attractive as a center for treatment." Although the linac has moved no closer to other medical centers, other aspects of the proposal have matured since the panel's review, says Didisheim.

For the U.S. high-energy physics community, the best news from last week's agreement may be that the SSC will probably not eat up any more scarce research dollars. DOE already has some $735 million reserved for the SSC. With the actual costs of termination estimated to be only $524 million, DOE expects to be able to settle up with Texas without asking Congress for additional funding. Boehlert and others plan to make sure that DOE keeps its word.

–Christopher Anderson