Kingdom, Germany, Japan, Brussels, and the United States. Jacques Bordé is CNRS's representative in London. He gave up a research career in quantum mechanics to move to Britain 6 years ago. "The number of cooperations was ridiculously low. I saw there was really something to be done," he says. Bordé says he has personally been in touch with 400-500 labs since he came to Britain and has a database listing more than 1000 collaborations. And although he modestly refuses to accept much of the credit, joint publications by Anglo-French teams increased by 50% in the 4 years after he arrived. It's not all plain sailing, however: Bordé wrote recently in the CNRS journal that "British researchers are exceptional partners but difficult to work with."

A particularly sweet success came last December with the establishment of the first "Associated European Laboratory (LEA)," a laboratory without walls that fuses research projects from the Institute of Astronomy in Cambridge, the Astrophysical Institute in Paris, and the Leiden University Observatory in Holland. "The initiative came from François Kourilsky, the director-general of CNRS," says Simon White, the LEA director. "His idea was that there was need for a collaborative structure somewhere in between a small collaborative research project and the very large-scale projects like CERN." Four more such laboratories are now being created in materials science, plant molecular biology, magnetism, and viruses and cancer.

One key element is missing from this picture of the emerging Europeanization of science, however: an active lobby from the scientists themselves for international collaboration. Alas, when it comes to fighting for the greater European good, scientists have shown themselves to be just as bad as their political masters with their squabbles over small concessions to other countries.

Although many scientists join European organizations out of a sense of duty, every effort to set up true pan-European academic societies—ones that could lobby for science throughout Europe—has so far disappointed. Just like national governments, national academic societies have never proved willing to back pan-European societies wholeheartedly. The result is that the pan-Europeans are left with an endless struggle for funds: After 24 years of difficulties, the European Physical Society is now trying to reconstitute itself; the 13-year-old European Neuroscience Association is even considering that it might have to shut down (see p. 468); and the European Cell Biology Society and Developmental Biology Society are pale shadows of their U.S. relatives. If scientists lag behind soap salesmen, they have partly themselves to blame.

–Alun Anderson

With reporting by Peter Coles

MOLECULAR BIOLOGY

U.S. Juggernaut Overwhelms Divided European Elite

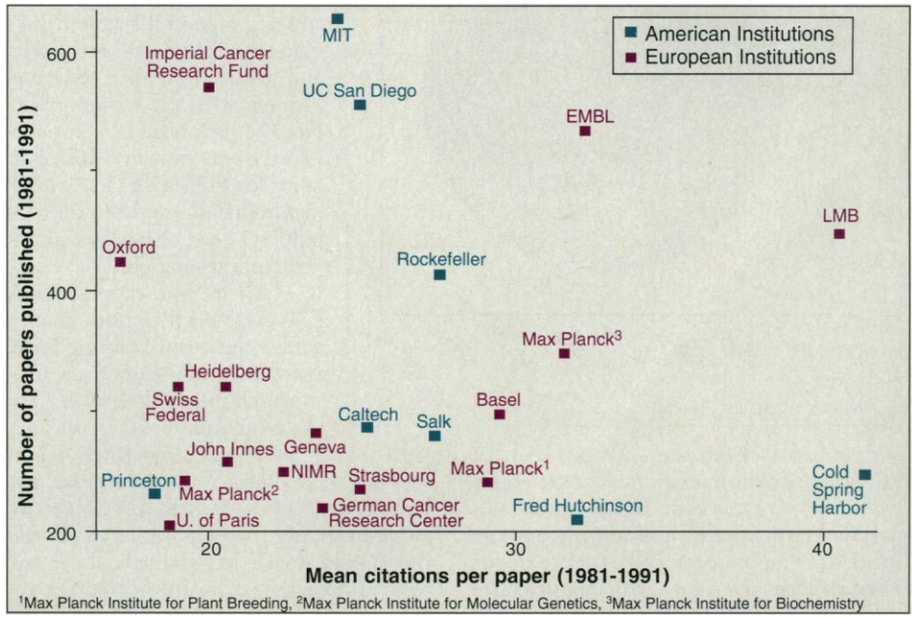
"Molecular biology worldwide is 80% American, more or less," says Pierre Chambon, director of the Laboratory of Molecular Genetics of Eukaryotes in Strasbourg. "We are lagging behind the United States," says John Tooze, executive secretary of the European Molecular Biology Organization (EMBO) in Heidelberg. "It's not a total disaster—there are many areas where Europe does excellent work—but we're behind."

Data on citations and manuscript output confirm the opinions of Chambon and Tooze (see chart): After a European lead, when people like Max Delbrück, John Kendrew, Francis Crick, Fred Sanger, Jacques Monod, and François Jacob virtually created molecular biology, most of the action is in America.

What would it take to raise European molecular biology to the U.S. level? More money is the obvious answer, given that the difference between the two continents is quantity not quality. The best research teams and institutes in Europe are as good as any in the United States—some are even better. In the frequency with which its papers are cited, the Laboratory for Molecular Biology (LMB) in Cambridge beats every other molecular institute in the world, except for the much smaller Cold Spring Harbor Laboratory. And the European Molecular Biology Laboratory (EMBL) in Heidelberg is not far behind, ranking third among the world's elite institutes. The problem for Europe is that there aren't enough labs like LMB and EMBL—and it's wishful thinking to suppose that Europe's national funding agencies are about to increase research support dramatically. "The funding will not be better," says Chambon, who points out that over the past 10 years, the budget of the U.S. National Institutes of Health (NIH) has increased in constant dollars by more than 50% while France's support hasn't changed. Instead, several of mainland Europe's senior molecular biologists suggest that strength lies in unity: There should be more central funding and peer review of Europe's highly fragmented molecular biology and greater mobility of young scientists, they argue.

"We are not well equipped to become competitive unless we join together," says Lennart Philipson, head of the EMBL. "If we took advantage of everything in Europe we could do much better."

Like European economists of a decade ago, Philipson and his colleagues are essentially arguing for a free market and open competition. Why not make grant reviewing Europe-wide so that money goes to the best in all Europe,



World ratings. At the very top, America and Europe come out even. List institutes (excluding small ones) by the frequency by which their papers are cited and Europe takes half the top 10 places (2. LMB, 3. EMBL, 5. Max Planck Institute for Biochemistry, 6. University of Basel, 7. Max Planck Institute for Plant Breeding). But a little further down the list, the United States weighs in with scores of high-quality laboratories. Source: ISI Science Indicators Data Base. To obtain more detailed listings, see p. 488.

regardless of nationality, they ask. And why not set up new categories of research fellowships, to get around current restrictions that force young predoctoral students to study in their own countries?

Concerted action. The questions are not new. As the heads of Europe's two true multinational molecular biology organizations, EMBL and EMBO, Philipson and Tooze have raised them often before. The new wrinkle, however, is that other senior biologists are beginning to pick up the message. Last December, Philipson launched one initiative, calling for an "NIH for Europe." And last June, in a wider initiative, the European Union of Societies for Experimental Biology (EUSEB)—was set up with European Commission support to represent 15,000 of Europe's biologists.

Number one topic on the Europeanists' agenda is to internationalize refereeing of grant applications. Smaller countries have particular difficulties providing their own referees. "In Switzerland," says Charles Weissmann, head of the Institute of Molecular Biology at the University of Zurich, "we cannot muster enough people to have site visits." Even big countries have their problems: "In France we don't have all the experts in all the fields of biology," says Chambon. And in Italy, molecular biologists see external peer review as a lifeline that could rescue science from political interference (see p. 477).

Only the British seem perfectly confident that their refereeing is on the ball. Aaron Klug, director of the UK Medical Research Council's LMB, says he frequently reviews grant proposals for NIH, and MRC can easily call on U.S. experts. But he, after all, heads what is probably the best molecular biology lab in the world.

When criticizing European refereeing, it's not just national problems that scientists have in mind, but even more, the review process of the EC. Researchers feel that the EC, which has the only really large source of multinational funding in Europe, should be setting an example of how to run pan-European funding, and so far they feel let down.

"The community does not have straightforward peer review," says Harald zur Hausen, head of the German Cancer Institute. "It's clear that they don't have the best possible experts to evaluate the projects," says Chambon. Brussels does not agree. Charges that the EC's experts are not up to standard amount to "the cheapest rumor in Europe," responds an angry Andreas Klepsch, who administers the EC human genome program.

Too much bureaucracy. But, while EC administrators defend their advisers, they have a tougher time dealing with charges that delays and politics bedevil their work. "Three years is a world record for getting funding for a new program," says Andre Goffeau, professor of biochemistry at the University of Louvain and one of the EC's biotechnology administrators. And once a program gets the green light, the need to spend its budget on a strict schedule sometimes means that interested scientists have only a few months to prepare grant proposals. The result: Grants frequently go to insiders who have been following the program's political progress—often they are the advisers who helped set up the program. "Up until 1990 the AIDS committee hadn't awarded any money to anyone outside the committee," claims Gordon McVie, research director of the UK Cancer Research Campaign.

Stories like that convince scientists they should look somewhere other than Brussels for a model of pan-European funding. And they usually look just as far as EMBO—an organization that wins as many plaudits as the EC wins brickbats: "EMBO is superb," says Bronwen Loder, a scientific administrator at the Human Genome Organization. "It does the right thing by encouraging the mobility of the brightest and best."

EMBO runs dozens of courses and workshops, produces the EMBO journal, and gives out 350 long- and short-term fellowships each year that can be held in any member country, other than that of the applicant (see map).

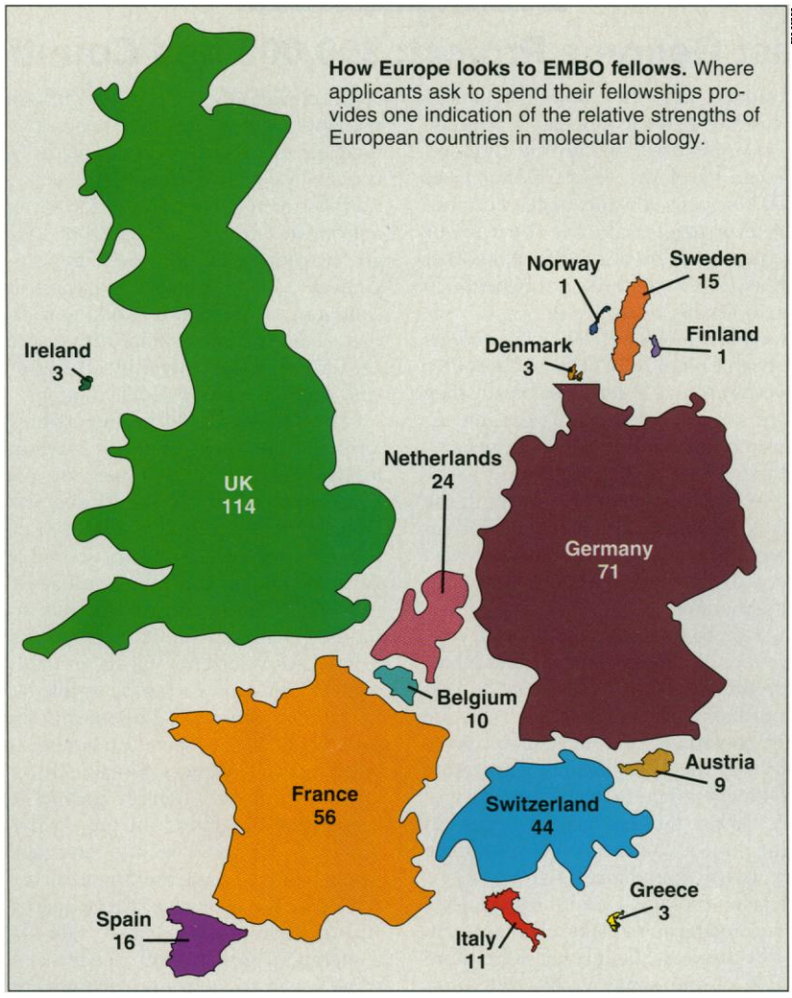
EMBO's trick is that it stays very close to the community it serves: Although paid for by the governments of 17 nations (including Israel), it is actually a self-governing organization of 700 of its member-nations' top molecular biologists. That means the advice it gets is always international—in choosing fellows, Europe and Israel's best get to select the best. A danger in this system is that the rich countries would mop up all the fellowships, but so far that hasn't happened, says EMBO director Tooze. "Spain is doing really well, there's a real renaissance there," he says.

But even if EMBO's international refereeing could be duplicated on a broader scale, reformers would still have another major problem to solve: the lack of mobility among young scientists. In dramatic contrast to the United States—where the best universities "even send out expensive color brochures," as Tooze puts it, to attract people from all over the nation to their graduate schools—the European research market is highly restricted. Until they reach postdoctoral level, most Europeans stay in their home countries.

The EC is not much help. In 1985 the European Court of Justice ruled that Article 7 of the Treaty of Rome, which prohibits job discrimination on nationality grounds, did not apply to the research grants given out to support doctoral students.

One example cited by Tooze of the distortions that can result: On several occasions Cambridge's LMB has not been able to find enough really excellent British candidates to fill its research studentships, and has gone without. It's a policy Tooze characterizes as, "It's better to have no graduate students than foreign ones."

LMB director Klug agrees that more European mobility for young researchers would be



How Europe looks to EMBO fellows. Where applicants ask to spend their fellowships provides one indication of the relative strengths of European countries in molecular biology.

EMBO

Yeast Genome Project: 300,000 and Counting

BRUSSELS—Next month, European molecular biology will pass a major milestone. A team of researchers in labs scattered across the continent will publish the entire sequence of chromosome III of the yeast *Saccharomyces cerevisiae*. At 300,000 base pairs, it is the longest continuous stretch of DNA ever sequenced. The paper, to be published in *Nature* next week, is also a first of another kind: With 147 authors, it looks more like a publication in particle physics than molecular biology.

This dramatic example of biology-as-big-science comes courtesy of the European Community's (EC's) Yeast Program, an ambitious effort to put *S. cerevisiae* on the map as the first eukaryotic organism to have its genome sequenced—all 16 chromosomes and 15 million base pairs. Thanks to a unique system of support possible only in the EC, the effort is like no other sequencing project in the world in the way it is organized, financed, and carried out. But it does share at least one common feature with other genome projects: It has sparked a controversy over access to the data it generates.

The project is now on to its second phase, with one-quarter of the sequences of chromosomes II and XI already completed. Eventually, EC-backed groups will directly sequence about half the genome, predicts Andre Goffeau, the project's organizer, who wears two hats as both an administrator at the EC's research directorate and a professor of biochemistry at the University of Louvain. "We don't want to monopolize it," he says. In fact, an independent project to sequence chromosome IX is already under way in Bart Barrell's group in the Laboratory of Molecular Biology, Cambridge; projects are planned in Canada and Japan to tackle chromosomes I and IV; and David Botstein and Ron Davis at Stanford University will tackle chromosome V. By 1995, says Goffeau, half the genome will be sequenced, and the job should be completed by 2002.

One feature that distinguishes the EC's part of the operation is the massive scale of the collaboration involved. "Like building the Great Wall of China," is how Steven Oliver, professor at the University of Manchester Institute of Science and Technology describes it. Oliver was DNA coordinator for chromosome III. The sequence was laboriously assembled by the work of 31 teams working at laboratories spread through 11 EC nations. Each lab agreed to sequence 10 kilobases of DNA handed out by Oliver in the first 2 years of the project. Most of the 35 labs in the second phase are now trying to hustle and do 25 kilobases a year.

This "cottage industry" approach initially came in for criticism. Many scientists thought that it would prove impossible to coordinate and fund, but they hadn't reckoned on the fact that EC funding is specially designed to build large-scale network collaborations between nations (see p. 458). Moreover, the EC has a strong incentive to make it work: "The aim is not just to get the genome but to boost European science," explains Goffeau. So far, it seems to be paying off by building a new community. "We're now working with a group in France that we had had no contact with before this project," says Les Grivell at the University of Amsterdam, one of many who were led into new collaborations.

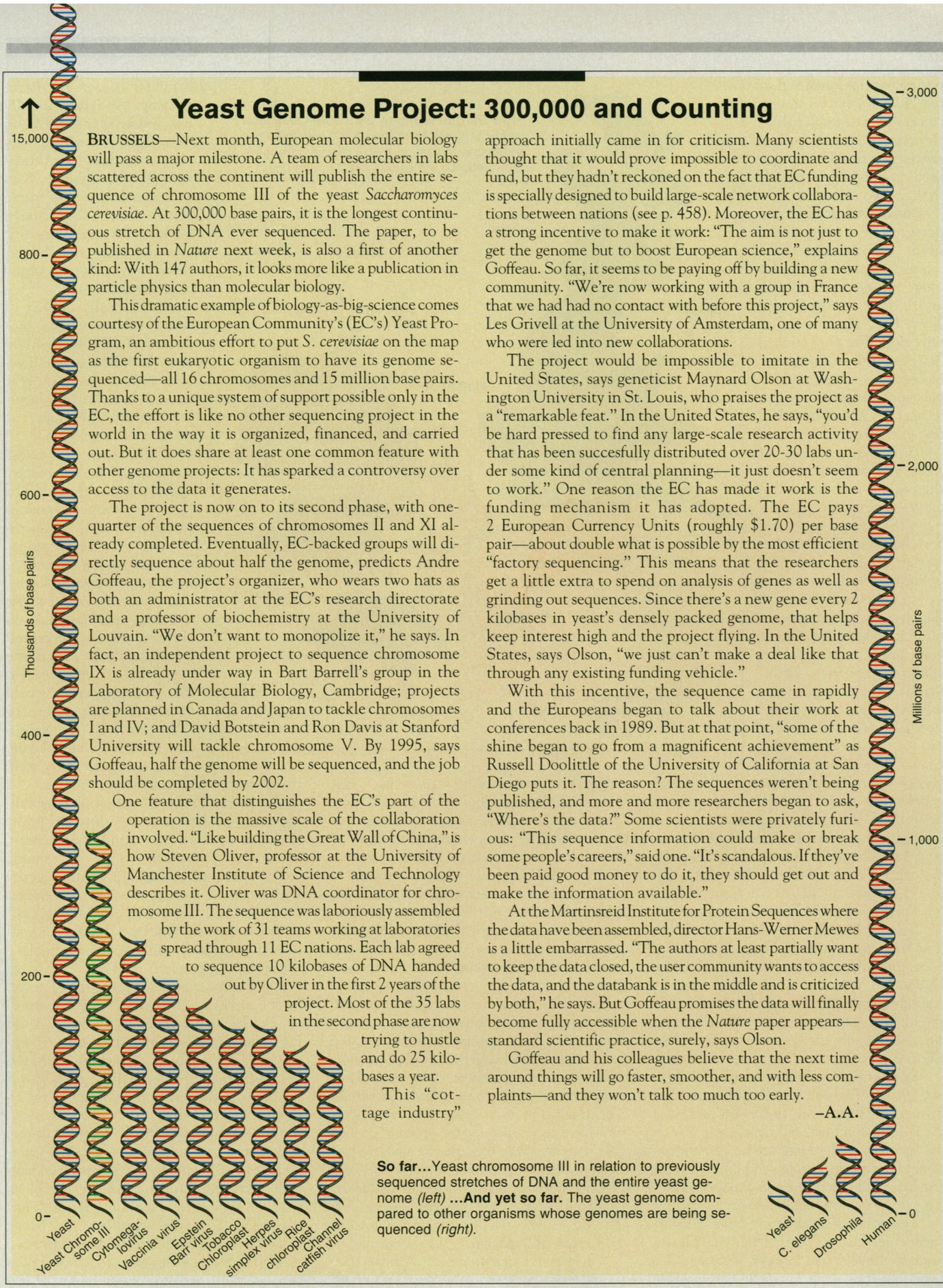
The project would be impossible to imitate in the United States, says geneticist Maynard Olson at Washington University in St. Louis, who praises the project as a "remarkable feat." In the United States, he says, "you'd be hard pressed to find any large-scale research activity that has been succesfully distributed over 20-30 labs under some kind of central planning—it just doesn't seem to work." One reason the EC has made it work is the funding mechanism it has adopted. The EC pays 2 European Currency Units (roughly $1.70) per base pair—about double what is possible by the most efficient "factory sequencing." This means that the researchers get a little extra to spend on analysis of genes as well as grinding out sequences. Since there's a new gene every 2 kilobases in yeast's densely packed genome, that helps keep interest high and the project flying. In the United States, says Olson, "we just can't make a deal like that through any existing funding vehicle."

With this incentive, the sequence came in rapidly and the Europeans began to talk about their work at conferences back in 1989. But at that point, "some of the shine began to go from a magnificent achievement" as Russell Doolittle of the University of California at San Diego puts it. The reason? The sequences weren't being published, and more and more researchers began to ask, "Where's the data?" Some scientists were privately furious: "This sequence information could make or break some people's careers," said one. "It's scandalous. If they've been paid good money to do it, they should get out and make the information available."

At the Martinsreid Institute for Protein Sequences where the data have been assembled, director Hans-Werner Mewes is a little embarrassed. "The authors at least partially want to keep the data closed, the user community wants to access the data, and the databank is in the middle and is criticized by both," he says. But Goffeau promises the data will finally become fully accessible when the *Nature* paper appears—standard scientific practice, surely, says Olson.

Goffeau and his colleagues believe that the next time around things will go faster, smoother, and with less complaints—and they won't talk too much too early.

–A.A.



So far... Yeast chromosome III in relation to previously sequenced stretches of DNA and the entire yeast genome *(left)* **...And yet so far.** The yeast genome compared to other organisms whose genomes are being sequenced *(right)*.

an excellent idea. But he stresses that Britain's terrible pay has been the main reason for past difficulties in recruiting the best to LMB: A doctoral student currently has to make do on $850 a month.

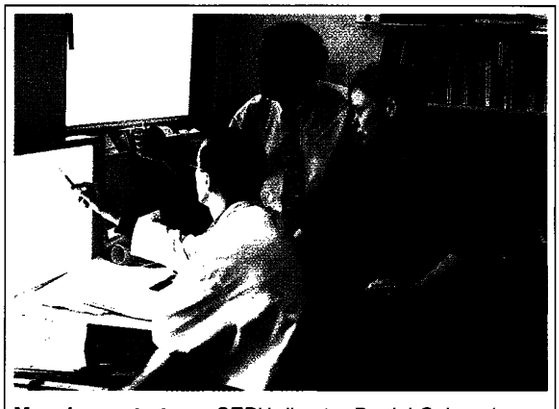
Increasing mobility and opening up the European research market will not be easy. Potentially the most ambitious solution comes from Tooze and Philipson with their initiative to set up a pan-European research fund, akin to NIH. "If we are to compete with the USA, we have to have a federal agency like NIH," says Philipson, who makes his own case for an independent European funding agency on p. 478. Tooze is also trying to round up support for a European predoctoral grant program that would make a start on tackling the mobility problem (EMBL already has a tiny scheme of its own). A first meeting of potential allies—heads of 10 pan-European biological societies plus Paolo Fasella, EC director general for research—took place in Heidelberg in December.

But where to turn for funding? National governments will be unwilling to relinquish their funds, said Fasella, which leaves the EC as the most likely source. A "great deal of politicking," lies ahead, Fasella warned, stress-

Gene Mapping the Industrial Way

PARIS—"By the end of the year," says Daniel Cohen, head of Paris's Centre d'Etude du Polymorphisme Humain (CEPH) lab, "we'll have mapped 90% of the human genome." And he probably will too, thanks to the monster-sized YAC chromosomes developed in his laboratory by microbiologist Ilia Chumakov, a recent arrival from Moscow, and Denis Le Paslier. The map will, admittedly, have a very coarse resolution—and there's that unforgiving rule that the last 10% of a map takes 90% of the time—but the statement typifies Cohen's unabashed enthusiasm for his research. His ultimate goal is to make CEPH the Mercator of the gene world.

Together with its companion lab, Généthon, CEPH is already the world's largest combined center for human genome linkage analysis and data handling. The lab has plenty of fans in the United States. "They are powerful groups, doing fine work," says James Watson, who resigned this month as head of the Human Genome Project. But outside the human genome fraternity, few scientists know what CEPH is. Perhaps that's no surprise: In conception, funding, and even location, there is no other lab quite like it.



AGENCE FRANCE PRESSE

Mapping a strategy. CEPH director Daniel Cohen *(center)* has big plans to create a genetic linkage map.

To find CEPH you have to head into the unfashionable northeast neighborhood of Paris and pass by the St. Martin Canal with its barges, waterfront cafes, and itinerant flea markets. There, behind the 17th-century St. Louis Hospital, you'll find a drab building and an unmarked metal and glass door. Inside is CEPH, a private research institute created by French immunologist Jean Dausset and Cohen, a Tunisian-born physician.

When Cohen joined Dausset in his immunology lab as a temporary research assistant in 1978, Dausset was 62 and Cohen 27. "A friendly father-to-son relationship quickly formed," says Cohen, and he decided to say on. In 1980, Dausset, who had just been awarded the Nobel Prize for his work on HLA groupings, decided that the fastest way to search for the genes behind genetic diseases would be to take an "industrial approach," concentrating on a small set of very large families where conventional genetic analysis could be combined with molecular biological techniques.

The pair started their efforts on a small scale, with a $100,000 grant and using DNA from the large Mormon families studied by Raymond White at the University of Utah. Soon, a bequest from an art collector brought a windfall of $9 million and partnership with the French Muscular Dystrophy Association led to the joint creation of the Généthon labs in the Paris suburb of Evry. Généthon's objective is to search for hereditary disease genes, and it has built up efforts in genetic mapping and sequencing in collaborations bringing in the Pasteur Institute's Jean Weissenbach and Charles Auffray of the Cancer Research Institute of Villejuif.

CEPH-Généthon today has a budget of $20 million (mostly from private sources) and a staff of 250. Dausset has an office at CEPH but lets Cohen run the show making him, at 41, one of the most powerful and dynamic figures in French molecular biology, with more freedom of action than the heads of government-controlled institutions. CEPH has the world's richest collection of DNA from large families (about 60 families each of three to four generations) and from families containing individuals who have developed particular diseases. CEPH collaborates with 150 laboratories around the world (70% of them in the United States), supplying samples and data free of charge—on condition that all the linkage data they generate from the DNA must be put into CEPH's data banks. One-third of CEPH's 250 staff are now "informaticiens."

Typical of one part of CEPH-Généthon's approach is its success in finding a gene closely linked to one form of non-insulin-dependent diabetes, a disease affecting 5% of the world population. The work, published in *Nature* last month, began with a campaign in 1990 to find French families with the disease. Teams of vounteers then persuaded affected family members to supply blood samples and reconstruct their family's genealogical trees. In less than 2 years, with data from 492 families, analysis of inheritance patterns linked the disease to the glucokinase locus on chromosome 7, a gene known to be involved in regulating blood glucose levels.

Eventually, the goal is to combine a genetic map generated by such linkage data—created by CEPH and by the hundreds of teams worldwide that use their large-family resources—with the Human Genome Project's efforts to make a physical map of the human genome using hundreds of restriction enzyme markers.

That's why both the Howard Hughes Medical Institute and NIH were CEPH supporters from the start. But relations deteriorated in 1988 and NIH support soon dried up. According to Cohen, "An ambitious operation such as ours, controlled in France, was unacceptable" to NIH. Elke Jordan of the NIH's National Center for the Human Genome, has a different explanation: "We didn't want to cold-shoulder CEPH....We simply decided that funding genome research abroad was counter-productive, as it would discourage other countries' contributions." CEPH-Généthon's open policy has apparently won over its American critics, however, and NIH support to CEPH has again become significant.

–Alexander Dorozynski

Alexander Dorozynski is a science writer based in Paris.

An Institute Without Bosses

BASEL, SWITZERLAND—Ask Fritz Melchers, director of the Basel Institute for Immunology, how this tiny European laboratory of 50 scientists has won several Nobel Prizes and gained an enviable international reputation in its 22-year lifetime and he'll give you a cryptic answer. The institute, he says, is "scientifically chaotic and technically Swiss."

That the institute's support staff and management pride themselves on their Swiss perfectionism is no surprise. The city of Basel has built its reputation on the quality of its biomedical research: It is home to the university with its famous Biozentrum, Ciba-Geigy's Friedrich Miescher Institute, the huge basic research labs of Sandoz and of Hoffmann-La Roche—and the Basel Institute of Immunology, also supported entirely by Hoffmann-La Roche.

But "scientifically chaotic?" The chaos comes from the institute's unique commitment to its researchers' independence and equality. Age and experience may vary, but at the institute there is only one scientific rank, that of "member," which is held by anyone with a Ph.D. Most researchers work with just one technician each—and that's it. There is no hierarchy and "every scientist in the house has the right to be independent," says Melchers.

BETTMANN

Another Nobel. Founding director Niels Jerne welcomes member George Köhler to the club.

This "horizontal structure," as the institute officially calls it, was not originally planned. Niels Jerne, the Danish immunologist who became the institute's first director, initially had difficulties recruiting established people to the institute because of its links with Roche. "At that time, people were simply afraid to place their fate in the hands of a company," says ex-member Norman Iscove, now at the Ontario Cancer Institute. But Jerne had less trouble attracting young researchers, and, rather than appointing bosses, he decided to honor their wish to work as equals. "This type of structure was unheard of in Europe. It was considered shocking. People thought it would never work," says Iscove.

The gamble paid off. Within a few years the institute had built a sterling international reputation. Both Jerne and Susumu Tonegawa did their Nobel Prize–winning work there, and George Köhler was a member when he shared a Nobel Prize with Cambridge immunologist César Milstein for developing monoclonal antibodies.

The first hint that the Basel Institute is an enclave from "the real world," as some members call everywhere else, is its setting. A visitor steps off the busy main street into a small green courtyard with an endlessly turning model of the DNA double helix by Swiss artist Jean Tinguely. Inside, instead of the usual laboratory posters of metabolic pathways or genetic maps, the walls are lined with photographs of the parties for which the institute is famous; the staff has produced both an opera and a ballet about the immune system.

Aside from its intimate style, it is the freedom from daily worries over money and administration that makes the institute "close to paradise," as one member puts it. "As an assistant professor in America you don't spend much time worrying about science," says Charley Steinberg, an American who has been at the institute since it opened. "You worry about grants, teaching, department heads, and your struggle to run a group. [The Basel Institute] succeeds because young people can spend their time thinking about science."

Several researchers have made use of their freedom to move into unconventional areas. Experimental organisms include sponges, turtles, and reptiles—not exactly objects of mainstream immunological study. "I never could have done the work I did here anywhere else," says Jim Kaufmann, a 10-year veteran who studies the evolution of the immune system and now works on salamanders. "Their T-cells don't do much in our standard assays," he says, "but they don't seem to be sick. We want to know why not." Alongside some of the more bizarre creatures are some of the world's best facilities for working on frogs (which fascinate immunologists because their immune systems totally reorganize as they turn from tadpole to frog) and sheep (ideal for following the maturation of lymphocytes).

Diversity of people and backgrounds is also crucial to the institute's success. "If we were six or seven principal investigators, each with our own group, [the institute] would be much more narrowly focused," says member Gek-Kee Sim. And that diversity, in turn, nurtures collaborations, even tempting members into areas where they might otherwise fear to tread. "When I first came here I wanted to grow human T-cells, which is tricky," says Gillian Griffiths. "I wouldn't have tried it on my own. But I went upstairs to Antonio [Lanzavecchia], and it worked right away."

The Basel Institute has only one obvious catch. Researchers cannot forget productivity in this scientific garden of Eden: The typical 2-year contract serves as a reminder that they can be cast out. "There's lots of worry about the next contract," says one member, although another qualifies this by saying that "if you're doing well you don't have to worry." For many researchers, though, success at the institute carries an ironic twist: They begin to want a group of their own. Each year, some 10 members leave the institute and set out to build the traditional scientific groups possible only in the "real world."

–Patricia Kahn

Patricia Kahn is a science writer based in Heidelberg, Germany.

ing that there is a big difference between running a small, focused organization like EMBO and a European research council.

EUSEB is the other likely focal point for developing a new pan-European structure—at least in the view of its leaders. EUSEB president Hamish Keir, professor of biochemistry at the University of Aberdeen, wants the society to help bring biological disciplines together through meetings and workshops and do all the things FASEB does. In addition, Keir envisions using the society's network of biologists to give better advice to the EC.

That's just for starters. "Twenty-five years from now I'd like there to be a European research council with hundreds of millions," says Keir optimistically. But all that could be just a pipe dream, for EUSEB is facing immediate problems that threaten its very existence—it's running out of money. EC help is going to be essential in the early stages. Expect some years to pass before it's clear whether EUSEB (or Philipson's "NIH") could be in a position to lead Europe's biologists toward their own common market—and whether molecular biology is going to lose that label: "80% Made in America."

–Alun Anderson

With reporting by Michael Balter and Peter Aldhous