quirements of its sole prey, the apple snail. In short, the whole process worked against both the snail kite in particular and the Everglades in general."

In fact, the Audubon panel concludes that studies cited to support the jeopardy opinion were flawed and that, while maintaining the status quo could produce short-term benefits for the snail kite, it would probably cause serious problems in the long run. "The only way to protect the snail kite, and the other endangered species in the Everglades, is to gradually restore the entire system," said Orians.

The report stressed that restoration must begin immediately. Sugarcane and citrus farms in the area are becoming less productive and some are already going fallow because land in the region has lost much of its topsoil and is subsiding at a rate of several inches a year. As a result, real estate prices have fallen. The Water Management District has already purchased some of the land, but the panel expressed fears that in the future farmers may try to have their land zoned for commercial or domestic development to increase its resale value. If this should happen, and prices shoot up to the point where the government cannot afford to purchase the land, "the overall goal of restoring the hydrology of the area cannot be accomplished."

Another critical recommendation in the Audubon panel's report is to separate Miami's water supply from the Everglades. The greater Miami area gets much of its water from wells sunk within the Everglades, but since the city lies above a "superbly permeable aquifer," it should be possible to recharge that aquifer with water that is currently being dumped out of the Lake Okeechobee drainage area into the Atlantic Ocean in the name of flood control.

Ecologists are hoping that publication of the Audubon panel's report this fall will help jump start the stalled restoration plan. If so, it will remove clouds over the future of the wetland that are darker than any brought by Hurricane Andrew. But beyond the Everglades, the report, with its emphasis on the entire ecosystem and multispecies management, could provide a model for other threatened natural areas. By staying within the provisions of the Endangered Species Act and at the same time preserving overall biodiversity, that plan could help to realize a goal that is bound to become increasingly important in environmental policy in the years to come.

**–Joe Alper**

GENE THERAPY

# Monkey Tests Spark Safety Review

Since early this year, the Food and Drug Administration (FDA) has been grappling with two key questions about the safety of human gene therapy: What is the chance that the "vectors," the crippled viruses used to transfer genes to human patients, could cause disease? And how should researchers who regularly use those vectors test them to make sure they're safe? These questions have always hovered in the background of experimental attempts at gene therapy, but late last year they took on added urgency when studies at the National Institutes of Health (NIH) showed that certain viruses, which might contaminate the vector preparations, can cause cancer in monkeys.

In the wake of those studies, unconfirmed reports began flying that the FDA was about to stop approving new gene therapy protocols until the safety questions were resolved. FDA is now trying to scotch those rumors: "There is no moratorium," says Gerald V. Quinnan Jr., deputy director of the FDA's Center for Biologics Evaluation and Research. "We are still reviewing new protocols and INDs (investigational new drugs) as we get them. The routine approach to [safety] testing will continue to evolve with time, but there is no big new problem with gene therapy."

Quinnan's declaration means practitioners in the embryonic field of gene therapy can breathe easily, at least for the moment. But the debate over safety hasn't gone away. Indeed, questions about safety testing dominated the 13-14 September meeting of the Recombinant DNA Advisory Committee (RAC), the NIH group charged with reviewing new gene therapy protocols.

The objects of concern are the laboratory cell lines that produce the hobbled mouse retrovirus used to transfer genes to human beings. Ordinarily, the viruses from these cells are not capable of reproducing ("replication competent," as virologists say), but occasionally the cells do produce virus particles capable of replicating and causing infection. RAC and FDA require testing to ensure that vector preparations are free of infectious virus. But even if a small amount of replication-competent virus got through, researchers have long believed there was little risk. The reason: Experiments in the mid-1980s, in which NIH scientists intentionally injected infectious mouse retroviruses into healthy monkeys, suggested that the viruses weren't capable of causing disease.

> **"There is nothing to indicate that the current standards are not adequate."**
>
> **–Nelson A. Wivel**

But last year, Arthur Nienhuis, chief of clinical hematology at the National Heart, Lung, and Blood Institute, got different results. In Nienhuis' lab, three of eight rhesus monkeys involved in an NIH gene transfer experiment developed lymphoma, a cancer of the lymphatic tissue. The monkeys had been treated with a preparation known to contain viable viruses, but on the basis of the previous studies, Nienhuis' group assumed they were harmless. FDA took the results seriously. "When Art Nienhuis' monkeys got lymphomas, that was the first data which said replication-competent virus can be pathogenic," said FDA's Paul Aebersold. "These data necessitated a rethinking of viral testing."

That rethinking has already begun at the companies that want to pursue gene therapy experiments. On 13 September, FDA officials met with scientists from Gene Therapy Inc., (GTI) a Gaithersburg, Maryland, biotech company that has submitted several protocols for new gene therapy experiments. As a result of the safety concerns, GTI proposed adding several sensitive tests for infectious virus.

Despite the concern over Nienhuis' results, NIH and FDA experts agree that none of the nearly 30 humans who have received genetic transfers worldwide has been harmed. "There is no indication of any human risks," said Aebersold. "None of the patients have shown any problems which could be attributed to the fact that they had [gene] marked cells or genetically transduced cells." RAC director Nelson A. Wivel adds: "There is nothing to indicate that the current standards are not adequate."

In discussing the recent events, FDA officials have adopted several different tones. Some have tried to downplay the intent of the FDA's review. "It was not meant to throw a scare into the industry about dangers to the patients," said FDA scientist Phil Noguchi. "We are just smarter than we were a few months ago." Aebersold, on the other hand, concedes that "if Art's experiment had been done 3 years ago, we might have had a different timetable for the initiation of gene therapy. Additional testing would have been required from the beginning."

But since the results weren't available 3 years ago, the reconsideration must be done in midstream. The RAC has put the issue on the agenda for its December meeting, and FDA is still deciding what safety tests it will require. FDA sources predict the internal discussion on that issue should be complete in a month.

**–Larry Thompson**

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