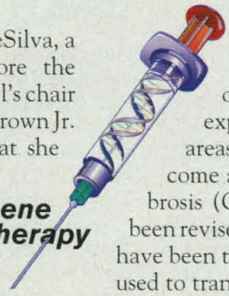
Gene Therapy's Growing Pains

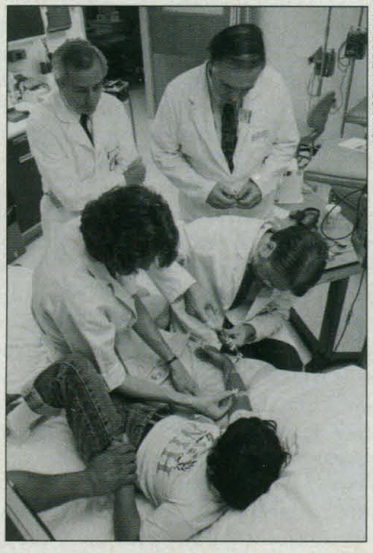
With more than 100 clinical trials started and hundreds of millions of dollars at stake, the field is struggling to meet expectations

Last September, when Ashanthi DeSilva, a cheerful 8-year-old, appeared before the House Science Committee, the panel's chair at the time, Representative George Brown Jr. (D–CA), was moved to declare that she was "living proof that a miracle has occurred." DeSilva made history in 1990 when she received the first authorized human gene therapy ever attempted. She had been born with a defective version of the gene that normally makes the essential enzyme adenosine deaminase (ADA)—a condition that, if left untreated, causes a fatal malfunction of the immune system. Four years after receiving her first injection of cells containing functioning ADA genes, Ashanthi, apparently in good health, was chatting with members of Congress.



Since that epic treatment, gene therapy has taken off like a rocket. More than 100 clinical trials, aimed at treating conditions ranging from inherited disorders such as cystic fibrosis to cancer and AIDS, have been given the go-ahead. The National Institutes of Health (NIH) is spending an estimated $200 million a year to develop and test tools and techniques for gene therapy. Private companies have raised hundreds of millions of dollars to enter the field and are now sponsoring most of the clinical trials. Many academic centers have created gene-therapy programs and joined the jockeying for a piece of the action.

Yet in spite of this enthusiasm—bolstered by media hype—all is not well in the world of gene therapy. So far, there has been no unambiguous evidence that genetic treatment has produced therapeutic benefits. Even data from the pioneering ADA trials are not decisive: Ashanthi and the other children who have since been treated with gene therapy are also being given routine injections of synthetic ADA, and these conventional treatments may be responsible for their good health (see box on p. 1051). Gene therapists are still encountering difficulties in transferring genes to adequate numbers of target cells and getting them expressed. This problem afflicts all areas of gene therapy, but it has become acute in efforts to treat cystic fibrosis (CF): Several CF protocols have been revised because of side effects that may have been triggered by the adenovirus agent used to transfer genes, and some researchers say that adenovirus-based therapy for CF must now be rethought (see box on p. 1052).


JOHN CRAWFORD/NIH

High hopes. The first attempt, in 1990, to correct an ADA gene defect.

Faced with such fundamental problems, several biomedical leaders, including NIH Director Harold Varmus, are saying it's time for NIH to pause, examine what gene therapy has accomplished, and determine what role NIH should be playing in the field. "Despite the growing support for gene therapy," Varmus said at a public meeting in May, the field "remains at a very early stage of development. While there are several reports of convincing gene transfer and expression, there is still little or no evidence of therapeutic benefit in patients—or even in animal models." Nor, he added, is there a consensus about which gene delivery systems will be most effective, and he said he wasn't confident the field was choosing the best lines of attack.

Of particular concern to Varmus and some leaders in the field is the possibility that the intense commercial interest in gene therapy is prompting a stampede into clinical trials and pressure for quick results—before the basic science has been worked out. Drew Pardoll, a Johns Hopkins University co-investigator in a gene-therapy trial for prostate cancer, deplores the lack of rigor in many studies. "There's been an emphasis on glitz," he says. "It's produced a culture in which getting into clinical trials—getting into the club—has been more important than getting a meaningful result."

These concerns have prompted the most intensive review of this burgeoning field since that first ADA experiment 5 years ago. Earlier this year, Varmus created two high-level panels to advise him on how NIH should proceed. The first, chaired by Inder Verma, a geneticist at the Salk Institute, is looking into NIH's procedures for approving gene-therapy clinical trials (see box on p. 1054). The second, co-chaired by Arno Motulsky, a geneticist at the University of Washington, Seattle, and Stuart Orkin, a hematologist at Harvard University, has been asked to chart a strategy for how NIH should invest in gene therapy, choose areas to emphasize, and help shape guidelines for medical practice. Both panels will issue recommendations by December.

The Motulsky-Orkin panel is drawing a lot of interest—and some nervousness—from gene-therapy researchers in part because Varmus deliberately set it up to take an independent look at the field. Varmus chose its members, he said, for their "stature in the scientific community" and because none is directly involved in running a gene-therapy company or clinical trial.

Varmus's intramural adviser on gene therapy, virologist Nelson Wivel, director of the NIH Office of Recombinant DNA Activities, says he "would not be surprised" if the panel suggests backing off from the heavy emphasis on clinical trials today. Instead, Wivel suggests, the panel may stress the importance of funding basic virology and immunology. "This is the primary question," Wivel says: "Should you be doing more [clinical] trials before you've solved other major technical issues," such as making vectors more efficient and less toxic? These recent developments at NIH, the cradle of gene therapy, suggest the soaring enthusiasm for clinical experimentation may be cooling.

A glass half full?

That enthusiasm is still very visible these days—particularly in the media. "Gene Therapy Techniques Advance as Potential Treatments for Cancer," reported *Genetic Engineering News* on 1 March. "The Birth of a Megamarket," proclaimed *Fortune* on 15 May, featuring Canji Inc., a gene-therapy company in San Diego. "Gene Therapy May One Day Help Doctors Fix Ailing Hearts," announced Johns Hopkins University on 28 July. "Gene Therapy Boosts Radiation Therapy for Cancer," said a University of Chicago press release on 31 July.

Beginning with a wave of media attention

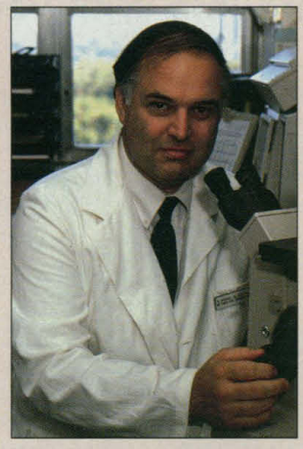
Jury Still Out on Pioneering Treatment

Every time physician Melissa Elder opens a vial of the enzyme she injects into two young brothers she treats, it costs $2200. Elder says the two boys use a total of five vials a week; it costs more than $40,000 a month to keep them healthy.

These brothers—Rhett, age 4, and Zach, age 2—lack a gene that expresses the enzyme adenosine deaminase (ADA), essential to the immune system. Failure to produce ADA leads to a deadly condition: severe combined immunodeficiency disease. To fend it off and keep infection at bay, Elder, an immunologist at the University of California, San Francisco, treats Rhett and Zach with a synthetic form of the enzyme known as PEG-ADA.* She says the parents are acutely aware of their sons' vulnerability—and of the cost of using PEG-ADA: "The parents lose sleep worrying about what will happen when their insurance reaches its cap." The policy has a limit of $1 million, already half spent.

This is exactly the kind of misfortune gene therapy is meant to prevent. But it hasn't in this case: Zach has received gene therapy to replace missing ADA genes since shortly after he was born. Like the other children who have been given ADA gene therapy in the United States and overseas, he still gets weekly injections of PEG-ADA. Even the two girls who made history 5 years ago as the first patients to receive ADA gene therapy receive PEG-ADA shots. The reason: Physicians have seen other children's immune function decline when PEG-ADA was reduced, and they worry that it would risk the children's health to rely on gene therapy alone.

Elder and other physicians treating the handful of children who have been given gene therapy for ADA deficiency say their patients' health has improved. But as long as the children continue to get PEG-ADA shots, researchers cannot say for sure how much of the credit should go to the gene therapy.



NCI

Proof seeker. NIH's Blaese aims to prove ADA therapy works.

Even principal investigators in the gene therapy trials—Michael Blaese of the National Institutes of Health (NIH) and Donald Kohn of the Los Angeles Children's Hospital—agree that the mixed treatment clouds the role of gene therapy. "There are a lot of questions to be answered," Blaese concedes. But he argues that, in the case of his first two gene-therapy patients, "the experiment was valuable irrespective of whether [the children] were on enzyme or not." He says the experiment proved that it's possible to transfer corrective genes to humans and to get the genes to express ADA "at a very good level" in at least one patient—Ashanthi DeSilva—for several years.

Ashanthi was given her first dose of gene therapy in 1990; a second patient was treated in 1991. Both were also put on PEG-ADA, approved as a standard therapy in 1990 by the Food and Drug Administration. In attempting gene therapy, Blaese and a team at NIH focused at first on T cells circulating in the girls' bloodstream—removing blood, treating T cells with stimulants, inserting a new ADA gene, and infusing the cells back into the patients. Each girl received 11 to 12 treatments. Blood tests conducted 3 years later showed that more than 50% of Ashanthi's circulating T cells contained the new gene, says Blaese.

But, in a telling indication of the hit-or-miss nature of this new technology, only 0.1% to 1% of the other patient's did. Clinical signs have improved in both girls, however. In Ashanthi's case, "it's very hard to say this was due just to enzyme [PEG-ADA]," says Blaese, although he recognizes that in the other case, "there just isn't enough" of the new gene present for it to deserve much credit.

Other researchers say it's easy to overestimate gene therapy's contribution. Ricardo Sorensen, a physician at the Louisiana State University Medical Center who treats ADA-deficient children, notes that the infusion of stimulated T cells alone may have been beneficial for these young patients and that the PEG-ADA must have helped. The best way to sort out what each treatment did, says Sorensen, would be to give T cell therapy, PEG-ADA therapy, and gene therapy independently to patients with similar conditions. Short of that, says Michael Hershfield, the Duke University researcher who developed PEG-ADA, a good way to get an answer would be to withdraw PEG-ADA from children who have received gene therapy and see how they do. That is exactly what Blaese and his colleague Kohn are doing right now.

Together, they have been running an experiment in which Zach and two other ADA-deficient boys were given a new type of ADA gene therapy in 1993, at their birth. In all three cases, researchers removed blood from the children's umbilical cord and attempted to inject an ADA gene into long-lived "stem" cells, which give birth to other blood cells and are relatively abundant in cord blood. The goal: to create a permanent source of ADA-competent T cells. Preliminary data suggest partial success: Up to 10% of their circulating T cells now seem to carry a healthy gene, and Kohn says the hope is that, with time, these healthy cells will accumulate and predominate.

These children have also been receiving PEG-ADA since birth, says Kohn, because "it is a standard therapy, and we felt it wouldn't be ethical to withhold it." However, the PEG-ADA helps keep genetically defective cells alive, and in theory, its use retards the rate at which they can be cleared from the bloodstream to make room for healthy cells. For this reason, Blaese and Kohn are eager to see the boys' PEG-ADA shots curtailed. Since January, Blaese says, the level of PEG-ADA given these three patients has been cut in half (to 30 units per kilogram per week). By the end of the year, he had hoped to cut it close to zero.

But the experiment is not advancing as rapidly as Blaese would like. Physicians for all three boys—including Elder—say they are reluctant to cut the PEG-ADA doses below the present level. Elder, for example, says: "The more PEG-ADA I give, the better the white cell count" and the stronger the immune function. Already the patients' white cell counts have dropped with the initial decline in PEG-ADA doses, although the fraction of "cured" T cells has increased. Physicians are watching closely to see whether the boys can tolerate further reductions before allowing the experiment to proceed. If so, and if the transplanted genes eventually provide all the ADA Zach and the other two boys in this test require, it would be the first unambiguous demonstration that gene therapy has cured a patient's disease.

–E.M.

* Polyethylene glycol–ADA, bovine ADA with artificial surfaces added to prolong life in the bloodstream, manufactured as Adagen by Enzon Inc. of Piscataway, N.J.

generated by NIH's attempt to fix Ashanthi DeSilva's defective ADA gene 5 years ago, encouraging reports like these have swelled to a flood. Most such reports are based on research developments that have yet to be tested in clinical trials, however. And the clinical trials that have been conducted over the past 5 years have yielded very few published results—so few that the Motulsky-Orkin panel will have little hard data to analyze as it tries to figure out how the field is progressing.

NIH's Recombinant DNA Advisory Committee (RAC), which reviews all NIH-funded clinical research protocols for gene therapy, discovered for itself the paucity of data when it established a subcommittee to see where the field is heading. The panel, led by Brian Smith, a Yale University oncologist and RAC member, and NIH staffer Debra Wilson, scanned all trials approved by the RAC and the Food and Drug Administration (FDA) through June 1995. The panel found little concrete information on the results of these trials, but it did paint a remarkable picture of how rapidly the field has grown—both in terms of the numbers of trials and the wide range of disorders gene therapists are boldly trying to treat.

The RAC team found that 567 patients are involved in 106 RAC-approved experiments. Almost half (268) are new recruits, having entered trials since December 1994. Only a small fraction of these experiments are aimed at correcting defective genes. Instead, most protocols aim to induce specific cells, such as cancer cells or cells infected by HIV, to produce proteins that would make them vulnerable to attack by the immune system. Others are attempting to use gene therapy as an adjunct to traditional chemotherapy for cancer (see chart on next page).

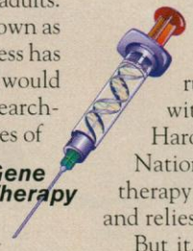
The field, in short, has moved a long way from the popular notion of gene therapy as a cure for genetic disease. Indeed, the RAC panel identified only 20 trials focusing on single-gene deficiencies such as ADA. Of these, 11 aim to replace the defective chloride transport gene that causes cystic fibrosis, using an adenovirus vector to shuttle functioning genes into a patient's lung cells. Three other trials aim to treat Gaucher disease, a metabolic disorder; single trials are aimed at each of six other rare diseases including ADA deficiency. Little has been published from these efforts: Only preliminary data have seen the light of day in peer-reviewed journals.

In contrast to the few efforts aimed at single-gene disorders, almost half the 106 trials are aimed at cancer. One reason for the

The Trouble With Vectors

Cystic fibrosis (CF) is a lethal inherited disease for which gene therapy offers a rare hope of relief. CF patients—of whom there are more than 30,000 in the United States—lack a gene that enables cells to process the chloride ion, causing their lungs to be plagued by mucus and infection. Gene therapy's promise is that one day it may be possible to replace defective genes with healthy ones, lengthening the lives of CF patients, who generally die as children or young adults.

Already, researchers have transferred a working gene (known as *CFTR*) into the surface airway cells of lab animals. This success has inspired 11 human trials. But any expectation that these tests would quickly demonstrate therapeutic benefits has dwindled as researchers have run into problems in transferring sufficient quantities of the *CFTR* gene into patients' cells. In addition, the virus vector they are using as the transfer agent has provoked an immune reaction in some patients.



CF researchers are not alone in encountering such difficulties. Indeed, right from the start, gene therapists have recognized that their central challenge would be to find safe vectors capable of transporting genes efficiently into target cells—and getting the cells to express the genes once they are inserted. Although there have been promising developments in some areas, it remains the central challenge for every area of gene therapy. Francis Collins, director of the National Center for Human Genome Research (NCHGR), sums up the situation bluntly: "None of the currently available techniques is clinically useful for systemic gene delivery," the kind that can provide a permanent cure. For that reason, NCHGR has joined in a major program to improve vectors and make them available to clinicians (*Science*, 11 August, p. 751).

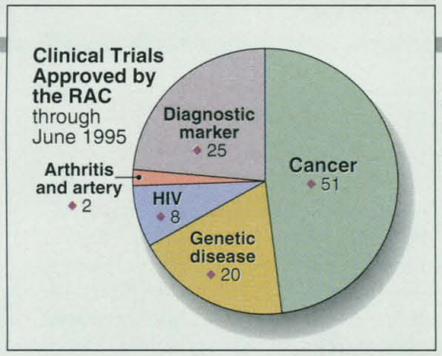
The most popular vector used so far is one based on a retrovirus that normally infects mice. A crippled version of this retrovirus, loaded with therapeutic genes, has been used in 76 of the 106 human trials approved to date, most of which involve patients with cancer or HIV. This mouse virus is the most efficient agent yet identified for transferring genes, although rates of transfer and expression vary dramatically in different patients (see p. 1051).

The stark variation among patients isn't the only problem. Another is that retroviruses insert genes only into cells that are actively dividing and growing, such as T cells. This rules out their use for treating diseases such as CF, where the target cells aren't dividing. A second drawback is that retroviruses insert themselves randomly into host DNA, posing what's thought to be a small—but real—risk of cancer. If a retrovirus gene should settle alongside an oncogene or tumor suppressor gene, it might trigger tumor formation by turning on or off the native gene. For these reasons, retroviral vectors have been used in "ex vivo" procedures—in which cells are removed from the patient, treated, and replaced—and when increased risk of cancer is not considered an obstacle to therapy.

In contrast to those trials, therapy for CF patients has relied primarily on a vector based on a crippled adenovirus. This DNA virus infects 75% of young people, usually without causing illness, according to adenovirus expert Harold Ginsberg, emeritus of Columbia University, now at the National Institutes of Health (NIH). It's attractive for CF therapy because it seeks the lungs. It penetrates nondividing cells and relies on these host cells to express viral DNA.

But it, too, has drawbacks. Adenovirus genes express proteins that trigger immune responses. In consequence, large concentrations of wild virus—and even crippled virus—provoke inflammation along with an immune attack that neutralizes cells containing adenovirus genes. For this reason, the effects of adenovirus vector therapy are likely to be short-lived, lasting about 6 weeks. And, because the immune system "remembers" antigens and attacks them with extra vigor on a second encounter, repeat dosing with adenovirus vector seems impractical at present—unless a strong immune response is desired, as in some types of cancer therapy.

Research on CF gene therapy by Richard Boucher and colleagues at the University of North Carolina, Chapel Hill, indicates that clinicians using adenovirus as a vector are caught between two problems. When administered at low concentrations it is inefficient: The virus doesn't get into many human nasal cavity or airway cells, and few cells express the corrected *CFTR* gene. At high doses, however, it appears to cause acute inflammation, Boucher says. He notes that three or four CF gene therapy trials have been compelled to stop or adjust doses to deal with acute reactions in patients. Some researchers, such Ronald Crystal, who pioneered this field at NIH and is now at the Cornell University Medical Center in New York, think past problems with CF therapy may not involve fundamental issues so much as a need to find the right way to deliver existing materials. But Boucher and Ginsberg believe immunogenicity has been and continues to be a fundamental problem.



SOURCE: RAC

Broad focus. The majority of trials now target diseases with large patient populations.

growing emphasis on this disease, says Wivel, is that private investment in gene therapy is increasing, and companies can't justify large R&D expenses unless they can expect to treat large patient populations. Another reason is that these patients often have no alternatives in conventional medicine and are therefore eligible for experimental therapy.

Thirty of the 51 cancer trials are designed to insert into tumor cells a gene expressing a substance such as the lymphokine interleukin-2 (an immune-system signaling molecule), in the expectation that it will stimulate a natural immune attack on the tumor cells. Another 11 studies aim to induce tumor cells to express the herpesvirus protein thymidine kinase, which makes them vulnerable to treatment with the drug gancyclovir. The remaining 10 trials test three other strategies, including four trials that seek to stop cancer by activating tumor suppressor genes. No results have yet been published from these trials.

Another fast-growing area is gene therapy for AIDS. Indeed, the majority of patients enrolled in clinical trials approved in the first half of 1995—168 out of a total of 268—are participating in tests of an anti-HIV therapy sponsored by Viagene Inc. of San Diego. (These include a trial approved only by FDA; private trials need not obtain RAC approval.)

Viagene has focused on a succession of strategies in at least four RAC-approved HIV trials. These studies aim to put genes that express HIV proteins into some of a patient's cells, in the hope that the cells will express antigens that will prime the immune system to attack infected cells carrying the same antigens. In addition to Viagene's trials, five others go after HIV with other strategies: They seek to disrupt viral functions by creating decoy molecules to compete with, sequester, or cleave products produced by HIV, or they try to cause HIV-infected cells to express thymidine kinase or other molecules that make them targetable by chemical attack. Clinical results have not yet been published from any of these trials.

These two vector types—retrovirus and adenovirus—account for more than 85% of those used in clinical trials. But leading researchers and a few companies are looking for other vehicles. For example, Joseph Glorioso, director of the gene-therapy program at the University of Pittsburgh, is focusing on herpesvirus. It infects the central nervous system and carries a remarkable "latency gene" that hides it from immune attack. In theory, herpesvirus vector could be used to insert DNA into the nervous system. But it is difficult to manipulate and may have hidden risks. Eventually, Glorioso hopes to seek approval to use it for cancer therapy.

R. Jude Samulski, leader of the gene-therapy program at the University of North Carolina, is investigating adeno-associated virus (AAV). It has no known toxicities and replicates only in the presence of a "helper virus," making it look very safe. It may have other advantages, says Samulski: It is simple, and its "life cycle suggests it may be able to persist and deliver genes for a long time."

But Samulski acknowledges a common criticism: AAV is difficult to produce in large quantities. One leading gene-therapy researcher who asked not to be named claims that current AAV technology is inefficient and expensive, adding: "AAV is like an onion—the more layers you peel off, the more you cry." So far, only one human trial using AAV—for treatment of cystic fibrosis—has been approved; no data are yet available. But Samulski predicts, "You'll see more and more AAV protocols."

Viagene Inc. of San Diego is investigating sindbis—an African virus that infects the nervous system—as a new vector. Its virtues include a unique and highly productive method of replication. Other groups are looking into HIV as a vector, although probably only for treating HIV patients.

The hottest alternatives to viruses are oily substances known as cationic liposomes. These concoctions, which come in many varieties, can slip DNA into the cell's nucleus and cause genes to be expressed. One skilled user of the technology, Gary Nabel, a Howard Hughes Medical Institute investigator at the University of Michigan, predicts liposomes will improve dramatically in the next few years, increasing levels of gene expression by "an order of magnitude or more," and that they will quickly be adapted for clinical use. In addition to liposomes, two other nonviral vectors have been adopted for clinical trials: direct injection of plasmid DNA into the muscle (two trials) and air-gun injection of a DNA-coated pellet (one trial).

These examples should make clear that there is as yet no perfect vector. And many researchers say we shouldn't expect one: Instead, there will be a confusing array of viral bits and pieces, combined with other gene-transfer agents, all of them used in custom tools designed for specific applications. But if a perfect vector were to be created, it might look something like the one being pursued by the intramural research staff at NCHGR.

NCHGR has launched a project, led by Melissa Rosenfeld and Paul Liu, to develop what they call a "human artificial chromosome." The idea is to create a synthetic 25th chromosome, big enough to transport whole "suites" of genes into the nucleus of a target cell, including all the regulatory sequences that surround a critical gene. Collins told a review panel in May that NCHGR is collaborating with a few extramural groups in an "intense" effort to push this "high-risk" project forward. But a staffer notes that it hasn't yet achieved "proof of principle." For the present, Collins observed, "the paucity of clinically acceptable gene transfer techniques severely limits the potential applications of gene therapy."

–E.M.

VECTORS IN RAC-APPROVED CLINICAL TRIALS

Vector	Number of clinical trials	Pluses	Minuses
VIRAL			
Retrovirus	76	Efficient transfer Easy to make	Small capacity Random DNA insertion Dividing cells only Replication risk
Adenovirus	15	Nondividing cells Possibly targetable	Immunogenic Replication risk
Adeno-associated virus	1	Nonimmunogenic	Small capacity Hard to make
Herpesvirus	0	Nonimmunogenic Targets CNS	Risks unclear Hard to make
NONVIRAL			
Liposomes	12	No replication Nonimmunogenic	Low efficiency
Naked or particle mediated DNA	3	No replication risk Nonimmunogenic	Low targetability Low efficiency

SOURCE: RAC

RAC's Identity Crisis

From the start, gene therapy has been one of the most contentious fields in biomedicine. In the early days, debate focused on safety—on the possibility, for example, that engineered DNA might create novel infectious viruses or trigger new forms of cancer. To minimize such risks and reassure the public, the National Institutes of Health (NIH) beginning in 1980 asked all government-funded gene therapy researchers to submit protocols for prior approval by a public panel. Today, these reviews are carried out by NIH's Recombinant DNA Advisory Committee (RAC), a mixed group of 20 scientists and nonscientists who meet quarterly at NIH. RAC has voted on virtually every gene therapy trial in the United States.

Now, after 5 years of clinical experimentation and no evidence that gene therapy poses a general risk to the public, fears are fading and, with them, the justification for RAC. Some leaders in gene therapy—especially researchers eager to get experiments launched and companies with large sums hanging on clinical trials—are saying it's time for RAC to think about retiring. They point out that the law already requires the Food and Drug Administration (FDA) to monitor clinical trials and clear therapeutic products for safety and efficacy, which means that gene therapy has to pass two federal checkpoints.

Stephen Marcus, an executive at Genetic Therapy Inc. of Gaithersburg, Maryland, says, for example, that RAC delays by 2 months or more decisions ultimately made at the FDA. "It may be a little hyperbolic" to suggest that lives are being lost as a result, Marcus says, "but the concept is there." Likewise, Thomas Reynolds of Targeted Genetics in Seattle complains that RAC has become a "bottleneck." He'd rather see it focus on "novel issues, like germ-line therapy, new vector systems, new disease targets"—not on reviews of individual protocols.

Members of the RAC themselves have also expressed uncertainty about the role they're expected to play, NIH Director Harold Varmus has observed. While public members of the panel tend to focus on safety and ethics, those with expertise in biology often zero in on technical aspects of proposals that they find inadequate. RAC has thus suffered from a split personality. To clarify the committee's proper role, Varmus has taken a couple of steps in the past year. First, he has asked RAC's staff and the FDA to work out a unified review process, now being put into effect, that may allow researchers to submit a single application for review by both agencies. Only those that raise new technical or ethical issues would be debated by the RAC.

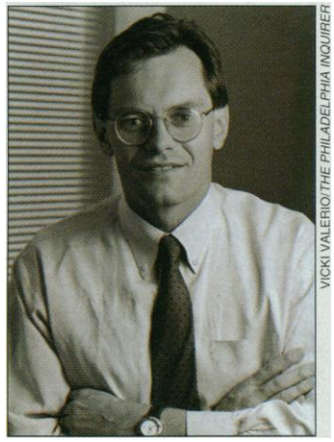
Second, Varmus has appointed a special ad hoc study group—headed by oncogene researcher Inder Verma of the Salk Institute in La Jolla, California—to consider how NIH should review gene therapy in the future. One of the big questions to be addressed is: Who, if anyone, should scrutinize clinical trials for scientific value? Officially, that isn't RAC's job, although expert members find it hard not to comment on technical quality. The Verma panel will deliver its recommendations on this and other broad questions about how NIH should handle gene therapy trials to Varmus by December.

–E.M.

Most of the other trials reviewed by RAC are not aimed at delivering therapy: They are designed to tag specific cells with genetic markers to provide information about the fate of the cells. When RAC members sifted through the catalog of these "gene marking" trials in June, they found that although this area gets little public attention, it is in fact scientifically the most encouraging area. Smith says they have produced at least four peer-reviewed publications laden with "hard data." The research has shown, for example, that cancer relapse following autologous bone marrow transplants—in which a patient's bone marrow is removed before intensive chemotherapy and later replaced—often is caused by tumor cells that survive in the marrow. It indicates that clinical research should zero in on ways to purge tumor cells from the marrow.

Whether this overall picture is judged positive depends in large measure on who's being asked. Pioneer gene therapists and industry leaders tend to view the explosion of trials as evidence of progress. Independent academics, on the other hand, often see the glass as half empty. But both sides can agree that, at the least, the field isn't harming its patients. Clinical trials, says Smith, have shown few signs of toxicity and no hints of runaway genetic mutations: "There are no three-headed cows" of the kind anticipated in "*National Enquirer*–land," he jokes. But the disappointing news, Smith finds, is that so far only hints of therapeutic benefit have appeared.

Wivel notes that nearly all the gene-therapy trials so far have been "phase I" trials, designed to test safety rather than efficacy. So they can't really be judged on effectiveness. But that hasn't discouraged some gene-therapy leaders from trying. Stephen Marcus, a vice president at Genetic Therapy Inc. of Gaithersburg, Maryland, cites a brain cancer patient who, after surgery for glioblastoma, was treated with GTI's anti-cancer gene therapy and has survived for more than 2 years. This is almost unheard of, Marcus says, and is clearly "a case where there is some evidence of effectiveness." He notes, however, that "we realize this is anecdotal."


VICKI VALERIO/THE PHILADELPHIA INQUIRER

Back to basics. James Wilson wants less hype, more research.

But the RAC members who reviewed cancer trials—Robert Erickson of the University of Arizona and R. Jude Samulski of the University of North Carolina—deemed it "too early" to reach any conclusion. Erickson found several unpublished reports that gene therapy had reduced tumor size, but noted that other, simpler therapies have produced similar reports in the past. Samulski pointed to a common theme running through the cancer studies that raised some concern: low rates of gene transfer.

Indeed, difficulties in getting genes transferred efficiently to target cells—and getting them expressed—remain a nagging problem for the entire field. Virus-based vectors have been the most efficient for inserting genes into cells in the lab, but they have run into problems in the clinic. Often the fraction of cells receiving the new gene is low, particularly if these targets of gene therapy are long-lived "stem" cells that give birth to other cells. Researchers say it has been difficult to achieve a 1% rate of gene transfer into stem cells, for reasons not fully understood. And even when genes are inserted in stem cells, they may not be active in second-generation cells, yielding less-than-adequate therapy.

Boosting the rate of gene transfer by increasing the concentration of vector or by dosing patients repeatedly may create another problem, however: It may stimulate the immune system to attack and neutralize the therapy-bearing cells. Francis Collins, director of NIH's National Center for Hu-

man Genome Research, told the Motulsky-Orkin panel in May that "many problems must be solved before gene therapy will be useful for more than the rare application."

Voting with their checkbooks

Academic researchers are still grappling with many fundamental issues in gene therapy. But industry leaders and their financial agents are gung-ho. Investors have poured hundreds of millions of dollars over the past 5 years into gene-therapy companies, drawn by hopes of blockbuster discoveries. And big companies are now getting into the act. Late last year, Switzerland's Ciba-Geigy Ltd. acquired a 49.5% share of Chiron Corp. of Emeryville, California, which then turned around in April 1995 and began buying Viagene. Less than 3 months later, another Swiss pharmaceutical giant, Sandoz AG, bought GTI—an investment that gives Sandoz rights to GTI's broad patent for "ex vivo" therapy, in which cells are removed from the patient, given new genes, and replaced (*Science*, 31 March, p. 1899). Also last fall, the French company Rhône-Poulenc Rorer struck agreements with a network of small companies to gain access to the latest research (*Science*, 18 November 1994, p. 1151).

One result of this burgeoning investment is that private companies have come to dominate clinical trials of experimental gene therapies. By June, according to the RAC, 13 firms had won approval to run at least 34 gene-therapy trials—so that now, 60% of all therapeutic trials are privately funded. Industry also plays an indirect role in physician-sponsored trials, supplying vectors at little or no cost.

This trend is worrying some leaders in the field, who say biotech companies are forcing the pace and direction of research, and not always in ways anchored in the best science. Varmus, for example, says that while it's "a good thing" that investors are willing to pick up the tab for "very expensive" clinical experiments, these trials absorb "a lot of resources and talent," and he isn't sure that they "are scientifically as worthy as other things that could be done." He's concerned about understanding the biology of viruses used to transfer genes and of the immune reactions they provoke.

Varmus isn't alone in expressing concerns. James Wilson, director of the Institute for Gene Therapy at the University of Pennsylvania, says private funding is important, but he worries that expectations may be raised prematurely. People who invest in gene therapy anticipate a big payoff, but they may not realize how long it will take, Wilson says. "The actual vectors—how we're going to practice our trade—haven't been discovered" yet, he notes, "so it may be early for the impatience of venture capital–supported biotech."

This commercial pressure may also account for some of the hype surrounding developments in gene therapy, says Wilson. If you're the leader of a gene-therapy company, "you try to put as positive a spin as you possibly can" on every step of the research process, he notes, "because you have to create promise out of what you have—that's your value." But, Wilson says, "that's not what we need right now." What the field needs is "a lot of basic research on vectors and cell biology."

Pardoll of Hopkins is equally critical; he says that in the rush to get trials approved, "biological principles are not well thought out—especially immunological principles." Varmus says this happens because the main concern of small companies is to survive, and "one way to survive is to have a clinical trial—show that you're actually on the scoreboard." But promoting the company doesn't necessarily promote gene therapy, Varmus notes: "We're not talking about an industry that's in an advanced state of competence."

Another effect of commercial investment, some researchers say, has been to channel energy into intellectual property disputes and turf battles. For example, Dusty Miller, a virologist at the Fred Hutchinson Cancer Research Center in Seattle, argues that the gene-therapy patent issued to NIH and GTI in April will have a "chilling effect" on research. The patent covers all forms of ex vivo therapy. Miller—who was among those involved in the research that led to this patent but was not named as a co-inventor—calls it "the patent from hell" because it's so broad. He thinks it may discourage newcomers and stifle collaboration. When Miller made this comment at a RAC meeting in June, GTI President James Barrett rose to say the company considers the patent "valid" and will negotiate reasonable terms that are "idiosyncratic" for each use.

Academic scientists may think it's too early to be talking about financial returns, but not company executives and some industry analysts. Take Wall Street biotech analyst Jeffrey Swarz of the investment bank CS First Boston. Swarz delivered an enthusiastic assessment of the field at last year's congressional hearings and was equally bullish in a recent interview with *Science*. Gene therapy for cystic fibrosis, he said, "has been successful; ADA disease has been successful; brain cancer has been successful. ... So far, the technology looks fabulous." He predicts a gene-therapy product will reach the market by next year.

At a recent meeting in Washington, D.C., organized by the Institute for International Research, gene-therapy business chiefs were asked when they thought their industry's first product would hit the market. Few were as optimistic as Swarz, but the forecasts ranged from very soon—in 1997, according to David Nance, president of Introgen Therapeutics of Austin, Texas—to reasonably soon—in 2000, according to Harvey Berger, chair of Ariad Pharmaceuticals in Cambridge, Massachusetts. One attendee, Mark Edwards, managing director of Recombinant Capital, an independent San Francisco firm that analyzes biotech companies, was less ebullient, saying he didn't expect a commercial product until 2003. Whether one's an optimist or not, concluded Berger, "we've got to make sure the biology matches the enthusiasm."

Many academic gene therapists agree with Berger, and some have said they hope the critical review Varmus has ordered from the Motulsky-Orkin panel will cut through the hype that surrounds the field and inform the public that it could be many years before the money invested in clinical trials yields a product. "It may be time for some realism," says Michael Knowles of the University of North Carolina's cystic fibrosis program. Adds Joe Glorioso, director of the University of Pittsburgh's gene-therapy program: "We just can't be wimpy about this; we have to be in for the long haul."

–Eliot Marshall

U.S. GENE THERAPY TRIALS SPONSORED BY INDUSTRY

Company Sponsor	Founded	Capital ($millions)	No. of Trials	Topic
Applied Immune Sciences	1982	209	1	Cancer
Canji	1990	21	1	Cancer
Cell Genesys	1988	103	1	HIV
GenVec	1992	20	1	Cystic fibrosis
GeneMedicine	1992	50	1	Alpha-1 anti-trypsin
Genetic Therapy	1986	103	6	Cancer, CF, Gaucher
Genzyme	1981	74	5	Cancer, CF, Gaucher
Immune Response	1986	128	1	Cancer
Ingenex	1992	5	2	Cancer
Introgen Therapeutics	1993	NA	3	Cancer
Somatix Therapy	1979	102	3	Cancer
Targeted Genetics	1989	46	1	HIV
Viagene	1987	106	6	Cancer, HIV
Vical	1987	46	4	Cancer, HIV

SOURCE: COMPANY DATA AND RAC