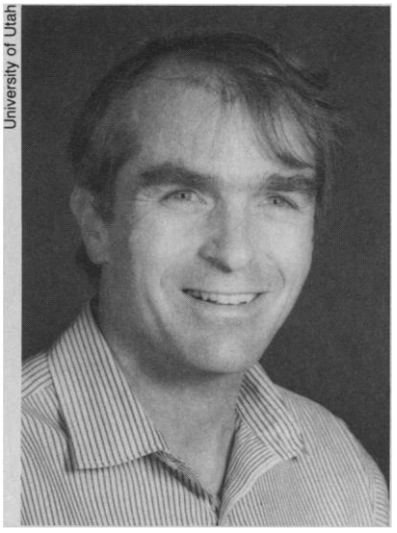
The Genetic Map Is Back on Track After Delays

After some public criticism, NIH has a new strategy for the genetic map, and the community has agreed to divvy up the work

AFTER A BRIEF DIVERSION the genetic map, the first goal of the Human Genome Project, is back on track. At a small, closed meeting last week at Cold Spring Harbor Laboratory, the mapping community signed on to a new strategy for the genetic map—an "index" map of special markers spanning all the chromosomes—and agreed to parcel out the work to get the job done.

"The system is working," exults David Botstein of Genentech, which is quite a contrast to what he was saying just a few months ago. At the December meeting of the committee that advises the National Institutes of Health on its genome project, Botstein, Maynard Olson of Washington University, and Leroy Hood of Caltech charged that the genetic map had fallen by the wayside, in part because of a lack of leadership at NIH (*Science,* 19 Jan., p. 281).

"There is zero probability" that a fine-resolution map of all the chromosomes will be done within 5 years without a change in policy, said Olson at the December meeting. And that was a shame, Olson and company said, because the map was both doable and immensely valuable as a tool for tracking down disease genes.



Ray White: *"Can't we just do it and quit making logistic plans?"*

James Watson and his staff at NIH's Center for Human Genome Research heeded the complaints and set up a working group to look into how best to speed progress toward the genetic map. Botstein and Olson are on that working group. The new strategy grew out of a March meeting in Salt Lake City of the working group and some of the nation's top mappers, including Helen Donis-Keller at Washington University, Ray White at the University of Utah, and Jim Gusella at Massachusetts General Hospital. They decided that what is needed now is a map with exceptionally useful "index" markers spaced every 10 or 15 centimorgans—roughly 10 or 15 million bases—along the chromosomes.

A genetic map consists of landmarks or markers, which are short detectable pieces of DNA, spread along the chromosomes. At least in theory, any gene can then be located between two markers. What sets the index markers apart is that they are, in mapping lingo, "highly informative"—meaning they will provide useful mapping information in about 70% of the population. Only about 10% of known markers meet that criterion. This means that even though the new markers will still be a hefty distance apart, the index map will be immediately useful for gene hunters.

The group also agreed to sequence a small chunk of each marker to create a "sequence tagged site," or STS (*Science,* 29 September 1989, p. 1438). This will enable the index markers to be easily placed on the other type of map being developed, the physical map, thereby linking the two maps.

The index map is by no means the ultimate goal for the genetic map. The 5-year goal, which now looks achievable, is still a genetic map with markers spaced every 2 centimorgans or so. The new plan is to finish the index map within 2 years and then fill in the spaces with other markers to construct the higher resolution map.

Once the group at the Utah meeting agreed on the transitional goal for the genetic map, the problem was how to achieve it. It was clear to everyone, says Botstein, that "ordinary bureaucratic procedures were slowing things down." So the group came up with the democratic idea of parceling out the work among everyone involved in mapping instead of relying on the few groups that are doing large-scale mapping—primarily Donis-Keller and White but also Gusella.

Much of the credit for this idea goes to White. "I looked around the room and saw all these people who were getting funded for mapping, and I said, 'Wait, can we each redirect a little of our effort—can't we just do it and quit making logistic plans?' "

The major players agreed, which was no small feat in itself, since the tensions among the groups are no secret. As one observer describes it, the three realized it would serve their interests, Watson's interests, and the interest of science to have a map, and so they had better just get on with it. "They decided they would play."

And that was the idea the group sold to 18 or so of their colleagues at Cold Spring Harbor Laboratory last week. Donis-Keller agreed to take on chromosomes 2, 6, 7, 8, 12, and 14. White took on 5, 10, 16, and 17. Gusella took on 9 and 22, Ann Bowcock from Stanford took 13 and 15, Sue Naylor of the University of Texas took 3, and so on, until all chromosomes were accounted for.

Each of these "chromosome leaders" will be responsible for seeing that the map gets done, either by doing it themselves or by coordinating the efforts of other labs—a job White describes as "not an honor but a public service." They will get together in October at the American Society of Human Genetics meeting to report on the status of each chromosome map and to lay out what needs to be done. Many of the 300 or so index markers needed for the map are already in hand, but some will have to be generated.

Meanwhile, the staff at the genome center are working out the details of the new plan. Everyone has agreed, for instance, that the DNA markers and data must be freely available, but just which database will be used or where markers will be deposited has not been decided.

Then there is the question of money. Some investigators said they could redirect part of their existing funds; others said they would need extra. Just how much money is needed, however, is not clear. "The feeling is that $2 or $3 million extra will probably take care of it, but that is off the top of someone's head," says Elke Jordan, deputy director of the genome center. The center may solicit proposals and is looking into ways to expedite review so that grants could start in early 1991. And finally, the center wants to get the word out to any investigators they may have overlooked. "If others want to come in, the door is wide open," says Botstein. "There is no exclusivity. This is not about credit but responsibility."

All of this needs the imprimatur of the genome advisory committee, which meets in June, but the members are already enthusiastic, as is Watson. ■ **LESLIE ROBERTS**