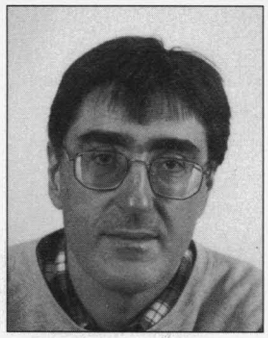
Germany Warily Maps Genome Project

The government has quietly been putting together a major genetics research program, but disagreements over emphasis have stalled its launch

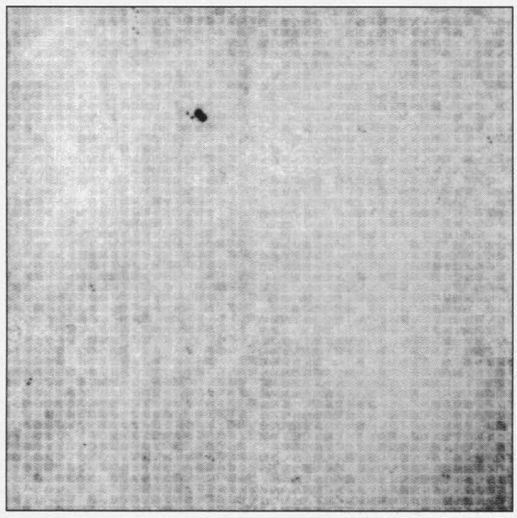
HEIDELBERG—A month ago, the German government was poised to announce its belated entry into the big leagues of genetics research with an 8-year, $285 million human genome program. The effort had been quietly put together by a small group of researchers and government officials anxious to give a major boost to research on human genetics and biotechnology, areas stifled for decades by fierce public opposition in a country still scarred by the horrific crimes of Nazi eugenicists. But the announcement was hastily postponed at the eleventh hour, when two groups of scientists persuaded the government minister responsible for research, Jürgen Rüttgers, to put on the brakes and fundamentally rethink the program.

Now, after a month of suspense, scientists can breathe a sigh of relief: The government will soon come up with a new proposal, said Rüttgers at a press conference in Heidelberg this week—to be announced within the next 3 weeks, his assistant, Thomas Sondermann, later told *Science*. That assurance has been welcomed by researchers across the board. For, despite their differences of opinion on what to emphasize and how to structure the program, "I haven't heard of a single [scientist] who doesn't think it is absolutely essential," says molecular biologist Klaus Rajewsky of the University of Cologne, one of the researchers who urged Rüttgers to hold off. Indeed, getting the program right is viewed by all concerned as crucial for the future of genetics research in Germany. But the dispute reveals how difficult that is for a country where political sensitivities over genetics are still so deep-seated that the plan took shape behind closed doors. It also reflects the scientific difficulties Germany faces in trying to become a major player in a field where others are already racing ahead.



The abrupt change of plan was sparked by two letters, signed by 24 molecular biologists in Heidelberg and Cologne, urging Bonn's Federal Ministry for Education, Science, Research, and Technology (BMBF) to rework the proposal. For the ministry, the letters landed "like a bomb," says one insider. They hit only days before the planned announcement—just as the project's scientific advisers, including leading genome researchers from abroad, converged in Bonn to discuss the proposal for the first time.

The letters questioned key parts of the plan, from its scientific aims to the types of labs it should fund. The signatories were also concerned, as several of them told *Science*, that the proposal had not been discussed or circulated among the broader scientific community. "This whole game was not open enough," says Hermann Bujard, director of the Center for Molecular Biology in Heidelberg.



Hot filter. Grids used to screen 60,000 DNA fragments, developed by Hans Lehrach *(left)*, will be a centerpiece of the genome resource center. Dark spots indicate hybridization.

A few points are widely accepted by all sides. Given its late start, Germany should not just imitate everyone else's genome programs but should look for a special niche. "Mapping and sequencing [the human genome] will be done with or without Germany," says molecular biologist Svante Pääbo of the University of Munich. "We have to ask ourselves what we want to do 5 or 10 years from now, when a [complete human] sequence is there, so Germany is at the forefront. ... It's a chance to go into questions others are ignoring." And there is general agreement that one focus should be studying important genes and how they work. "We have to focus on gene function and ... on disease genes, developmental genes, other interesting genes," says molecular biologist Ernst-Ludwig Winnacker of the University of Munich, a member of the program's Scientific Advisory Committee.

But some key questions are still undecided. One controversial issue is how much emphasis to put on particular areas, a point signatories say the original BMBF proposal leaves open. "There is no clear statement of priorities," says Benno Müller-Hill of the University of Cologne. For example, "[the proposal] gives no hint of whether there should or shouldn't be a large sequencing effort," he says. "There should be clearer boundaries." And there are different ideas about how to study gene function. The BMBF plan called for an emphasis on methods to automate the analysis, while some of the signatories favor a more question-driven approach.

Overcoming the legacy of the past

Although these thorny issues are still not settled, Germany's geneticists and molecular biologists are grateful for the prospect of any program at all. Just a few years ago, the notion of a German genome project seemed "completely unthinkable," says Winnacker, one of a handful of scientists who began lobbying for a program in the late 1980s. "I was resigned. I thought nothing would ever come off, that everything was being done elsewhere," he says.

Winnacker had good reason to be pessimistic. Strong public opposition led to a "serious neglect" of biotechnology and genetics in Germany in the late 1980s and early 1990s, says Harald zur Hausen, director of the German Cancer Research Center (DKFZ) in Heidelberg. And many pharmaceutical companies—fed up with long, bitter legal battles for approval to build recombinant drug labs—"moved outside of Germany with gene technology and left this country virtually deserted," he says. The polarized atmosphere sometimes turned violent, with several bomb threats and attacks on molecular biology labs. Winnacker, who played a very visible role in the public debate, spent months under police protection after his name turned up on a terrorist group's "hit

list" of possible targets, and again after death threats followed an appearance on a television news program.

But the tide eventually turned as the public began to see that gene technology is vital to medicine, and German industry showed renewed interest at home. For advocates of genome research, this meant that doors started opening—although very slowly. More tangible success came in 1993, when the BMBF set up a $71 million program for research in genome-related technology, with industry footing part of the bill. But its cryptic name—"Technology for the decoding and use of biological blueprints"—reflected the nervousness of industrial backers. As one of the project's planners told *Science*: "Some of them said, 'If the word 'genome' is used, we'll pull out. ... We don't want protesters out front tomorrow throwing Molotov cocktails.' "

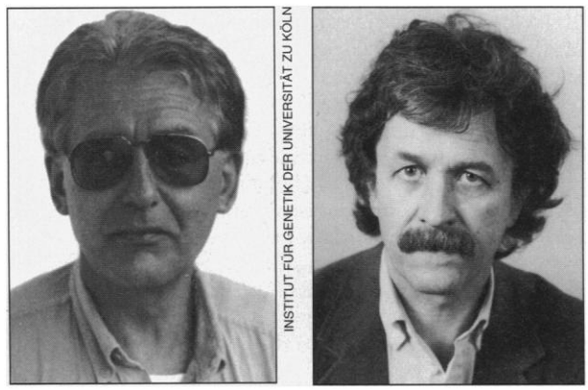
At the same time, a proposal for a full-scale genome research program was slowly making its way through the BMBF. It began in 1992 as an initiative from Heidelberg scientists, including zur Hausen and gene mapper Annemarie Poustka, and the Deutsches Forschungsgemeinschaft, the government's major research grant agency, under then–Vice President Winnacker. That circle expanded into a planning committee that included more scientists, industry representatives, and the heads of the major research agencies. The ministry was receptive, but fearful of igniting another public campaign against gene technology. "You have no idea how difficult it was to convince [the ministry]," says Poustka. Other than some informal discussions with scientists outside the committee, the tentative plan was not circulated or widely known.

And that laid the groundwork for last month's bombshell. Rajewsky says he had no idea a program was even in the works until he heard about it by chance, just days before the planned announcement. "I found it absolutely astounding that we were not informed, at the point that it was almost put into practice," he says. And, while he had heard about the plan, says another scientist, "we were not asked for our ideas but for how we might fit into their concept."

Building a resource

Once the ministry gives the green light, the first item on the agenda will be to fund a central resource center for genome materials—a plan already approved by the program's advisers. It will be run by Austrian genome researcher Hans Lehrach at the Max Planck Institute of Molecular Genetics in Berlin, with a few activities at the DKFZ under Poustka. After that will come the selection of up to three sites for research centers plus a score or so of individual research groups, based on competitive proposals.

The resource center is planned as an expanded version of the "reference library system" launched by Lehrach and Günther Zehetner in 1987, when they were at London's Imperial Cancer Research Fund, and which now has some 1200 users in 32 countries. Its mandate is two-fold: as a "one-stop shop"—a convenient site for researchers to access many different DNA libraries and probes—and a central point to deposit their results. The aim, says Lehrach, is to get scientists to work on the same biological material, which vastly simplifies the task of comparing the data later on. And it isn't only for mappers and sequencers: Researchers can use it to pull out "their" gene from a different species, or to clone a gene based on its proximity to a known DNA marker, Lehrach says.



Get it right. Klaus Rajewsky *(left)* and Hermann Bujard were among researchers who argued that the program should be rethought before it was announced.

The system also makes it "infinitely quicker and easier" for scientists to use the DNA libraries, says genome researcher Peter Goodfellow of the University of Cambridge, U.K. The key is a method for scanning the tens or hundreds of thousands of DNA fragments in one library all at once. With the help of specially designed robots, the fragments are spotted onto a 22-centimeter-square nylon filter at minuscule distances from one another, so that some 60,000 spots fit onto one filter. Then researchers expose these "high-density grids" to a labeled DNA probe and look for any spots that hybridize. That, in turn, tells them which of the library's clones—live organisms, such as yeast or bacteria—produces the DNA they want.

Then comes a swap. Researchers inform the center's database of the match, and in return get the clone. This exchange salvages valuable information—for example, what genes map to which clones—which might otherwise never see the outside of a lab notebook.

While plans for the resource center are well defined, there are still diverse opinions on the hard part of the program: its scientific direction. The split is essentially between those who believe Germany should play a major role in efforts to automate gene analysis and those who argue that funds should be spread more widely to study specific questions about important genes.

Among those arguing for automation is mouse developmental geneticist Peter Gruss of the Max Planck Institute for Biophysical Chemistry in Göttingen. "For me, a focus on systematic functional analysis is crucial," says Gruss, who wants the program to find ways to scale up approaches now used on single genes so they can be applied to hundreds or thousands of genes in parallel. "Even if someone has his or her beloved gene, that should not be part of [the program]. It can be funded by existing mechanisms," he says.

The original BMBF proposal called for supporting a whole battery of such approaches. The aim, says Lehrach—who helped shape the plan—is to build up a catalog of basic information about all genes. "People usually try to do the same set of things with every new gene," he says—for example, seeing when and where it is expressed in the organism, expressing the protein product, looking for interacting genes, and knocking out its expression in mice. That means the same things are done over and over, at huge effort and expense. If some of this information were available in a "gene catalog," says Lehrach, "you can start doing interesting things immediately instead of 3 years later."

To generate such a catalog will require the identification of all the 50,000 to 100,000 genes in humans—an immense task, currently being tackled by two industry-backed projects in the United States. Lehrach has developed a filter-based method he says can "increase their efficiency dramatically," especially in finding rare genes—work he hopes to fund partly through the German genome project.

Other researchers in Germany, including many who signed the protest letters, believe in taking a different tack. Rather than putting a lot of money into automated data collection, says Bujard, the project should fund primarily question-driven research in flexible centers with small, independent groups. This view partly reflects Bujard's skepticism about how much information automated analysis across the board can yield, given the subtleties of each gene and its complex network of interactions with other genes. What's more, he says, putting lots of money into big centers with robots and technicians does nothing to counter the weaknesses of Germany's research system: too many large groups, too few independent young people, and little flexibility to move into new fields.

This way of thinking is likely to stimulate project proposals with a very different look and feel. In Heidelberg, one group of scientists is discussing ideas for an Institute of Genome Research that would bring together basic studies of genes with disease models and clinical work, especially in neurology, oncology, and cell biology. The Max Delbruck Center in Berlin is also planning a proposal focusing on medical questions, according to bioinformaticist Jens Reich, but with an epidemiological slant—collecting and analyzing family material for common multigene diseases and studying the diversity of the relevant genes.

Mapping the right path

Another hard decision for Germany's genome program will be how heavily to invest in human mapping and sequencing. Many of the researchers who spoke with *Science* feared that this could eat up the money fast and reduce the chances for Germany to find a special niche internationally. Others worried that it is not realistic—or worthwhile—to jump in now, with human genome work so advanced elsewhere in the world.

But it may be hard to stay out. One reason could be pressure to contribute from countries now carrying most of the cost and effort. "Mapping and sequencing the human genome shouldn't be left to any one country or individual," says Cambridge's Goodfellow. "The project is so large and so important, it should be shared. It's a moral issue. ... Germany can't say, we're not interested in this; we'll exploit what others have done and do the fun bits ourselves."

And in fact, the time is now especially good for newcomers. In the early years, genome researchers pursued a whole battery of approaches. But there is now a "major change in strategy," says David Bentley of the Sanger Center in Cambridge, U.K., with sequencing likely to begin much earlier than originally planned (*Science*, 2 June, p. 1270). That, in turn, helps researchers zero in on the essential tasks: making sequence-ready maps for 99% of the genome, plus the entire job of sequencing—still "a gigantic amount of work," he says. What's more, there is still only a handful of labs that can churn out megabases. So the bottom line is, says Bentley, "the more people on board, the better."

What's more, despite Germany's reputation as a desert for genome work, it has at least some groups already involved in mapping and sequencing. An emerging international consortium of labs to map and sequence the X chromosome includes both Poustka and André Rosenthal at the Institute for Molecular Biotechnology in Jena, while other German groups are involved in European Union–sponsored genome projects on yeast, fruit fly, and *Arabidopsis*.

Another argument for investing in large-scale sequencing is that the technology is crucial to many questions about function and can therefore help Germany find its special niche in genome research. Munich's Pääbo hopes to use comparative sequence analysis across species to look at key events in evolution, such as how animals adapted to living on land, the origin of the vertebrate body plan, and the evolution of the human brain. Rosenthal's lab is involved in sequencing the puffer fish genome, which is emerging as an important model, particularly in pointing researchers to control regions in the human genome, he says. Then there's the issue of genetic diversity, which Rosenthal calls "the future of the genome project."

So perhaps, after all its past agonies, Germany's genome project will end up with the best of all problems—having to make a choice among lots of good ideas. Says one German scientist, a longtime observer of genome research: "The future is bright, but the road is tortuous."

–Patricia Kahn

GENETIC ENGINEERING

Russia Readies Its First Gene Law

MOSCOW—Brandishing a transgenic potato before the Duma, the lower house of Russia's parliament, Viktor Shevelukha, deputy chair of the Duma's committee on culture, education, and science, persuaded deputies to pass the country's first law governing genetic engineering at the end of last month. The legislation, which sets up a regulatory system similar to those in place in the West, has come as a relief to some scientists, because early drafts of the law would have imposed much tighter controls.

"We wanted to adopt an internationally compatible law which at the same time would take into consideration the present situation in Russia," says geneticist Konstantin Skryabin, who heads the Council for Biotechnology of the Russian Academy of Sciences and chaired a committee that drew up the new law. The committee—which included leading scientists involved in genetic engineering, representatives of the relevant government ministries, and a strong contingent of environmental scientists—had to tread a fine line between the needs of a rapidly developing biotech industry and demands from the general public for tough environmental regulation.

The committee completed a draft late last year and asked UNESCO to assess it. It didn't get a good reception. UNESCO asked a panel of 15 scientific, legal, and ethical experts to review the draft, and some of them judged it far too restrictive. "The draft law was awful," says biochemist Julian Kinderlerer of the Institute for Biotechnological Law and Ethics at the University of Sheffield in the United Kingdom. "It required the government to register all researchers considered competent to carry out biotechnological research and to carry out an annual examination to ensure they are keeping up standards. No one else requires this." The draft also required researchers to obtain a license from the government for any genetic manipulation experiments, even completely harmless ones.

"We wanted to adopt an internationally compatible law ... [consistent with] the situation in Russia."
—Konstantin Skryabin

Four of the panel members, including Kinderlerer, visited Moscow in March for further discussions with the drafting committee. "We strongly recommended that they follow either the European Union or the U.S. line," Kinderlerer says. The committee took heed: The version presented to the Duma last month bears striking similarities to European genetic-research legislation.

All experiments are graded in risk from 1 to 4, with grade 1 experiments deemed harmless and grade 4 having the greatest potential risk. All experiments that involve deliberate release into the environment are graded 3 or 4. For grades 1 and 2, researchers will have to obtain permission from a special commission within their own institution. For experiments graded 3 and 4, they must apply to a new Interdepartmental Committee, which will then apply to the relevant ministries for licenses on their behalf. "The aim of such a pattern," says Skryabin, "is to free scientists from as much bureaucratic formalities as possible, as the researchers will have to deal with only one federal body."

The Russian government hopes to obtain half of the $1.6 million cost of setting up the system from industry. Running the system will cost about $200,000 a year, but importantly for cash-strapped Russia, the drafting committee expects that income from licenses will make the system profitable in just over 2 years.

–Andrey Allakhverdov

Andrey Allakhverdov is a science writer in Moscow.