Shifting Sentiments Over Sequencing the Human Genome

The latest gathering to discuss the prospects for sequencing the entire human genome experienced an important change of priorities; mapping is now seen as the preferred goal

THE drive to initiate a Big Science project to sequence the entire human genome is running out of steam. Leroy Hood, of the California Institute of Technology, forcefully summarized the newly gathering sentiment at a recent meeting organized by the Howard Hughes Medical Institute: "It would be a serious mistake to jump into a full-scale sequencing effort with the cottage industry techniques we have at the moment," he said. "If we make the proper investment in developing technology then in 5 years time we will be able to do the job more effectively, both technically and financially."

While all-out sequencing is slipping to the background, the idea of generating a complete physical map of the human genome advanced strongly and is clearly going to be vigorously promoted as being more immediately useful as well as being of more modest scale. Mapping might involve fragmenting genomic DNA into 40-kilobase-long segments, identifying each piece in some way, and establishing how the pieces fit together in the intact chromosomes.

As a result of the recent meeting Donald Fredrickson, president of the Howard Hughes Medical Institute, will at the beginning of August recommend to his trustees that the institute commit substantial financial and organizational support to an international human genome mapping effort. The project "is worth pushing hard for," he said.

The meeting, which was held on 23 July at the National Institutes of Health, Bethesda, Maryland, was entitled "Informational Forum on the Human Genome" and included representatives from Europe and Japan. It was the latest in a series of similar gatherings that scatter the calendar of the past year, but, compared with the focused enthusiasm for sequencing apparent on earlier occasions, this one was more wide ranging in views expressed. It undoubtedly marked a turning point.

It is true that all the previous discussions on the subject of the human genome have addressed mapping as well as sequencing, both of which have been judged to be technically feasible and valuable. Nevertheless, it has been the idea of obtaining a complete readout of the sequence—all 3 billion bases of it—that unquestionably fueled the excitement. The gargantuan scale and cost of such an operation, which might consume 30,000 man-years of effort and $3 billion, only seemed to make the prospect yet more attractive. Biology would finally move into the realm of Big Science. Or so it seemed.

Donald Fredrickson, *president of the Howard Hughes Medical Institute, which sponsored the meeting.*

When the idea was aired informally at this summer's Cold Spring Harbor symposium there emerged for the first time serious reservations, not about the technical feasibility but about the wisdom of the whole venture (see *Science*, 27 June, page 1598). James Watson told the NIH gathering that although he had qualified support for the proposal, "everyone else at Cold Spring Harbor was against it." These people are young, he explained. "They are scared that if sequencing goes ahead there will be fewer funds available for their research." With a megaproject sucking up $3 billion, there is a real and valid fear that funds will be diverted from existing research.

Given this fear, one might have expected that some of the new, more modest figures presented at the recent NIH meeting would have brought comfort. For instance, David Smith, of the Department of Energy's (DOE) Office of Health and Environmental Research, estimated that with current and projected advances in automated instrumentation, the scale of sequencing the entire genome would be slashed to 300 man-years of effort at a cost of $300 million.

Instead of being greeted as good news, this prompted Walter Bodmer, of the Imperial Cancer Research Fund in London, and chairman of the NIH meeting, to interrupt Smith and say, "But this doesn't address the issue of mapping that we know to be so important." This moment was crucial, because it marked unambiguously the publicly espoused shift of priorities from sequencing to mapping. "It's been a red herring to say that total sequencing is our goal," he added later. The spirit of Cold Spring Harbor was clearly exerting its effect.

The moment was also interpreted by some as the beginnings of the inevitable political jostling inherent in a venture of this magnitude.

So far the DOE has been instrumental in promoting the human genome project, principally through initiating some of the early workshops on the subject. The department sees its interest in the project as a natural extension of its existing support of, among other things, the National Laboratory Gene Library Project and GenBank, the national database for DNA sequences. A considerable volume of funds has therefore already flowed from the DOE to research in human genetics, both in its own laboratories and in universities. And more is in the pipeline. "We intend to stimulate the development of physical mapping of the human genome, automation of key techniques and the handling of databases," said Smith.

With the prospect of future funding to the tune of some $20 million or so over the next few years, researchers might be expected to

be happy, especially as this would be in addition to NIH and National Science Foundation funding. Nevertheless, there is a palpable sense of unease about the extent of involvement apparently already developed by the DOE in these early stages of the project and the prospect of yet greater control. There were clear indications at the recent NIH gathering of a desire to organize and coordinate the mapping (and subsequent sequencing) project within the university and research institute community, "without being encumbered with hidebound bureaucracy," as Bodmer repeatedly stressed.

Perhaps in response to this new mood, Smith was strikingly less bullish in promoting the DOE's role in the future of the genome project than he had been at the Cold Spring Harbor gathering at the beginning of June.

With the notable exception of Walter Gilbert, of Harvard University, who earlier proposed the establishment of a Human Genome Institute that would be focused on sequencing the human genome, most of the United States contingent at the NIH meeting was distinctly cool about sequencing as against mapping. From Europe, John Tooze, of the European Molecular Biology Organization, said that he had elicited "a distinct lack of enthusiasm for sequencing the whole genome, until the process could be extensively automated." Sydney Brenner, of the Medical Research Council's Laboratory of Molecular Biology in Cambridge, England, said that "The idea of trudging through the genome sequence by sequence does not command wide and enthusiastic support in the U.K."

In Japan, by contrast, researchers at the University of Tokyo and the Riken Institute in Tokyo are already gearing up a $3 to $4 million, highly automated sequencing effort that, within 2 years will be churning out 1 million bases a day. The idea is then to sequence the smallest of the human chromosomes, number 21, which has 48 million bases, within a 5-month period. "But there is no plan to sequence the entire genome," said Nobuyoshi Shimizu of Keio University, Tokyo. "Sequencing the human genome is an organizational challenge and no such structure exists in Japan."

Enthusiasm for sequencing the entire human genome can therefore be seen to have generally diminished and has been replaced by enthusiasm for mapping. "Doing the sequence should be phase 2 in our plans," said Watson. "Phase 1, which is getting a library of overlying cosmids, a map, is acceptable. There should be more urgency for pursuing phase 1 than there is, because of the great benefits for genetic diseases and common diseases. We can't think intelligently about phase 2 until we have phase 1."

A switch of favor from sequencing to mapping represents something of a victory for classical genetics. It is true that the existence of a physical map of the genome would facilitate tracking down genes and cloning, which is the stuff of molecular genetics. But for classical genetics a map is even more valuable, provided that it is scattered with informative markers. With such markers it would be possible to carry out linkage studies with many loci, which would at last give a real insight into some of the common but genetically complex diseases, such as heart disease, psychiatric disease and autoimmune disease.

Phase 1, the mapping effort, might be completed within 3 years, given sufficient coordination and about $20 million. The cost and duration of phase 2 will depend entirely on the state of sequencing technology and the proportion of the genome that is considered worth sequencing. For, although some observers insist that it should all be done, others argue that only a small proportion is actually of interest. On to this Gilbert adds phase 3: "the complete understanding of all human genes; this is the goal of all biology."

Reflecting on meetings of molecular biologists at NIH just a decade ago, when the beginning of recombinant DNA technology stirred uncertainty and fear, Fredrickson characterized the current prospects as follows: "We now face a new challenge, this time more awesome than dangerous." ■

ROGER LEWIN

Tracing a Young and Malleable Moho

The boundary between the continental crust and the mantle in Nevada appears to be younger than the continent itself

If the earth is like a layer cake, the 30- to 40-kilometer-thick continental crust would be the thin uppermost layer, thin enough really to be a glaze of icing that overlies the darker, denser mantle layer extending 2900 kilometers to the core. In 1909 Andrija Mohorovičić detected the boundary between crust and mantle in the differing velocities of seismic waves in the two layers. Called the Moho for linguistic simplicity, this seismically detected boundary between chemically differing layers became in the eyes of many geophysicists as clean, simple, and unchanging as the layers of a cake. Modern applications of Mohorovičić's techniques suggested that the boundary might actually have a thickness of several kilometers, but the image of the Moho remained fuzzy at best.

The application of a second, higher resolution seismic approach, the seismic reflection technique borrowed from oil exploration, has revealed a complex and variable Moho of interleaving crust and mantle. A new seismic reflection study of the Moho beneath Nevada and western Utah reveals not only a complex reflective zone at the base of the crust often resembling a double Moho, but also evidence that the Moho there formed long after that part of North America did. Among the explanations of how a new boundary between crust and mantle could form is the idea that the lower crust grew at the expense of the mantle.

The new study is based on an exceptionally long, 1000-kilometer seismic profile made by the Consortium for Continental Reflection Profiling (COCORP) across the Basin and Range province of Nevada, where crustal stretching has broken the surface into wave after wave of mountain ranges separated by sediment-filled basins. In reflection profiling, truck-mounted vibrators send seismic waves downward that reflect back to receivers on the surface from any variation in rock properties sufficiently strong to act as an obstacle to the waves, much the way radar works in the atmosphere at far shorter, electromagnetic wavelengths. The resulting 50-kilometer-deep, 1000-kilometer-long image can reveal details in the horizontal dimension larger than about 2 kilometers and in the vertical larger than about 100 meters. That is a far sharper picture than that obtainable by refraction profiling, the original method used to define the Moho.