adenosine deaminase. Blood transfusions are not an ideal therapy, however, because eventually iron from the transfused blood accumulates in the heart, causing heart failure. But the transfusions show that even a small amount of adenosine deaminase can keep some immune system cells alive.

The reason for believing that even a little bit of HGPRT might be therapeutically useful is that persons who inherit a defective HGPRT gene and make only 1 percent of the normal amount of this enzyme have none of the neurological symptoms of Lesch-Nyhan syndrome. Their only clinical complaint is gout caused by high uric acid levels and that can be treated.

But there is no guarantee that the neurological symptoms of Lesch-Nyhan syndrome will be alleviated by gene therapy with the HGPRT gene. The symptoms seem to be caused by a lack of HGPRT in the brain, yet the cells that would get the HGPRT gene with this therapy are in the bone marrow. Whether much or any HGPRT would get from these blood cells to the brain is open to question. Finally, it may simply be too late for treatment once a child is diagnosed as having Lesch-Nyhan syndrome. Irreversible brain damage may already have occurred.

For these reasons, Mulligan feels very strongly that to emphasize gene therapy as a possible treatment for Lesch-Nyhan syndrome is to offer false hope. Others disagree. As Schulman points out, there are diseases such as Wilson's disease in which serious neurological symptoms, including intellectual impairments, disappear once a metabolic defect is corrected. The same may be true for Lesch-Nyhan syndrome. Therefore, Schulman says, "The only way to find the effect of gene therapy in Lesch-Nyhan syndrome is to try it. I favor trying because the risks are fairly minimal and the prognosis for the disease is so bad."

What happens, then, when investigators find that they are able to insert adenosine deaminase and HGPRT genes in mice and get them to function? At what point do they try treating human patients? "We will have to sit down and think pretty seriously," Caskey says. "We have to be certain that we will do no harm." But Caskey and the others doing this gene transfer work are confident that the day is not far off when patients will be treated. "We're obviously excited about the work, and the diseases are certainly worth the effort. Let's just say that I'm optimistic but I'm not unrealistic," he remarks.

—GINA KOLATA

National Networks for Molecular Biologists

After years of highly productive but somewhat dispersed programming efforts in DNA sequence analysis, a national facility is to be established

The National Institutes of Health has awarded $5.6 million over 5 years to a small Palo Alto company, IntelliGenetics, to establish a national computer resource for molecular biology. In addition to giving researchers ready access to national databases on DNA and protein sequences, the resource, named BIONET, will provide a library of sophisticated software for sequence searching, matching, and manipulation. An equally important aspect of BIONET, however, will be the development of further software, both by IntelliGenetics personnel and in collaborative ventures with outside researchers.

Peter Friedland, a Stanford computer scientist and a cofounder of IntelliGenetics, likes to emphasize a further stated BIONET goal: to establish a community of molecular biologists who can communicate rapidly, effectively, and frequently with each other over a computer network. "In my area, artificial intelligence, I can plug into 60 or 70 electronic bulletin boards, through which 400 or so people in the community can pose questions about problems they are stuck with, and get instant suggestions for answers," he says. "We hope molecular biologists will be able to do the same."

Richard Roberts, a molecular biologist at Cold Spring Harbor and a member of the site-visit team that reported to NIH on the IntelliGenetics proposal, endorses the community idea. "Molecular biologists need something like this. An effective communications network would be extremely valuable." And, as Allan Maxam of Harvard Medical School points out, a lot of people have been tackling similar problems in isolation, thus leading to a great duplication of effort. "There has been a great deal of reinventing the wheel," he comments.

With DNA sequencing proceeding apace in laboratories throughout the world, the need for effective data handling is inescapable, and has been for some time. The number of bases in sequences known so far is fast running up to 3 million, with the prospect of its doubling before very long. Efforts to have NIH underwrite a national DNA database were under way by the beginning of 1979, but the instruments of bureaucracy and a certain political uncertainty mired progress. It was not until August 1982 that a contract—$3 million over 5 years—was awarded to a Cambridge-based company, Bolt, Berenek and Newman, to set up the national database, now known as GenBank.

The NIH initiative to establish GenBank was supposed to be part of a coordinated effort with scientists at the European Molecular Biology Laboratory (EMBL), Heidelberg. But, frustrated by American tardiness, the Europeans finally went ahead alone: EMBL announced the availability of its Nucleotide Sequence Data Library in April 1982, 5 months before NIH agreed on funding for the U.S. version. The original notion of having a coordinated approach is, however, now almost achieved, with the two databases more or less harmonized and only some formatting disparities to be resolved. Future data collection will be shared between the two centers.

IntelliGenetics had been an unsuccessful contender for the GenBank contract. Unbowed, the company's scientists turned their attention to what had become known as project 2, which was to be the provision of a national facility for computer analysis of DNA sequences. For reasons of financial stringency, however, NIH was forced to abandon the idea, or so it seemed. Nonetheless, through the persistence of IntelliGenetics representatives and creative financing arranged by NIH personnel in the division of research resources, the BIONET proposal was approved and a $5.6 million, 5 year "cooperative agreement" awarded this month, just a little more than a year since the proposal was formally submitted. IntelliGenetics faced

no competing bids for the award, which is the largest of its kind by NIH to a for-profit organization.

The major difference between the defunct project 2 and the extant BIONET is the very large research and development component of the latter. And, under the terms of the cooperative agreement, a National Advisory Committee will direct policy issues, such as how access to the resource will be controlled, which programs will be included initially, and how user fees might be phased in. Six names have been agreed upon so far for the committee: Joshua Lederberg of Rockefeller University, who has been a driving force in getting molecular biologists to become computer literate; Thomas Rindfleisch, who has been directing an NIH medically and biologically oriented computer resource—SUMEX—at Stanford; Saul Amarel, chairman of computer science at Rutgers; Fotis Kafatos, chairman of biology at Harvard; and Richard Roberts and Allan Maxam. One other name will be added shortly to the list.

IntelliGenetics has its origins in a collaborative project that started in 1975 between computer scientists and molecular biologists in various departments at Stanford. Known as MOLGEN, the project was meant to apply artificial intelligence methodology to molecular biology, particularly in the design of experiments. In addition, however, MOLGEN personnel began making available to outside researchers existing and new DNA analysis software on the SUMEX facility. Very soon the burgeoning need for sequence analysis and scrutiny became more than obvious, as the guest account (GENET) for such manipulations on the SUMEX computer swelled and threatened to overload the system. The SUMEX resource was meant primarily as a research tool, not a service facility.

In 1980 Friedland joined with fellow artificial intelligence expert Edward Feigenbaum and two Stanford molecular biologists, Douglas Brutlag and Laurence Kedes, to form IntelliGenetics, "as a means of achieving technology transfer to the commercial molecular biology community." The company raised close to $9 million when it went public at the end of last year and now serves some 80 organizations with software. One quarter of these customers are in universities while the remainder are in commerce or government.

The GENET account, meanwhile, had imposed so great a load on the SUMEX facilities that as of 1 November 1982 it had to be terminated, with its 300 users thrown to their own devices. Some researchers continued to use the same software, which was made available through IntelliGenetics, while others looked elsewhere or developed their own.

GENET users, of course, never did represent the sum total of computer-minded molecular biologists: many researchers spent a good deal of time writing their own programs on their own facilities, some of which were modest, some quite powerful. The demise of GENET meant, however, that this dispersed effort multiplied. The fruits of all this creativity have been evident in the several special issues of the journal *Nucleic Acids Research* that have been devoted to software development. By making public through these special issues many of the programs developed by numerous researchers, it was hoped to reduce duplication of effort. Moreover, creative energies began in a number of places to marry with entrepreneurial spirit, and analytical software packages that included GenBank data began to become available, either on an informal or even embryonically commercial basis. It remains to be seen how these potential sources of competition to BIONET will fare in the face of the NIH award to IntelliGenetics.

The company might well find itself offering facilities—both software and hardware—in a newly created market unencumbered by serious competition from elsewhere.

Researchers who have access to relatively powerful facilities can perform virtually all the sequence analysis they might require, provided the software and databases are available. But even these fortunate people sometimes find themselves constrained in what they can do, however. For instance, Edward Ziff of New York University Medical Center has access to a PDP 11, and yet for his current project he has need of a bigger machine, such as the Digital Equipment DEC System 2060 owned by IntelliGenetics. Ziff and his colleagues have a series of DNA copies of messenger RNA's from brain cells and would like to be able to scan known protein sequences in the hope of matching some up. "If BIONET were available now we would have made heavy use of it during the past two months," he says.

Potent though it is, BIONET's brain is not the key element of the system. In any case, as computer hardware becomes ever more powerful and ever cheaper, more and more laboratories will be able to have their own capacious facilities. The key element of BIONET is that it is the means by which computer-oriented molecular biologists can communicate more effectively as a community.

Compared with GENET, which could accommodate two users at any one time, BIONET will have between 10 and 15 ports, giving an annual figure of about 30,000 connect hours. The matter of privacy of unpublished data on the system, which once was a subject of much anxiety among molecular biologists, is no longer an issue, says Friedland. Any user will be able to run a new sequence through BIONET's analytical programs without fear that others will have access to the sequence before it is formally published.

As BIONET is an NIH facility, access will require some kind of peer review, the form of which might be the responsibility of the advisory committee. Use of the facility will be free initially, but a user fee, unknown as yet but probably in the region of $12 to $32 an hour, will gradually be phased in.

Although there is an undercurrent of discomfort that a commercial organization should be providing this kind of national facility, and some direct criticism that IntelliGenetics has been more than a little pushy in achieving its favored position, most people seem satisfied with the arrangement. "I suppose you could quibble about whether this sort of thing should be run by a commercial or a public group," comments Ziff, "but it is not a major concern." Maxam notes that five years ago there would almost certainly have been a strong reaction to commercial involvement, but not now. Roberts is very enthusiastic about the whole thing. "If IntelliGenetics does what it promises to do with BIONET, everyone will be ahead: the molecular biology community, the company, everyone."

Under the terms of the cooperative agreement IntelliGenetics cannot profit directly from the award. But, as Anthony Slocum, the company's president, says, "there will of course be tremendous benefit to us through positive exposure to the community." And by the time the NIH funding for the project runs out, the company might well find itself offering facilities—both software and hardware—in a newly created market unencumbered by serious competition from elsewhere.—**ROGER LEWIN**