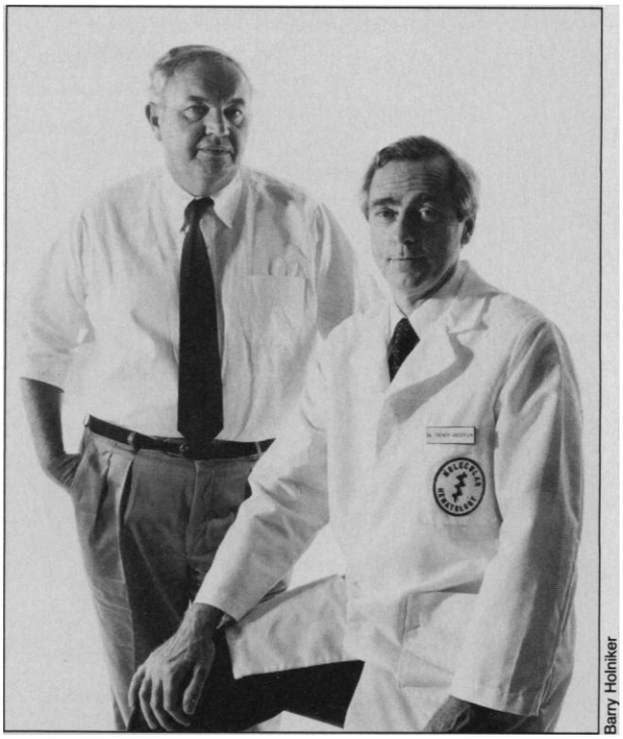
NIH, Inc.: The CRADA Boom

NIH, responding to Congress' call for technology transfer, is doing its patriotic duty—forming collaborations with industry. Will the "culture" of NIH change in the process?

NIH IS GOING INTO BUSINESS. After a lifelong aversion to the private sector, the National Institutes of Health has nearly 200 close collaborations with business either in the bag or in the works.

The story of hematologist W. French Anderson of the heart institute and a busy new company called Genetic Therapy, Inc., is the very model of the new NIH, which has adopted the philosophy that collaborating with industry is good for the country and good for the NIH. Not everyone agrees.

Three years ago, Anderson got a call from a venture capitalist named Wallace Steinberg who wanted to start a gene therapy company. Would Anderson run it? Anderson, practically born and bred at NIH where he has been since 1965, instinctively said "No." The culture of NIH held pure, basic research as its highest value. Working for business would mean crossing over to the other side.



Barry Holniker

Business partners. *GTI president James Barrett (left) and W. French Anderson of the heart institute.*

Then came a new reality. Four good people in Anderson's lab were on the verge of leaving for better paying jobs. Because of a federal hiring freeze tied to the national deficit, he would not be able to replace them.

On the other hand, a little heralded law—the Federal Technology Transfer Act of 1986 —offered a way out. The law, predicated on the assumption that valuable research ideas were languishing in government labs, revised patent policies pertaining to federal labs, enabling NIH to collaborate with business in a relationship that included granting patent rights and exclusive licenses. The law, in fact, virtually mandated that NIH scientists form industrial partnerships to foster technology transfer as well as international competitiveness.

Anderson went back to Steinberg with an offer the New Jersey investor found attractive. Steinberg would form his company and Anderson would work with it without leaving NIH. How? Anderson's lab and Genetic Therapy, Inc. (GTI), would sign a CRADA, or cooperative research and development agreement, that would, in effect, make GTI an extension of Anderson's NIH lab. The deal was struck. In the process, Anderson even managed to save the four people who were going to leave his lab. They simply went to work for GTI in Gaithersburg, just a few miles away from NIH. In a single stroke, Anderson says, "I just about doubled the size of my lab. By staying at NIH, I continue to have the resources of the Clinical Center," NIH's huge research hospital. "And I have GTI's resources added to my lab's for basic studies." Steinberg launched GTI with an investment of $2.5 million in 1987. Today, it has raised a total of $7 million in venture capital.

As for personal finances, if GTI succeeds, Anderson will get a share of the royalties from any invention that comes from his collaboration. The new technology transfer act flat out requires that the government scientist be allocated at least 15% of NIH's share. But if there are no royalties, if indeed the CRADA spends more money than it earns, it is GTI—not Anderson or NIH—that will suffer the loss. Meanwhile Anderson has the benefit of GTI's research resources.

GTI president James Barrett, a chemist turned entrepreneur who has a reputation for developing small companies, adds his view that there is something special about corporate culture that makes the collaboration valuable. "GTI can do things on a scale that NIH cannot," he says. For instance, the company produces supernatant in 50-liter batches for Steven Rosenberg and Michael Blaese who, with Anderson, are conducting the first human gene transfer experiments (*Science*, 23 June, p. 1430). Production may be a primary part of a GTI scientist's job. "The role of a young person at NIH is to publish and move up, or move to an academic position," Barrett says, whereas scientists with biotech companies are not necessarily judged by those academic yardsticks.

It seems like a deal made in heaven. But there are potential problems. The most serious is the threat that this and other similar CRADAs pose to the culture of NIH which prizes open communication. In theory, at least, NIH is a place with no research secrets. Everyone shares data with everyone else.

Anthony S. Fauci, director of the National Institute of Allergy and Infectious Diseases, is worried that NIH will succumb to "CRADA fever." CRADAs not only allow researchers to keep certain company data secret—they actually *require* confidentiality. Fauci says that "for the first time in 21 years at NIH, I detect an inkling of hesitation among scientists about sharing information."

There are indications that Fauci's worry is well founded. Most researchers *Science* called about CRADAs were eager to talk about their collaborations, but some were reluctant to even identify the general subject area. "I can't tell you that," one man said, although he subsequently relented.

How much information is too much is not always clear, says Barney C. Lepovetsky, CRADA officer for the cancer institute. His

advice to researchers: check with the company. "Any inquiry about the details of research would have to be cleared," he told *Science*.

Even Anderson is concerned about what the new CRADAs, with their accompanying rules about confidentiality and conflict of interest, mean for NIH. A year ago he tried to get that straightened out when he wrote a memo to Philip Chen, the CRADA official in the NIH director's office. It has become known as the "Who can talk to who?" memo.

Anderson is the NIH collaborator par excellence. In addition to his collaboration with GTI, and with Rosenberg and Blaese who also have CRADAs with GTI, Anderson is collaborating with Robert C. Gallo on a proposal for gene therapy of AIDS. GTI is in on that too. Anderson and Ira Pastan, another cancer institute person, are working together on a marker gene called mdr. Anderson and Arthur Nienhuis of the heart institute have a joint bone marrow transplantation/gene transfer study in the works.

Will these be undermined by the new CRADAs? In his memo to Chen, Anderson said, "We would like clarification as to how to maintain previous, as well as how to initiate new, collaborations when some members of the collaboration are in my lab, others are at Genetic Therapy, Inc. (GTI), the company with which my lab has a CRADA, others are at NIH labs not associated with GTI, and others are in NIH labs in which the lab chief is on the scientific advisory board of GTI.

"Who can talk to who without incurring a conflict of interest?"

And further, he asked, "When is a collaboration a collaboration? How large must it be? How many people? How many resources?"

Last December, NIH held a retreat at which 42 legal and scientific experts met for 2 days at a former convent on the edge of the campus to contemplate these nearly metaphysical questions.

Unambiguous answers have yet to be promulgated, but NIH lawyers are working on some. They say that a CRADA manual ought to be out soon. It is likely to be dozens of pages long and spell out procedures for keeping communication flowing as freely as possible.

Reid G. Adler, an attorney who had been in private practice, has been hired to run the NIH's office of invention development—the CRADA office. He acknowledges that there has been some slow going but says that things are now getting on track. His goal, he told *Science*, is to make the mechanics of negotiating a CRADA "drop out of sight" as NIH-industry collaborations become "business as usual."

It isn't quite there yet.

One NIH lab chief tells this story: He wanted to send a member of his lab to a biotech outfit for several weeks to collaborate with company researchers on a gene expression project. The company suggested signing a CRADA. Everyone agreed it was a good idea.

So, the NIH lawyers and the company lawyers negotiated the details. And they negotiated. And they negotiated.

Then, the Japanese reported they had done the very experiment the Americans had been talking about. Needless to say, the CRADA became moot.

Adler says that won't happen again. And he cites with pride data that show how far NIH has come in what he describes as an effort to comply with the 1986 technology act, a law, he says, that "put technology transfer in every NIH scientist's job description."

There are two standards of measure. One is the number of CRADAs. In 1986 there were none. By the end of 1989 there will be about 200. Going from 0 to 200 in 3 years is pretty good, he believes. Some NIH researchers have more than one CRADA. Gallo has four, including one with GTI for gene therapy for AIDS. He has three more in the works. Anderson has several.

CRADAs Raise Conflict Issues

Whenever money is involved, the possibility of conflict of interest seems never far behind. But just what constitutes a conflict is not always easy to spell out.

The Federal Technology Transfer Act of 1986, which mandates that NIH and other federal scientists collaborate with industry, specifically says that researchers are entitled to a minimum share of the royalties (if there are any) of 15%. The Act also declares that taking royalty income does not constitute a conflict of interest. That much is clear.

But beyond that, there are more questions than answers to conflict questions as federal research agencies adopt an aggressive posture in favor of collaborating with industrial firms large and small. These are some of those questions.

An NIH scientist is working as a consultant for biotech company A. As a consultant, he is paid $12,500 a year—the maximum permitted under consulting regulations. But the research is going so well that both the scientist and the company agree that a full-scale collaboration, including joint use of laboratory staff and facilities, would be more productive.

Must the NIH scientist give up his consulting fees if he signs a Cooperative research and development agreement (CRADA) with company A? The answer is yes. A few have done so.

To avoid the appearance that company A is getting favored treatment, must the NIH scientist wait a year, as some NIH officials suggest, between the time he resigns as a consultant and signs up as a CRADA collaborator? That has yet to be decided. But most researchers who have spoken to *Science* about this already know what they would do. "A 1-year waiting period would kill the whole thing," said an NIH investigator who has several CRADAs. "Within a year, the science you proposed doing would be obsolete. Things are moving too fast."

What if an NIH CRADA company bids for an NIH contract on a totally unrelated topic? On the one hand, a contract and a CRADA are supposed to be entirely different legal agreements. On the other, even if cash does not change hands, NIH is accepting money from CRADA companies in the form of scientific personnel and resources. Might a CRADA be taken for a bribe if a CRADA company subsequently got an NIH grant? A legal opinion on that will be forthcoming.

What about "self-dealing?" Criminal statutes say that no government employee or family member may have a financial interest in a company with which he has an official association. If an NIH scientist's family owns stock in a company *prior* to his signing a CRADA does the stock have to be sold? What happens if a large corporation in which you have stock buys a small company with which you have a CRADA?

What is clear is that the laws and regulations on the subject are complex, sometimes outright conflicting, and subject to more than one interpretation.

Besides NIH's own effort to write some rules, Congress already is interested in these issues. Hearings are neither scheduled nor out of the question. ■ **B.J.C.**

CRADA fever has struck hardest at the cancer institute, which records a total of 60.

Adler notes that the second measure of NIH's bent for technology transfer is the patent count. That too is climbing. In 1987, the institutes filed 90 patent applications. In 1988, 150 were filed. This year, there will be more than 200. In Adler's opinion, prompt patent filing is an important part of NIH's effort to keep communications open. Once a patent is filed, all pertinent data are public.

Cancer institute director Samuel Broder shares the view that quick patent filing is the answer to disclosure issues. "People are worried that if they talk too much about their CRADA research, they may inadvertently disclose proprietary information and be sued by the company. The ideal thing is to file a patent quickly and then fully disclose everything right away," Broder told *Science*.

Broder sounds enthusiastic about the advent of CRADAs. "Invention is in the American psyche," he said, and CRADAs encourage researchers to find useful applications for their work. "AZT [the AIDS drug] would never have become available without industry collaboration," he says.

Indeed, there is considerable enthusiasm for CRADAs, especially among NIH scientists who have them. Thomas Kindt of the allergy institute has been working with the gene for CD4—the protein that regulates the entry of HIV (human immunodeficiency virus) into cells—and wanted a good animal model for studying CD4 gene expression in lymphoid tissue. After reading one of Kindt's early papers, people from a Massachusetts company that makes transgenic animals called to propose a collaboration. They would make rabbits with the human CD4 gene, using their expertise at creating transgenic animals. Kindt would have the animal model he needed.

Says Kindt, "This is a nice, focused collaboration and provides my lab with resources we needed. I don't have the facilities for making rabbits." It does not cost Kindt a thing—the company pays for the breeding and care of the animals. And what does it get in return? The possibility that the rabbit will, in fact, turn out to be a good model for studying AIDS. Then, the company could make money selling these genetically special animals to people studying AIDS or testing AIDS drugs.

What would Kindt have done 3 years ago, before CRADA fever? He would have gone "hat in hand" to colleagues in academia who do research with transgenic animals. "I would have been asking for a favor," Kindt says, "and even if someone agreed, making animals for me would not necessarily be a top priority. With a CRADA I have a true collaboration."

Richard Jed Wyatt of the National Institute of Mental Health is another investigator who has made use of a CRADA to get needed research rabbits. A neuroscientist interested in how the AIDS virus gets into the brain, Wyatt began collaborating with a colleague at NIH who had developed an animal model. But she did not have facilities for breeding and keeping rabbits. Neither did Wyatt. The solution: find investors to form a company that can make rabbits. Wyatt did and RRI of McLean, Virginia, was formed. Then Wyatt and his colleagues signed a CRADA with RRI. The researchers have their rabbits, the company has a possible product. Another good deal.

But traditionalists worry. If CRADAs become common, will they really be true collaborations with intellectual, scientific input from both sides? Or will they just be another form of contract—one in which NIH benefits without having to pay?

Conversely, could CRADAs eventually turn NIH into little more than a giant contract lab if companies lure NIH scientists into cooperative agreements that serve the companies' need for NIH brain power at the expense of basic research?

Jonathan Eberhart, a long-time NIH scientist who is now a senior adviser to the director, has expressed concern about this. He would like NIH to eliminate liaisons with industry, leaving it free to concentrate on basic research without "commercial distractions." Martin Gellert, another long-time NIH scientist, also worries that CRADAs may simply invite companies to "shop" at NIH for research they want done. And NIH deputy director Joseph E. Rall fears that CRADA fever will irrevocably change the NIH culture because emphasis on the quick development and application of technology is "bound to influence scientists."

On that point, no one could argue. But the key question is whether that new influence will be ultimately beneficial, as the sponsors of the technology transfer act believe, or whether in the rush to transfer research ideas to the bedside and the marketplace something vital will be lost.

What is certain is that the future is going to be different. In 1983, just 5 years ago, Health and Human Services Secretary Margaret Heckler had this to say during a visit to the campus: "NIH is an island of objective and pristine scientific research excellence untainted by commercialization influences." She could not say that today.

■ BARBARA J. CULLITON

Gene Mappers Meet on Strategy

"It's almost unique in science to do something like this," says Norton Zinder, chairman of the National Institutes of Health (NIH) Human Genome Advisory Committee, speaking of last week's "retreat" at Cold Spring Harbor's Banbury Center, where a small group of research leaders got together on 28 to 30 August to plan the future of the U.S. genome project.

The meeting was unencumbered by the usual bureaucratic constraints. There was no formal agenda, reporters were banished from the room, and attendees were told to roll up their sleeves and get down to business.

Participants included members of the NIH and Department of Energy genome advisory committees as well as staffs of the two agencies and some additional invited scientists. Agency staff will use the ideas generated at the meeting to write a plan that will be presented formally to the two agencies' advisory committees later this year, and then submitted to Congress next February.

"I think it's going to be a fairly non cohesive draft based on the discussions we had," says Benjamin Barnhart, head of the DOE genome office. Zinder agrees: "You really can't plan because you never know when a new, good idea is going to come. And to have a new, good idea presented right in the middle of a planning meeting is really exciting." That seems to have happened last week when a new approach for physical mapping of chromosomes came out. The meeting centered on a technique called polymerase chain reaction (PCR) which amplifies sections of DNA. The idea is to place tagged probes along the length of a particular chromosome and use these as starting points for PCR to generate the intervening fragments. "The more [tagged probes] you have on a chromosome, the better the map," says Barnhart. Although this concept is brand new, he says scientists at the DOE genome centers are anxious to try it right away.

As always, future plans depend on money. Congress appears likely to reduce by some $40 million NIH's $100-million budget request for the genome project. DOE's genome budget looks safe at $27.6 million—the amount the agency requested.

■ JOSEPH PALCA