ing, he notes, but for the fact that he could tell he was getting good mathematical results along the way: Even if he hadn't found the master switch, he had lit up room after room. "If I'd spent 7 years and had nothing to show for it, then I might have reacted differently, but at any period during that time, I knew I was making progress," he recalled. Eventually he had explored enough of the mansion to formulate a blueprint for the proof. A key breakthrough in 1991 convinced him that "the proof was just around the corner." It was, "but the corner was a bit longer than I anticipated," he said in an oblique reference to the gap that threatened to thwart his quest.

The gap lay in Wiles's use of a relatively new and sophisticated mathematical tool called an Euler system, which promised to be more powerful than the original method. Unable to fix the gap in the Euler system, he enlisted Taylor's help to give the earlier approach another try, but he ran into the same difficulties that had prompted his detour into Euler systems. "I was beginning to be resigned at that point to a long haul," he told *Science*. In the end, though, it was his struggle with Euler systems that provided the missing insight for the original method.

"I was taking one last look at the Euler system and tried to formulate exactly what was wrong with it," he recalled. "Suddenly, on September 19 last year, I had this wonderful revelation." He "saw in a flash" the key to his original approach. "My problems were over. I was so amazed by this that for several hours I put it down and did some administrative chore, and then returned to it to check that it was still there. It was so simple and elegant that at first it seemed too good to be true." Actually, says Wiles, "it was too good to be false." Not only did the insight complete the proof, but it also simplified the parts he had laid out more than a year earlier.

The finished proof is still rough going even for the experts, but number theorists are eager to latch onto the methods Wiles has introduced. Fred Diamond, a former student of Wiles who is now at Cambridge University, has already extended Wiles's proof of the Taniyama-Shimura conjecture to a larger class of elliptic curves, and many are optimistic that the full conjecture may fall within a few years. Wiles won't say whether he will take on the task himself. "I'll have to take my time to think about what to work on next," he told *Science*.

For mathematics as a whole, the next task may be finding a suitable replacement for Fermat's Last Theorem: a new problem to tantalize future generations and draw youngsters to the profession. It's not clear how significant Fermat himself thought the problem was, Wiles says, but "I think he would be amazed at what his marginal note has done for the history of mathematics."

–Barry Cipra

Genome Mappers Have a Hot Time at Cold Spring Harbor

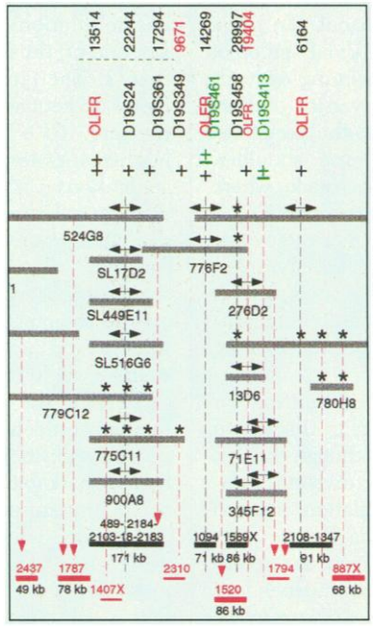
COLD SPRING HARBOR, NEW YORK—The "Genome Mapping & Sequencing" meeting held here from 10 to 14 May was electrifying. Huddles of geneticists debated how to start the final stage of the Human Genome Project (HGP)—large-scale sequencing. Then the outside world intruded as Francis Collins, director of the National Center for Human Genome Research at the National Institutes of Health (NIH), in an unscheduled address, asked the attendees to urge members of Congress to vote against budget cuts that could shrink the NIH budget by 20%. But even as conference attendees looked to the future with mixed elation and trepidation, they already have a sense of accomplishment, as the following samples attest.

A La Carte

One of the HGP's major goals has been to produce detailed maps of the human genome. Those maps, it is hoped, will lead to disease genes and provide guideposts for the ultimate sequencing effort. In mapping there has been plenty of progress, as the buzzwords bandied around at Cold Spring Harbor indicated. New terms such as "sequence-ready map," "integrated map," and "ultimate map" were on everybody's lips, while old ones such as "high-resolution" had taken on new meanings.

Last year, a genomic map counted as high-resolution if it contained one genetic landmark per 100 kilobases (100,000 bases) of DNA. "Now 'high-resolution' means ready to stick in the ABI [sequencing] machine," said mapping expert Ken Krauter of Albert Einstein College of Medicine. That means a new criterion has been added: The segments between landmarks must also be broken into overlapping fragments that by some people's estimates should be as short as 10 kilobases. That's an onerous task. But maps of at least two chromosomes, 16 and 19, have reached that stage, and they are expected to be the first chromosomes to be completely sequenced.

Once sequence information starts pouring off the production line, geneticists will need reams of additional data to work out what it all means—where the genes are hidden among the masses of noncoding DNA, for example, and which genes are likely to be involved in causing disease. Consequently, the information-rich "integrated maps" of human chromosomes 3, 11, 12, 13, 16, 19, 21, and 22 that were on display at Cold Spring Harbor attracted intense interest.



ANNE OLSEN/LAWRENCE LIVERMORE NATIONAL LABORATORY

Full of facts. A portion of the detailed chromosome 19 map is shown here.

To make integrated maps, researchers first establish the gross topography, the positions along the chromosomes of segments of human DNA that, for ease of manipulation, have been cloned in bacterial and yeast cells. Layered on top of these ordered DNA segments, which cover up to 98% of some chromosomes, are the specific addresses of hundreds of genes and DNA markers as determined by genetic linkage studies, which give their relative positions, or by physical mapping, which provides their actual sites on the genome. "A truly impressive accomplishment" is how genome scientist Maynard Olson of the University of Washington, Seattle, described the integrated maps.

While some attendees pored over maps of individual human chromosomes, others followed global interests. From France came Jean Morissette of Généthon, a private research institute in Evry, who offered the close-to-final version of Généthon's human genetic linkage map. That map now covers the entire human genome and is packed with 5300 markers—two-and-one-half times the number available 18 months ago.

And Isabelle Le Gall of the Centre d'Étude du Polymorphisme Humain (CEPH) in Paris presented a new and improved version of CEPH's physical map that comprises aligned,

overlapping sequences of human DNA cloned in extra-large Yeast Artificial Chromosomes or "mega-YACs." The team's original mega-YAC map, published in *Nature* in December 1993, was flawed because in some cases pieces of DNA from widely separated regions of the human genome become joined in the same mega-YAC, leading to false alignments. By adding more markers and eliminating false links, Le Gall and her colleagues have created a new version of the map covering up to 75% of the human genome with 33,000 YACs. "It looks like a pretty good map," said Lincoln Stein of the Whitehead Institute in Cambridge, Massachusetts.

Meanwhile, a team led by Whitehead's Eric Lander is steaming ahead with its sequenced-tag site (STS)–content map. That effort emphasizes mapping the order of STS markers, which are tiny sequenced fragments of DNA, rather than the large chunks of DNA contained in bacterial clones or YACs. The Lander group has developed a massively automated system called the "Genomatron" that can screen for hundreds of STSs in a matter of hours. Using that system and CEPH's collection of mega-YACs, the Lander team is putting STSs in order: Two STSs are considered to lie close to one another in the genome if they both occur together in two different YACs. So far the effort has placed 10,000 STSs into 50 groups per chromosome covering about 90% of the genome, says Lander. "It's a terrific effort," said Robert Gemmill of the Eleanor Roosevelt Institute for Cancer Research in Denver.

But along with the sense of achievement came a liberal dose of the letdown that accompanies the realization of any difficult feat. In 1989, at one of the earlier Cold Spring Harbor genome meetings, the obstacles to creating detailed maps of the human genome seemed insurmountable, remembers molecular biologist Stuart Fischer of Columbia University in New York City. "Six years later it's equally as depressing—it's all over!"

Returning to the Scene Of the Crime

In 1992, seven competing teams of gene hunters announced with much fanfare—and no fewer than six papers in *Science*, *Nature*, and *Cell*—that they had nabbed the defective gene that causes myotonic dystrophy, a devastating muscle wasting disease. New evidence presented in a poster session at Cold Spring Harbor by Keith Johnson of Charing Cross and Westminster Medical School in London suggests, however, that the massive hunt may have missed a key accomplice: a gene dubbed the dystrophia myotonica–associated homeodomain protein (DMAHP) that lies close to, and may even overlap, the original gene, dystrophia myotonica protein kinase (DMPK).

"[The finding] says a lot about disease gene cloning," says Lap-Chee Tsui, a molecular geneticist at the Hospital for Sick Children in Toronto. Genetic detectives should watch out, he says, because "just because you find a mutation, it doesn't mean you have" the culprit genes.

Johnson and his team—one of those that bagged DMPK in the first place—were led to the new suspect by an inconsistency unearthed during the original search. The mutation that triggers myotonic dystrophy, a genetic stutter called a triplet repeat, lies at the end of the DMPK gene, in the middle of a genetic landmark called a CpG island. But because CpG islands usually occur at the beginning of genes, Johnson says he and his coworkers were "highly suspicious that there was another gene in the vicinity." As the Johnson team investigated further, they discovered that the CpG island does indeed contain parts of a second gene.

When the researchers compared the partial sequence of the new gene with those already in the databases, they found a strong resemblance to a fruit fly gene called *sine oculis*, which is needed for eye development. *Sine oculis* is related to a family of mouse genes whose functions include regulating muscle development in the lower parts of limbs. Because eye cataracts and muscle wasting in the lower regions of the limbs are common symptoms of myotonic dystrophy, that suggested a defect in the new gene might contribute to the disease.

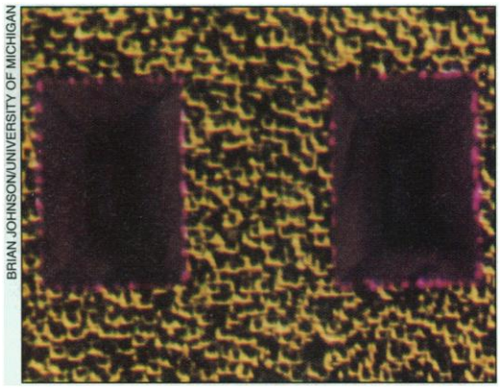
But even if it does, it won't let the original gene, DMPK, off the hook. Defects in DMPK, which encodes an enzyme that may help control muscle cell differentiation and excitation, could account for another symptom of the disease: muscle spasms. In fact, Johnson says, having two gene suspects helps explain why the symptoms of myotonic dystrophy vary widely, even within one family. "It could be that you get different [triplet] repeat lengths, in different tissues, affecting different genes, at different times of development," he says.

Now the Johnson team is working to find out whether the second suspect, DMAHP, is defective in myotonic dystrophy patients—the final piece of evidence needed to pin at least some of the blame on the new gene.

Xeroxing DNA Analysis

"Mind-boggling," said one meeting attendee. "Outrageous," said another. David Smith, who heads the Department of Energy's Human Genome Program, called it simply "the future." What fired up these participants at the Cold Spring Harbor meeting was a talk by mouse geneticist David Burke of the University of Michigan, Ann Arbor. Burke, who works with Michigan engineers Mark Burns and Carlos Mastrangelo, described the team's attempts to fashion a silicon chip to detect specific DNA sequences, including mutations in known genes and genetic markers that can be used to track down genes. If such a chip could be made, it would revolutionize diagnosis of genetic diseases and genetics research by making DNA analyses dirt cheap and lightning fast.

Although the Michigan team hasn't yet analyzed any DNA, conference attendees were excited because, unlike similar projects (*Science*, 7 April, p. 26), the researchers are going for broke. They are attempting to include all the elements needed for the analysis on a single chip, a plan that has inspired them to solve the vexing problem of moving liquids through lilliputian channels.



BRIAN JOHNSON/UNIVERSITY OF MICHIGAN

Ports of entry. The photograph shows the loading sites for DNA samples on a silicon chip.

At Cold Spring Harbor, Burke reported that he and his colleagues have modified prototype miniature components—including thermal cycling chambers for PCR, the reaction that copies DNA strands, miniature gels for separating fragments of DNA, and detectors for identifying radioactively labeled DNA—so that they all fit on a single chip.

The team's engineers have also developed a novel means of moving liquid samples from one component to the next. It's difficult for a miniaturized pump to generate sufficient external force to draw the liquids through the tiny channels—as narrow as 30 microns—on the chip. So the Burke-Burns-Mastrangelo team instead propels the droplets by heating them on one side, in theory creating internal forces due to changes in surface tension.

Even the enthusiastic Burke is quick to point out that numerous hurdles must be overcome before DNA analysis–on-a-chip becomes a reality. He worries, for example, that DNA will stick to silicon and other microchip materials, making it impossible to move the DNA. But, says Burke, it's worth trying to overcome the problems because the technology has many potential advantages, not least the fact that once a chip has been built, it's extremely easy to copy. "You can make new [chip-based] machines as easily as you make Xerox copies," he says.

–Rachel Nowak