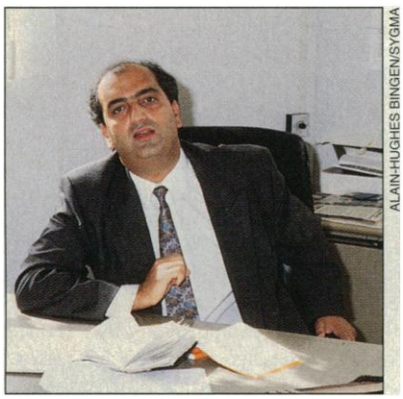
French Gene Mappers at Crossroads

A unique collaboration that produced the first maps of the entire human genome is being dissolved as the partners take on different–and even more ambitious–new challenges

PARIS—Football coaches are always leery of breaking up a winning team. But the leaders of Europe's premier genome-mapping collaboration have no such reticence.

Last December, a group headed by Daniel Cohen, the hard-driving director of the Centre d'Étude du Polymorphisme Humain (CEPH) in Paris, announced the completion of the first rough physical map of the entire human genome (*Science*, 24 December 1993, p. 1967). It was the fruit of a unique collaboration between CEPH, Généthon—the genome center Cohen cofounded in Evry, south of Paris in 1990—and the French Muscular Dystrophy Association (AFM), which has bankrolled Généthon with $50 million over the past 4 years from the proceeds of an annual telethon. And the partnership is finishing up another achievement: A Généthon team led by Jean Weissenbach of the Pasteur Institute will soon complete a genetic linkage map that complements Cohen's physical map.



ALAIN-HUGHES BINGEN/SYGMA

Mapping new territory. CEPH's Daniel Cohen is going after multi-gene diseases.

Now, you might think, the CEPH/Généthon collaboration would be consolidating its position as a world leader in human genome research. But when *Science* visited Paris last month, the two labs were in the midst of dissolving their symbiotic relationship. And CEPH was embroiled in a bitter internal row that could lead to the breakup of one of its own research teams over a proposed collaboration with a gene-hunting company. The dispute became public last week when a newspaper article raised questions about potential conflicts of interest on Cohen's part, and implied that an American company was trying to use French research to "line its pockets"—charges Cohen hotly disputes (see box, p. 1553).

CEPH and Généthon are parting company because Cohen and AFM are heading off in different scientific directions. The association wants to focus Généthon's work on the next stage of its crusade against muscular dystrophies: It plans to get out of genome mapping and use the two Généthon maps to begin hunting down and cloning the genes involved in neuromuscular diseases. Cohen is casting a wider net. His long-term goal is to unravel the genetic basis of more complex diseases—such as diabetes and obesity—that are influenced by a whole suite of genes. And that, he asserts, requires more intensive mapping to refine and integrate the two Généthon maps, together with analysis of DNA from thousands of individuals from families in which such diseases occur.

This parting of the ways comes as no surprise to scientists close to both Cohen and AFM president Bernard Barateau. Their partnership, says Axel Kahn, co-director of the Cochin Institute of Molecular Genetics in Paris, was "a clear, limited deal" based on a project of common interest—the production of rough but usable whole genome maps. Like most divorces, however, the separation has brought a difficult period of soul searching for both partners. The challenge for Généthon is relatively clear cut: Can the factory-style approach that is the lab's hallmark be adapted to AFM's new gene-cloning project (see box, p. 1559)? For CEPH, the future is strewn with more difficult scientific and political obstacles, as the lab's first brush with the commercial world suggests.

Life without Généthon

Cohen and Nobel Prize–winner Jean Dausset launched CEPH in 1983 with a gift from a wealthy art collector. (It now has a budget of about $10 million a year, two-thirds of which comes from the French government, and it is overseen by a board including several government ministers.) Their goal was to develop tools with which to study genetic disease. Cohen quickly realized that some of the tedious work in genome mapping might lend itself to automation, and he cofounded Généthon with AFM to apply this approach on a massive scale—a concept that at the time was controversial. Now that the strategy has paid off, however, Cohen no longer has Généthon at his disposal to conduct the large-scale DNA analysis that will be needed to find the genes underlying complex diseases like diabetes.

The traditional way to hunt disease genes is to determine which polymorphic markers—stretches of DNA that vary between individuals and have been mapped to specific locations on a genetic linkage map—are inherited together with the disease. This is done by analyzing DNA samples from members of families in which the disease occurs. Once a marker has been linked to a disease, researchers know that the defective gene must lie somewhere nearby.

These studies are time consuming even for diseases caused by a single gene mutation. And it will be a particularly daunting task to track down the genes underlying multi-gene disorders, says Cohen, requiring the analysis of DNA samples from thousands of individuals. "We have to do molecular biology with the dimensions of epidemiology," he says. And that, Cohen asserts, means that the best strategy is to link up with companies that are gearing up to conduct this work on a huge scale. Other influential geneticists agree. "Even if you could, do you really want to turn your research lab into a Généthon?" asks Peter Goodfellow of Cambridge University, who is advising one such company, Sequana Therapeutics Inc. of La Jolla, California.

Aside from mammoth genotyping facilities, Cohen believes the hunt for genes underlying complex diseases will also require better genome maps. He is the first to admit that his physical map—which is essentially a set of overlapping DNA clones with markers that allow them to be lined up in the order they appear on the genome—is just the starting point of efforts to map the human genome. "This map is very rough," he says. Cohen aims to refine the map by adding thousands of new polymorphic markers.

The U.S. genome project has similar plans. Among its 5-year goals, for example, is the creation of a so-called sequence tagged site (STS) map containing some 30,000 markers spread across the genome (*Science*, 1 October 1993, p. 43). But, typically for the man who pioneered whole genome mapping while the U.S. project was taking a chromosome-by-chromosome approach, Cohen is thinking big. CEPH is aiming to integrate fully the parallel physical and genetic linkage maps produced at Généthon, and to increase their resolution by an order of magnitude. Cohen's goal: an integrated genome map containing tens of thousands of poly-

Dispute Over Company Link Roils CEPH

For the past 3 years, Philippe Froguel has headed a team of more than 20 people at the Centre d'Étude Polymorphisme Humain (CEPH) trying to unravel the complex genetics of obesity and diabetes. But a bitter public row with his boss, CEPH director Daniel Cohen, now seems certain to bring about his departure from CEPH and has plunged the lab into what one scientist there calls "the worst crisis we've had."

Froguel's group is halfway through a planned 6-year effort to collect DNA samples from hundreds of French families afflicted by obesity and both non-insulin- and insulin-dependent diabetes. The eventual goal is to sift through these samples looking for genetic markers that are inherited along with the diseases—a mammoth task that Cohen argues is best done by an industrial-style lab. Last year, he came up with a candidate: Millennium Pharmaceuticals Inc. of Cambridge, Massachusetts, a company that Cohen helped found and in which he holds stock. Millennium is equipping a 5000-square-meter facility to conduct a mammoth genotyping effort.

ALAIN-HUGHES BINGEN/SYGMA

Outraged. Philippe Froguel questioned agreement with U.S. company.

Last December, however, when Millennium's lawyers produced a draft contract for the proposed collaboration, Froguel hit the roof. In return for payments to CEPH amounting to several hundred thousand dollars a year, the draft agreement would have given Millennium exclusive access, for a 2-year period, to the DNA samples Froguel's group had collected. Furthermore, claims Froguel, the proposed deal would have allowed CEPH to collaborate with other groups on diabetes and obesity only if any resulting patent rights were to revert to Millennium.

To Froguel, these conditions were unacceptable. In an interview with *Science* last month, he contended that Cohen was maneuvering CEPH toward a collaboration biased in Millennium's favor. "He doesn't know if he is working for Millennium or CEPH," said Froguel. Cohen vigorously rejects this charge. He says he took himself out of the negotiations with Millennium because of the potential conflict of interest, and he says he had not even read the offending document until a few weeks ago. Moreover, he points out that the decision on whether to approve any deal lies with the board of CEPH's governing body, the Jean Dausset Foundation, which includes government ministers. "I will not do anything if my government does not agree," he says.

Relations between Cohen and Froguel have now soured to the point where Cohen has asked Froguel to leave CEPH. And the dispute burst into the open last week with an article in the satirical publication *Le Canard Enchainé*, which took a strongly anti-Cohen and nationalistic line, implying he was trying to help Americans profit from French research. The fallout could be widespread, because the article noted that Froguel's work is financed in part by the French Muscular Dystrophy Association (AFM), which raises funds by an annual telethon. Last year, the association spent nearly $30 million on research in labs throughout France. Researchers who depend on AFM's largess are worried about the impact on fund raising of any suggestion that the money is being used to profit companies and private individuals. "[I]t's very damaging for everybody," says Jean Weissenbach of the Pasteur Institute and Généthon.

The intensity of Froguel's dispute with Cohen, say senior CEPH scientists, reflects a breakdown of communication at the lab, and a clash of two strong personalities. But while the general view is that Froguel overreacted to the draft agreement—which was still open to negotiation—some CEPH scientists agree that he raised several legitimate issues. The document, says geneticist Jacques Beckmann, who has been trying to mediate between Cohen and Froguel, contained "a large number of things that were totally unacceptable."

CEPH is not alone in confronting these issues. A handful of new gene-hunting companies are trying to forge links with academic labs that hold collections of DNA from disease-affected families (*Science*, 15 January 1993, p. 300). Like Millennium, several of these companies are asking for a period of ex-clusive use of the DNA in return for a financial commitment to the lab. "Some grace period will probably be required," says David Galas, formerly head of the U.S. Department of Energy genome project, and now vice president for research at Darwin Molecular Technologies Inc., a Seattle-based company that is going after the genes underlying autoimmune disease.

Some geneticists argue that this would be nothing really new. Academics, they note, rarely share DNA until they publish a result indicating the probable location of a disease gene. But other researchers—particularly those working on multi-gene diseases, where pooling data from family collections made by different groups may be necessary—are deeply troubled by this idea. "I don't think companies can really come in and buy [access to] DNA," says endocrinologist Leif Groop of the University of Lund in Sweden, who is studying the genetics of diabetes.

To blunt these concerns, Cohen is now proposing that CEPH should make all CEPH's DNA samples publicly available. Academics could use the samples at cost price; companies, he suggests, could pay royalties back to CEPH, if they develop a product from research using the samples. The basic idea is not new: Similar public repositories, each containing samples from more than 100 families affected by insulin-dependent diabetes, are being operated by the British Diabetic Association and the Human Biological Data Interchange, which distributes DNA from the Coriell Institute for Medical Research in Camden, New Jersey.

Froguel, after initially opposing the idea of a public repository, now says he supports the plan—but with two caveats. Groups receiving the DNA, he argues, should agree to deposit their own DNA samples and data in the public domain, and refrain from filing patents on any results obtained using the CEPH samples. That would effectively bar Millennium, or any other company, from making use of CEPH's DNA.

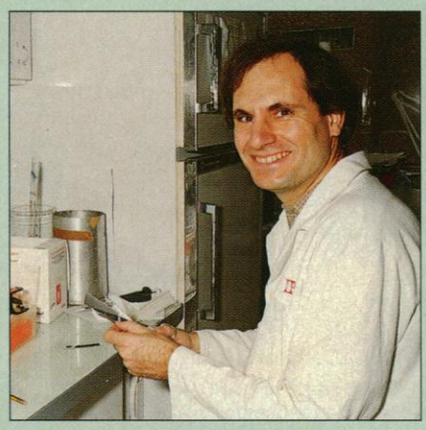
The French government must now decide what form the proposed public repository should take. But with Froguel now resigned to leaving CEPH, a question mark hangs over the lab's projects on diabetes and obesity. Cohen would like CEPH to continue working in the area, but that will depend on how many of Froguel's group decide to stay at the lab. Millennium officials say that they are still interested in working with CEPH. "It's...our policy to wait for them to decide what's best for themselves," says Mark Levin, Millennium's chairman and chief executive.

–P.A.

Généthon: An Industrial Approach to Isolating Genes

Gene mapper Jean Weissenbach of the Pasteur Institute is experiencing a certain *déjà vû*. Four years ago, he was greeted with skepticism from many of his colleagues when he joined with Daniel Cohen of the Centre d'Étude du Polymorphisme Humain to launch Généthon, a unique venture established to apply factory-style automation to genome mapping. At the time, many geneticists argued that filling a laboratory with robots tended by semi-skilled technicians was no way to do science. Today, Généthon's success in producing physical and genetic maps of the entire human genome has silenced most of the critics. But now, Généthon is being asked to apply the same industrial-style approach to a new problem, and it is facing renewed skepticism. And this time, Weissenbach himself admits to a degree of uncertainty.

Généthon's primary sponsor, the French Muscular Dystrophy Association (AFM), has decided to get out of whole genome mapping and focus instead on cloning the genes for neuromuscular disorders and other single-gene diseases—a project that AFM president Bernard Barateau has dubbed Généthon II. The big question now is whether this work is ripe for automation, or if it would be better to give grants to academic groups to pursue more traditional lines of attack. "Généthon might not be more efficient," says Weissenbach, who will head the effort. "We won't do big science for the sake of it."



ENVOI L'INSTITUT PASTEUR

Leader of the hunt. Jean Weissenbach, planning search for single-gene defects.

The starting point for AFM's gene hunt will be the maps produced during the first phase of the Généthon project. By the end of 1994, the genetic linkage map that is Weissenbach's main current responsibility at Généthon will contain nearly 5000 polymorphic genetic markers. With this map, gene hunters should be able to determine the approximate location of the genes underlying neuromuscular disorders using the standard techniques of linkage analysis. But even when a gene's rough position on a genetic map is known, it can take years to isolate it from the overlapping DNA clones that make up the corresponding physical map. "This is the next bottleneck," says Weissenbach.

To test whether that bottleneck can be removed through automation and economies of scale, a six-person Généthon team will spend the rest of 1994 examining the potential for scaling up the various techniques for isolating genes from the surrounding DNA. The problem, says Weissenbach, is that a range of methods can be employed for this task, and a successful gene cloning effort often demands day-to-day shifts in strategy—which will make automation difficult. Furthermore, he's wary of scaling up too soon and of risking getting stuck with obsolete technology. "This is a very fast moving field," says Weissenbach.

These uncertainties mean that Généthon II's precise scope and timing won't be decided at least until early 1995. But that hasn't stopped Barateau from planning Généthon III: an effort to unravel the metabolic function of newly identified disease genes, which will require the production of new transgenic mouse models. This phase will be headed by Axel Kahn, codirector of the Cochin Institute of Molecular Genetics in Paris.

Généthon III's startup date is highly uncertain, however—largely because of questions surrounding Généthon's long-term finance. So far, more than 90% of the lab's budget has come from AFM. AFM's latest fund-raising telethon, in December, raised more than $60 million, 16% up on the 1992 figure. But Kahn says it is unrealistic to rely on continued public generosity to fund two major new projects that—unlike the genome mapping effort—will last a decade or longer. "We have to find money for a very long time, from diverse sources," he says. Kahn and Weissenbach want to supplement Généthon's core budget from AFM with money from industry and government research agencies. So far, there's no commitment from either.

Some of Généthon's other scientific directions are more certain. A major cDNA sequencing effort headed by Charles Auffray, employing about 30 Généthon staff, is set to continue. And the lab has also begun to open up its shop to gene-hunters from the wider scientific community. For a nominal fee, researchers can use Généthon's automated genotyping facilities to analyze their own DNA samples. Already, more than 30 groups have used this service.

Still, to most academics, the question marks hanging over Généthon's future must seem like a strange reward for its scientific achievements. But then Généthon was never supposed to be a conventional lab. AFM's goal, say senior Généthon scientists, is to take the quickest possible route to effective therapies for genetic disease—and if that means dismantling a successful genome mapping lab to start the next phase of the project, then so be it.

–P.A.

morphic markers that can be used in linkage studies to track down disease genes.

Elke Jordan, deputy director of the U.S. National Center for Human Genome Research, says the difference between the U.S. approach and that advocated by Cohen is largely a question of timing. "Definitely, we want to correlate the genetic and physical maps," she says. But producing an STS map containing many polymorphic markers will be more expensive, she argues, so it's not an immediate priority.

CEPH's other priority is to resolve the problem of chimerism—the splicing together in a single clone of unrelated pieces of DNA—that plagues all physical maps made by piecing together overlapping stretches of human DNA cloned into yeast artificial chromosomes (YACs). A CEPH team led by Denis Le Paslier is experimenting with bacteria artificial chromosomes (BACs)—a DNA cloning vector developed in 1990 by Caltech's Mel Simon, for which chimerism is not a major problem. But BACs carry only about one-quarter as much DNA as their yeast counterparts, limiting their efficiency for mapping, so Le Paslier's team is trying to coax BACs to accept longer stretches of DNA.

The extent of CEPH's direct involvement in using its maps to hunt for genes underlying multi-gene diseases now depends on whether the row over CEPH's first flirtation with the commercial sector will lead to the closure of its in-house projects on diabetes and obesity (see p. 1553). Even if that does happen, Cohen notes that CEPH's continued work on genome mapping will be important for any group studying the genetics of multi-gene disorders. "Our main purpose," he says, "is to generate tools that will speed up the isolation of disease genes."

–Peter Aldhous