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How the gene-patenting race is affecting science

By BERNICE WUETHRICH

Since the National Institutes of Health first filed for patents on thousands of fragments of human genes in 1992, a sense of unease has permeated much of the international community of human geneticists. Perhaps it is just the disquiet that comes with sudden change and its unknown consequences — unrest that will dissipate as they work through ethical and legal questions now entwined with their research.

But many researchers are waving red flags. They are confronting difficult problems arising at the complex intersection of science, private enterprise, and the law.

C. Thomas Caskey, a Howard Hughes Medical Institute geneticist at the Baylor College of Medicine in Houston, offers a case in point. Last October, his team cloned the human gene responsible for creating wrinkles on the surface of the brain. These wrinkles are initiated during the first nine to 14 weeks of fetal development. If a mutation in the gene blocks their formation, a newborn will suffer from a severe form of mental retardation caused by lissencephaly, or "smooth brain" disease. The Caskey team is seeking a patent on the discovery. They hope to create a diagnostic test for detecting defective genes in the fetus.

Since filing for the patent, however, Caskey says he has learned that NIH scientists had serendipitously cloned at least six tiny fragments of that same gene in 1991. NIH included these anonymous genetic scraps in its massive gene-patent filing in 1992. If NIH's patents are approved, a legal battle may ensue, potentially delaying diagnostic use of the gene.

This scenario, says Caskey, is "going to happen time and time again" if the patent office rules that human gene fragments of unknown biological function can be "owned."

Geneticist Diane Wilson Cox tells of how codiscoverers of the gene for dystrophin — a structural component of muscle — have come to face a similar imbroglio.

Mutations in this gene cause Duchenne muscular dystrophy. In the late 1980s, two research groups found and began to sequence the huge dystrophin gene, with each group concentrating on a different section. Later, each group — one at Toronto's Hospital for Sick Children, the other at Children's Hospital in Boston — applied for a U.S. patent on its section, says Cox, a geneticist at the Toronto hospital.

The Boston group, anticipating approval, licensed patent rights to Genica Pharmaceuticals Corp., a biotechnology firm in Worcester, Mass. The Toronto group had to drop its application because it could not afford the $20,000-plus cost of pursuing the patent. Nonetheless, the Toronto researchers continued their work with the gene and with their young patients. Part of that work involves producing antibodies that correspond to the patented sections of the gene and then using those antibodies to diagnose dystrophin dysfunction. Genica patent lawyers claimed this was a commercial use of their product and threatened to file a lawsuit for patent infringement, Cox says.

The Toronto doctors had three choices: stop their work, pay royalties, or await a lawsuit. The situation remains unresolved. "This is one of the issues you get into when patenting gene fragments," Cox laments.

At the crux of the controversy are the pending patents filed by NIH on 6,122 gene fragments. Although lawyers at the patent office may argue for years before deciding whether these genetic scraps can be owned, Congress has meanwhile mounted its own investigation, mandating that the Office of Technology Assessment (OTA) report on policy options by next spring. In July, OTA sought out the opinions of an international group of scientists as part of that effort. They deliberated whether the U.S. Patent and Trademark Office should approve patents on genetic fragments and, if it does, how such decisions might affect genetic research and medical progress.

"We heard person after person, from virtually every country, saying that fragments and genes of unknown function are not patentable," says Cox. While their reasons ranged from the moral to the pragmatic, almost all participants at the meeting agreed on this point.

No similar consensus exists in the United States, however. Here, two contrasting perspectives frame the debate. One view asserts that the patenting of human DNA — including anonymous fragments — will stimulate further research, spur the development of new medical diagnostics, and generate lifesaving therapies. The other holds that such patents will stifle research, sow suspicion and secrecy among scientists, and slow medical progress.

Some U.S. researchers and companies — as well as NIH — are not idly awaiting the legal outcome of NIH's patent applications. Rather, they are filing their own patents, positioning themselves to have as much of a corner on the human gene market as possible. Their actions may reflect the reality of science and the marketplace in the United States. "The American practice is that we file for patents on these things," says Daniel Drell, a biologist at the Department of Energy (DOE).

So fast and furious is the race to identify human genes that within several years, patents may have been filed for every one of the estimated 100,000 genes nestled in human cells — the entire human genome. Thus, a small number of corporations, universities, and governments may soon "own" life's genetic code.

The human genome is nothing more than a varying series of four simple chemical units, called nucle-

otide bases. Billions of these bases link together to form molecules of DNA. The power of DNA resides in these bases: Their linear sequence along the DNA molecule defines a gene and, consequently, the protein for which the gene codes.

This sequence of information provides the substance of patent claims.

Since 1980, researchers have patented hundreds of complete genes, often claiming broad commercial rights to their potential diagnostic and therapeutic uses. Genes linked to cystic fibrosis, insulin, tissue plasminogen activator (used to treat heart attacks), and human growth hormone are a few of those for which patents have been approved or are pending.

At present, scientists understand the function of fewer than 1,500 human genes. The vast majority remain to be discovered, deciphered — and patented.

Decoding all these genes is the goal of the Human Genome Project, a $3 billion effort sponsored by NIH and DOE. The project, launched in 1988, aims to map each gene on its chromosome and to sequence the entire stretch of human DNA — all 6 billion nucleotide bases — by the year 2005.

The United States is not in this alone, however. Similar efforts are under way in the United Kingdom, France, Germany, Italy, Canada, Japan, Russia, and a network of Latin American countries, including Brazil, Chile, and Mexico.

Technological developments are speeding the gene hunt. Using the "old" techniques, scientists spent years searching for and tediously sequencing a single gene, base by base. Now, new technologies enable researchers to identify portions of hundreds of genes in a day and to rapidly sequence huge, uninterrupted stretches of DNA.

NIH based its controversial patent applications on one such technology. While working for NIH, J. Craig Venter developed an automated approach to identifying the entire repertoire of genes expressed within a particular type of cell, such as a brain cell or liver cell. Every cell in the human body has the complete set of human genes. But each type of cell expresses only a handful of the total — those it needs to perform its biological role — explains Mark D. Adams, a geneticist who worked with Venter at NIH and who now works with him at The Institute for Genomic Research (TIGR) in Gaithersburg, Md.

Venter's method works quickly, in part because it targets only a small portion of each gene. A gene can include hundreds of thousands of bases. However, the vast majority of these serve no known purpose. Perhaps only 2 to 5 percent of all bases are "expressed," or actually used to make a protein.

Venter's technique takes advantage of a cell's molecular machinery to zero in on these expressed portions, which are copied into strands of complementary DNA, or cDNA. Computers, in turn, sequence a tiny bit of the cDNA. These fragments, some only 18 bases long, are called expressed sequence tags (ESTs) because they can be used to track down the complete gene.

However, a large gap exists between identifying a tag and tracking down its complete gene. Thus, it will take even more work to characterize the gene's protein and develop useful products.

Yet the basic technique works so well that by the fall of 1992, NIH had submitted three large patent filings. The first, in late 1991, covered 347 fragments. This was followed by a filing for 2,375 fragments in early 1992 and a final filing of 3,400 genetic scraps the following autumn. "The three filings were intended to cover the complete set of sequences that Dr. Venter's group identified," says Reid G. Adler, the director of NIH's Office of Technology Transfer. In this way, "whatever policy decision was made would treat the whole group of sequences," he adds.

NIH claimed patent rights not only to the short tag, but also to the unknown gene of which it is part — and to the gene's unknown protein product. This shorthand approach departs radically from prior practice in gene patenting. In the past, scientists have applied for patents based on a gene's specific utility as gleaned from its complete sequence and from the biological function of its protein. The sum of this information has met the law's patent criteria: The discovery must be useful, novel, and nonobvious.

In December 1992, the patent office rejected NIH's bid, questioning the usefulness and novelty of the discoveries. NIH revised and resubmitted its applications early in 1993, dropping its claim on rights to the unknown protein but maintaining its claim on the whole gene.

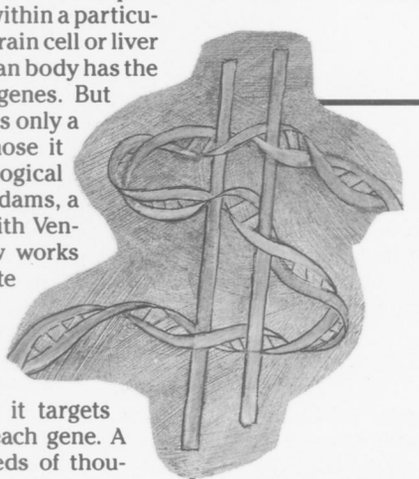
When NIH announced its massive application filing in February 1992, Bernadine Healy, then NIH director, described the rationale in a public statement. With the filing, she said, NIH hoped to foster debate over gene patenting, promote international cooperation, and ensure America's competitiveness in biotechnology. The paramount aim was "to encourage the rapid development of products for disease treatment." Patent filing, the reasoning went, would increase knowledge and the sharing of information and would provide economic incentives for product development.

"The goal," Adler stresses today, "is to get the issue addressed."

Not everyone within the agency agrees with the wisdom of patenting genetic fragments. "ESTs without known function are not and never should be patented," Francis Collins, the new director of NIH's National Center for Human Genome Research, told SCIENCE NEWS. In any case, he says, NIH should vigorously pursue its patent claim to settle the matter. Collins stepped into his post in April and was not part of NIH's original decision to file.

While the patent office is still in the midst of reviewing NIH's applications, competitors in foreign countries, university laboratories, and private industry have been staking their own genome claims by filing for similar patents. If NIH had not let the gene genie out of the bottle, someone else surely would have.

"In the last four years, we have sequenced 20,000 cDNAs," says Kenichi Matsubara, a geneticist at Osaka University in Japan. He says he hasn't decided whether to file for patents. However, "friends from the industry sector and the scientific community urge me to patent, in order to keep Japan's competitiveness," he says. Meanwhile, a private company, the Sagami Chemical Research Institute in Japan's Kanagawa Prefecture, jumped



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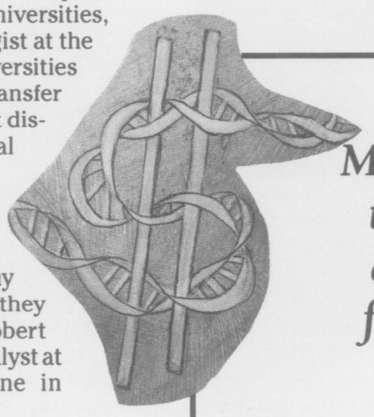
— Francis Collins

into the patenting fray last April, filing for 70 cDNA patents.

The British government is also sequencing cDNAs. While its Medical Research Council (MRC) in principle opposes patenting gene tags, MRC filed for patents on some 1,100 tags in August 1992 as a defensive response to the NIH filing, says Keith Gibson, head of MRC's Human Genome Mapping Project in London. MRC will soon decide whether to file patents for up to 1,000 more, he says.

In France, the government funds most genetic research, including cDNA sequencing. After the NIH filing, French researchers initially pursued patents on gene fragments but later dropped those claims, says Michel Cohen-Solal, a geneticist with the French genome research group GREG in Gif-sur-Yvette. The French government opposes patenting gene fragments on both moral and practical grounds, he says.

Within the United States, the Department of Energy funds cDNA sequencing at about half a dozen universities, says Daniel Drell, a biologist at the agency. Most large universities now have technology-transfer offices that push to patent discoveries with commercial potential. Because universities are not legally bound to disclose their patent activity, it is impossible to know how many or what kinds of patents they are submitting, says Robert Cook-Deegan, a policy analyst at the Institute of Medicine in Washington, D.C.



The largest players in the patenting race, however, are most likely private U.S. companies. At least two biotechnology companies are mass-sequencing cDNA and applying for patents on some of those findings.

Incyte Pharmaceuticals in Palo Alto, Calif., focuses on genes involved with the immune system, inflammation, and allergy. Researchers there use cDNA sequencing to track down the major proteins expressed by inflammatory cells, says Roy A. Whitfield, president of Incyte. This includes work with mast cells, a type of white blood cell implicated in bronchial asthma and allergy. Incyte hopes to work with drug companies to develop pharmaceutical products based on these sequences, Whitfield adds.

In an interview, Whitfield declined to specify how many cDNA patents his company is filing. However, he says the number of EST sequences in the NIH patent applications is "insignificant" compared with the number of sequences his company is working with. Furthermore, he says, "in our patents we certainly address the question of utility very strongly, and if we couldn't, then the new genes wouldn't have much value."

Probably the largest private enterprise sequencing cDNAs is TIGR (pronounced "tiger") and an associated company, Human Genome Sciences (HGS). Venter set up TIGR in July 1992 with 30 of his colleagues, who together left NIH. TIGR operates a virtual biogenetic factory, with dozens of sequencing robots running around the clock. "We are now finding several hundred ESTs per day, and we're not yet at full scale," says Chris Fields, director of TIGR's Comparative Genomics Laboratory.

HGS, a for-profit biotechnology company, funds TIGR, a not-for-profit research institute. HGS provided TIGR with a $70 million, 10-year grant in return for exclusive worldwide rights to information and materials TIGR produces. Much of TIGR's work focuses on genes expressed in the human brain, which may include one-third of all human genes, says Adams.

HGS has entered a strategic alliance with SmithKline Beecham, a major pharmaceutical firm. The agreement, announced in June, entitles SmithKline to exclusive worldwide rights to any therapeutic, vaccine, or diagnostic agents and services derived from gene sequences the two companies jointly identify. HGS will receive royalties on these products and will retain commercial rights to develop gene therapy, plant-derived drugs, and certain genetically engineered organisms. HGS has not revealed how many patents it is filing for ESTs.

Unlike NIH, universities and private companies generally have not publicized their patent filings. Thus, "only a small fraction of all the data that are relevant are public," notes Cook-Deegan. This makes the Office of Technology Assessment's study on the implications of human gene patenting all the more important, he adds.

Scientists, lawyers, and industry executives have a wide range of opinions on just what those implications are.

The gene-patenting debate has revolved around the question of utility. Short genetic tags have a real but very limited usefulness, says Max Hensley, a biotechnology patent attorney in Foster City, Calif. Their immediate use is simply in locating the whole gene — serving as a marker for a gene that is expressed in a particular kind of cell. However, "the burning issue is whether they [NIH] are entitled to [patent] the full-length sequence rather than just the little fragment," he adds.

Many scientists find this prospect troubling. They view the tags as an intermediate research result, easily obtained, and not a patent-worthy discovery. A huge difference exists between "all it takes to go from the bench to the marketplace and the relatively modest contribution one makes to have a robot mindlessly sequencing DNA," contends Thomas Kiley, a biotechnology patent attorney in Hillsborough, Calif.

Furthermore, because patent owners can prevent anyone else from making, using, or selling their inventions for 17 years, broad patents on fragments would position the owners to control the use of subsequent discoveries related to their patented DNA sequences. Some maintain that such protection would encourage investment in and development of new products; others say it would discourage those efforts.

Defending the benefits of such patents, Incyte's Whitfield argues that patent protection of intellectual property — discoveries of unique inventions — provides the lifeblood of the biotechnology industry. Furthermore, he says, "cDNAs are one of the most fundamental patent types in the industry." Whitfield insists that each EST should be judged on its individual merit, based on patent law. "The danger with saying [ESTs] shouldn't be patentable is that you risk creating a situation where there will be no more DNA patents at all issued," he adds.

Industry attorney Hensley contends that patents on gene fragments provide a protective safety net that will encourage

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investment and research. "If you say a sequence is partial and therefore [the inventor] is not entitled to the rest, then you open the way for predators to take the final step in the research direction and euchre the original inventor out of his or her invention," he says.

Marc Pearson, a geneticist and president of the new biotechnology firm Darwin Molecular Technologies in Kirkwood, Wash., disagrees. Filing for EST patents "has diverted attention from the important issue of identifying useful sequences and is a disincentive for biotechnology companies to develop real products at an enormous amount of expense and effort," he says. Others note that the prospect of litigation resulting from conflicting patent claims has a chilling influence on the ability of companies to obtain financing.

Researchers are also debating how the patent question affects the exchange of scientific information. Critics of large-scale EST patenting contend that it has already undermined science by sowing secrecy and impeding the rapid exchange of data that could speed gene mapping and discovery. Gibson cites his own experience, saying that Britain's Human Genome Mapping Project postponed the release of more than 1,000 tag sequences for a year while tangling with the U.S. and European patent systems. Concern over patenting "has held up and continues to hold up the exchange of information," he says. "[Scientists] want to be reassured that no patent issues are involved."

Others say that's just the nature of science. "It is relatively common practice in science to hold on to your data until you can get them published, so that you can get credit," says Adams of TIGR. "Many argue that data related to the genome project are different and that all information should be available instantly so everyone can work on it. But science is competitive."

Patenting can actually open up lab notebooks, Adams asserts. "By having patent protection you don't need to keep something secret," he says, "because you have legal protection. If you then publish it, no one can take it away from you."

Adams coauthored a report in the July NATURE GENETICS on 3,400 EST sequences that his team found while working at NIH. "NIH's filing for patents did not delay publication of that paper by one day. I don't know how that can be considered secrecy," he says.

Final resolution of the patent issues sparked by NIH's filing will have a major impact on the work of many researchers. Resolution, however, may take years.

If the patent office approves the revised applications, NIH can either license the patents and enforce those licenses, or release the patent information into the public domain. If the patent office rejects the applications, says attorney Kiley, NIH can appeal that decision — ultimately to the Supreme Court.

Another possible resolution could come from Congress. The OTA study on patenting DNA sequences, due next spring, will present policy options, some of which might be legislative, says Robyn Y. Nishimi, director of the OTA study.

Others note that Congress could pass a federal law prohibiting patents on gene fragments of unknown function. Less drastically, it could limit the kinds of infringement remedies that EST patent owners could pursue, says Kiley. He particularly favors limiting remedies for infringement of patents that are used by researchers. Similarly, Cook-Deegan favors carving out a legal "research exemption" to protect scientists from lawsuits.

The research community, the industries that will prosper from the fruits of genetic research, and the public will all feel the impact of the decisions made. As Darwin's Pearson points out, medical genetics has the potential to "define the molecular basis of disease [and] identify all targets for all therapeutics for all time." The implicit promise of this work makes resolution of the seemingly mundane issues of gene patenting and ownership all the more urgent. □