Carving up the Human Genome

The United States may hold the lead in the genome project, but the rest of the world wants a piece of the action

Valencia, Spain

IN TERMS OF DOLLARS AND TIME committed, the United States leads the effort to map and sequence the human genome. But, as a recent meeting in Valencia made clear, the rest of the world does not see this project as a U.S. monopoly. Said Alexander Bayev of the Soviet Academy of Sciences: "The data should not be the property or privilege of one nation, social group or private company."

The avowed purpose of the Valencia meeting* was to stimulate international cooperation on the genome project. But despite much lip service to cooperative science, there was little in the way of tangible suggestions, perhaps because the project is still so new. And at the end of 3 days and more than $1 million, paid mostly by Valencian government and industry, just how this gargantuan task can be divided among the world's scientists was not a whit clearer. The participants did draft a resolution, with the grandiose title, "Valencia Declaration on the Human Genome Project," calling for international collaboration, but its import, if any, remains to be seen.

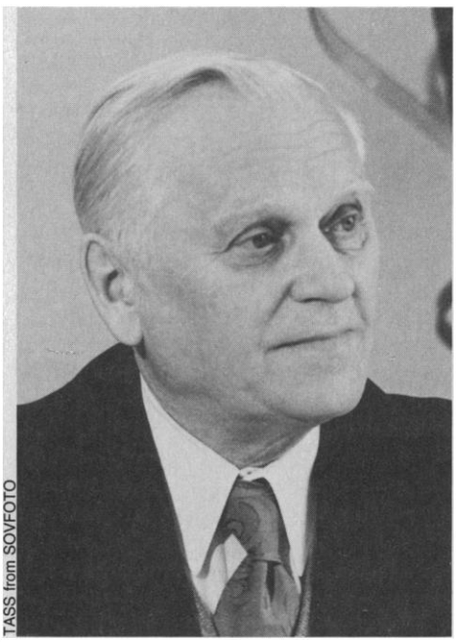
Nonetheless, the meeting gave a clear and sobering view of current capabilities in mapping and sequencing—and just how far there is to go (see box). And it provided a glimpse into the surprising amount of activity around the world.

Within the past few months the Soviet Union has launched its own genome project and has given it high priority, reported Bayev of the Soviet Academy of Sciences. Funding will begin in January.

The aims of the Soviet project are broad: genetic mapping, physical mapping, and sequencing of areas of medical interest and probably sequencing of other genomes, such as mouse, yeast, and *Drosophila*. Full-scale sequencing will await automation and more effective approaches. The Soviets plan to organize centers for DNA cloning, mapping, and sequencing.

The situation in Japan is trickier to read. Three agencies are still vying for control of what to date remains a modest effort. Despite congressional fears that Japan would outpace the United States, that nation has not moved anywhere near as quickly as has the United States.

The genome project was expected to be the centerpiece of Japan's new Human Frontiers effort, but it is not included in the initial stage, at least. And despite several years of lobbying by prominent scientists, the Japanese government has yet to endorse, much less support, an all-out effort to map and sequence the human genome.



TASS from SOVFOTO

Alexander Bayev: *"The data should not be the property or privilege of one nation, social group, or private company."*

Japan has, however, just started two promising pilot projects that, if successful, could pave the way for a larger effort. One is a collaboration between the Institute of Physical and Chemical Research, better known as RIKEN, and Maynard Olson and his colleagues at Washington University to sequence yeast chromosome 6. The other is a new national program to map and sequence human chromosome 21.

Meanwhile, the Japanese are continuing with their "super-sequencer," a series of machines, developed by a government-industry consortium, that automate various steps in the time-consuming manual sequencing process. The idea is to rig these machines together in one center to allow continuous, production-line sequencing. The goal, said Akiyoshi Wada of Tokyo University just a year ago, was to be able to sequence 1 million bases a day for 17 cents a base by 1990.

Now, Yoji Ikawa of RIKEN reported at the meeting, that goal has been scaled back to a more realistic one of 100,000 bases a day within a few years. The system currently has the capability to sequence about 10,000 finished bases a day, which is within the range of automated technologies in the United States. Two of the prototype machines were recently abandoned, and funding to refine the remaining machines has dropped to about $750,000 a year, said Ikawa; a similar amount is slated for mapping and DNA handling at RIKEN.

In Europe, Italy has launched a genome project, coordinated by Renato Dulbecco, that will focus on mapping and sequencing the X chromosome. France has a modest national effort, and Germany is planning one. While those are the only dedicated national programs, research is under way in every country, noted Peter Pearson of Sylvius Laboratories in the Netherlands.

In an attempt to pull together these splintered European efforts and avoid excessive duplication with efforts in the United States and Japan, the European Community is starting a new program called Predictive Medicine. The working party, which Pearson heads, is now drafting a plan that will go to the European parliament in January. If the parliament agrees, the project, budgeted at about $20 million for the first 2.5 years, could start this spring.

In a separate program, the European Community has begun a 6-year, $20-million effort to sequence small genomes, starting with yeast, which contains about 15,000 kilobases. Work will begin in January, said project leader Andre Goffeau of the Catholic University of Louvain, Belgium.

They plan to sequence the yeast genome chromosome by chromosome, beginning

*Workshop on International Cooperation for the Human Genome Project, 24 to 26 October.

with chromosome 3, which contains 360 kilobases. U.S. and Japanese scientists are already working on chromosome 6; Canadian scientists are working on chromosome 1.

Thirty-five European laboratories will collaborate on chromosome 3, with each lab receiving 22 kilobases to sequence within 2 years. They will be paid $5 per base pair, which some outside of the project say risks turning the labs into sequencing factories.

The second phase of the project has yet to be articulated in detail, but Goffeau has grand goals: "By 1990 the first chromosome will be available; in 1995 the first genome will be sequenced; and by 2000, the function of 6000 genes will be unraveled."

Unesco is starting its own genome project, but what it will do is uncertain. The organization sees its role as fostering international cooperation, instigating workshops, and perhaps providing modest study grants, which is much along the lines of what the newly established International Human Genome Organization, better known as HUGO, intends to do. One option being explored is that Unesco will provide financial support to HUGO.

All these efforts are dwarfed by the $50 million the Department of Energy and the National Institutes of Health are spending on the U.S. effort in fiscal year 1989.

Smaller and less developed nations are also trying to figure out how they can be a part of biology's biggest project to date. And they seem alarmed by the prospect of one powerful nation, or a few, having near-exclusive access to the universal genetic code. As Jorge Allende from the International Biosciences Network in Chile outlined, these nations want to be assured of access to data, and they want to participate, perhaps by working on genetic diseases that are prevalent in their countries. Help with training and access to new technology are essential.

There were lots of nods in that direction and some impassioned calls for international cooperation, but when the hot air cleared, the questions of how to truly foster cooperation, and what such efforts will entail, other than linking databases, remained murky.

David Schlessinger of Washington University calls some of the posturing "scientific doublespeak," noting that when many geneticists talk about cooperation they mean competition. The situation is perhaps not surprising: when the United States has yet to figure out how to compel its federally funded researchers to share their data, it is hard to see how to tackle the problem worldwide. "But that attitude will change," Schlessinger adds: "the amount of work is too massive and public interest too high for people to hang on to their data."

How the participants got from these rather vague discussions to drafting a resolution is something of a mystery, but much of the final afternoon was taken up with it. Jean Dausset of the Centre d'Etude Polymorphism Humain in Paris got the discussion going when he spoke of the dangers of the misuse of genetic information and the need for scientists to take responsibility for how the knowledge they generate is used. "Human patrimony should not be manipulated," he said, calling for a moratorium on any genetic manipulation of germline cells, which he said could open the door to Nazi-

A Sequencing Reality Check

Bart Barrell and Ellson Chen, who hold the world record for sequencing the largest contiguous chunks of DNA, provided the reality check on what is feasible. The news from these two prodigious labs is that DNA sequencing is still slow and tedious.

Barrell and his group at the Medical Research Council in Cambridge, England, have almost finished sequencing the entire cytomegalovirus genome, all 230 kilobases. Several years ago Chen and his colleagues at Genentech sequenced the human growth hormone locus; at 70 kilobases, still the largest stretch of human DNA to be sequenced. Considering that the human genome contains 3 billion bases, there is still a fair way to go.

Moreover, both groups did it by hand, using standard techniques, not with the much-touted automated sequencing machines. "Machines do not have the accuracy or the throughput for high-volume sequencing," said Barrell. With the improvements now in the works, he said, "we can expect to see machines overtake manual sequencing in maybe 2 years."

It took Barrell's group about 12 person-years to sequence the virus. The average rate, or throughput as it is called, was 20 kilobases a person a year, but toward the end of the last year it had climbed to perhaps 100 kilobases. "This is reality. You can establish the sequencing rate from these data." And, added Barrell, it is very different from the theoretical rate people are striving for, which is about 15 kilobases a day. "Sequencing is still an art. There are many failures and a lot of down time," said Barrell. The other problem, both he and Chen pointed out, is that finishing a sequence can be tricky. Said Barrell: "It can take as long to get that last 1 to 2% as it did to get the first 98 or 99%."

It took Chen's group 1.5 person-years to sequence the 70-kilobase human growth hormone locus and "cost me three technicians." Part of the problem is that human DNA is inherently trickier to work with than viral DNA because it is full of repeated sequences and "unclonable regions." Working flat out, Chen estimated, a skilled technician can sequence, on average, 100 kilobases a year. The problem is that no one can keep up that rate, simply because "the work is so boring." In actual practice, it would take one technician 2 years to sequence 100 kilobases.

At Barrell and Chen's sequencing speed, it would take at least 30,000 person-years to sequence all 3 billion bases of the human genome, and then it would have to be sequenced several more times for accuracy. In short, at least a tenfold increase in efficiency is needed before the project would become feasible.

All of which underscores the need for automation, and not just improvements in the current and first generation of machines, but entirely new ways of looking at the problem. At Valencia Radomir Crkvenjakov presented one such idea, a radical mathematical approach that aroused both interest and a hefty share of skepticism. He and Radoje Drmanac of the University of Belgrade have dubbed it sequencing by hybridization, and it reads "words," not individual letters, in the sequence.

What it involves, in essence, is first synthesizing some 100,000 specially designed short probes, the "words," and then hybridizing them to the DNA to be sequenced. Each probe would find its complementary piece of DNA, revealing one eight-letter word of the sequence. The process would be repeated some 100,000 times, then all the data would be fed into a computer, which would then extract the sequence.

The advantage is that this approach would bypass the traditional crunch in DNA sequencing, which is in chopping the DNA into pieces and preparing gels. But at this stage, said Chen, given the amount of work involved in synthesizing that many probes and running 100,000 separate hybridizations, "it would simply be substituting one horrendous task for another." ■ **L. R.**

like atrocities, and a ban on gene transfer experiments in early embryos.

Despite a few objections, momentum was clearly building behind his idea. It was so strong, in fact, that NIH director James B. Wyngaarden and Victor McKusick, president of HUGO, who were charged with leading the final session, came back with a draft resolution echoing Dausset's ideas and, often, his exact words.

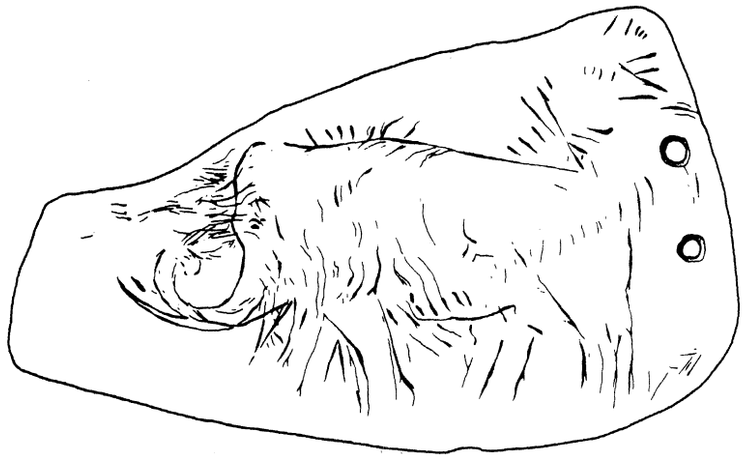
It was Norton Zinder of Rockefeller University who wisely steered the group away from banning anything, reminding them that, no matter what they thought, Valencia was no Asilomar—the groundbreaking 1975 meeting where molecular biologists drafted guidelines to govern recombinant DNA research.

The big difference, he said, is that the earlier group was a deliberative body of the National Academy of Sciences. "We did not present an ad hoc or ad hominen resolution." Zinder added, "I don't think this group is a deliberative body. The last thing in the world I would like to see is this meeting do something it has no authority to do and that would cause a negative reaction among the world's scientists."

Nonetheless, Dausset and meeting organizer Santiago Grisolia of the Valencia Foundation for Advanced Research pushed forward with the idea of drafting some type of resolution. The final version is bland by comparison with the first draft, for which the group may later be thankful. It is slightly more than a motherhood statement, saying that the participating scientists recognize their responsibility to ensure that genetic information is used only to enhance human dignity. It also calls for debate on the ethical, social, and legal implications of the use of genetic information.

The declaration endorses the concept of international cooperation and urges wide participation in some as yet undefined way. From there, it shifts into an outline of how the genome project should be done: with parallel studies in other genomes, continued efforts to develop compatible databases, and all information in the public domain. Finally, it endorses HUGO, rather than another group, such as Unesco, as the lead body to promote these goals.

But on whose authority the resolution was presumably drafted, and to what ultimate effect, remain unclear and, to some participants, somewhat troubling. Meeting organizer Grisolia seems quite pleased with the document and plans to present it to the King of Spain. Others, who were less enthralled with the whole endeavor, say that the best that can be hoped for is that the hastily worded resolution won't backfire in some way. ■ **LESLIE ROBERTS**



W. C. Sturtevant and G. R. Lewis

Mammoth Fraud Exposed

The uncertainty that has long surrounded one of the most infamous specimens in American archeology—the Holly Oak pendant—appears at last to have been dispelled. First reported to a skeptical archeological community in 1889 as putative evidence of ancient human occupation in the Americas, the whelk shell bearing a crude sketch of a mammoth or mastodon has recently been shown by accelerator mass spectrometry (AMS) to be only a little over 1000 years old. "The engraving on the shell is modern, made long after woolly mammoths and mastodons had become extinct in North America," note David Meltzer, of Southern Methodist University, and three colleagues from the University of Michigan and the National Museum of Natural History, Washington, D.C.

When Hilborne T. Cresson, an archeological assistant at the Peabody Museum of Harvard University, made the pendant public in 1889 the contemporaneity of humans and ice age animals in the New World had not yet been settled. Debate over the issue was intense, and, note Meltzer and his colleagues, there were "many hoaxes and forgeries which purported to demonstrate the antiquity of human remains." Cresson said that he had found the pendant in northern Delaware in 1864, the year that Eduard Lartet discovered a fragment of a mammoth ivory, bearing an engraved mammoth image, at the site of La Madeleine in southwestern France. Lartet's discovery was important in establishing human antiquity in Europe, and Cresson hoped the Holly Oak pendant might do the same for the Americas. Cresson never explained why he waited 25 years between discovery and announcement.

Cresson's standing in the archeological community was not high, and in 1891 he was fired from a Peabody Museum excavation site for stealing artifacts. Later he committed suicide, his mental state clearly disturbed. Meanwhile, scholars of the time rarely mentioned the pendant in connection with human antiquity in the Americas. It was not until the 1970s that the pendant gained prominence, after it was "reexcavated" from a Smithsonian Museum collection and cited as probable evidence of the coexistence of mastodon and Paleo-Indians, an issue that was no longer in dispute. Although John C. Kraft and Jay F. Custer admitted in a major article in *Science* in 1976 that fraud was a possibility, they vigorously defended the pendant's authenticity in a subsequent exchange of correspondence with Meltzer and William C. Sturtevant.

Meltzer told *Science* that during the past decade only one request was made to the Smithsonian Institution for permission to date the pendant, and that was using amino acid racemization, a notoriously unreliable technique. AMS dating became available in the early 1980s, and Meltzer and his colleagues are the first to apply it to the Holly Oak pendant. ■ **ROGER LEWIN**

ADDITIONAL READING

James B. Griffin *et al.*, "A mammoth fraud in science," *American Antiquity* **53**, 578 (1988).