and the skills of Bellcore scientists. "The board is very mindful of what it wants Bellcore to be: independent and supplier-neutral," he adds. "We would not take this step if we thought it would compromise our ability to get the technology we want."

The real world

These moves by the Baby Bells to focus more on near-term research and development and to contract out much of the work mirror developments in many other U.S. companies. AT&T Bell Labs, for example, is scaling back the basic research that made it famous, and RCA's renowned David Sarnoff Research Center—the birthplace of color television—has struggled to maintain its scientific expertise since it was sold to SRI International in 1986. Replacing the old centralized megalab approach is a flexible mixture of in-house work, outside contracts with universities, and outright purchase of new technologies from more innovative companies. Some, like MIT's Solomon, view this trend with alarm, while many industry executives say it's only copying what is being done profitably in other industrialized countries.

The burning question for Bellcore's 6200 employees is whether a company no longer sponsored by the Baby Bells can continue to attract the resources it needs to be successful. Not all Bellcore managers and alumni are worried. "I don't see why the right kind of applications research won't work," says Al Aho, a former Bellcore general manager for information science and technology and now a computer science professor at Columbia University. "And the divestiture of Bellcore gives it the opportunity to do things it previously could not"—such as aggressively seek new customers outside the Bell system.

Aho and others argue that the company will also be better off once it is freed from the need to win over seven bickering masters. Under the new plan, says John Seazholtz, Bell Atlantic vice president of network technology, "if three of us want to do a project with Bellcore on a proprietary basis, we can. We don't need everyone to agree to it."

However, Lucky and others worry that a shrinking research budget will mean a shrinking pool of ideas for new products. "There will be less time for untargeted exploration," says Lucky. "You can't promise someone a lithium-ion battery—you have no idea it can exist." And Lucky is concerned about what Bellcore will put on display at upcoming trade shows, and whether scientists like Warren will continue to move between the lab and the limelight. "Now we're all standing around selling products," he says. "But I don't know in the future what we'll be selling."

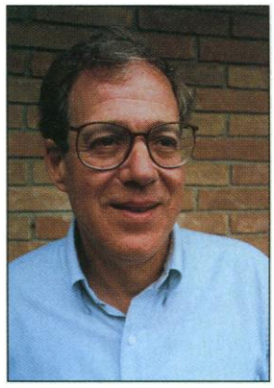
–Andrew Lawler

HUMAN GENOME PROJECT

Emphasis Turns From Mapping To Large-Scale Sequencing

No pistol shot marked the start, but the race to sequence the human genome began in earnest this spring. This was apparent to scientists attending recent meetings on human genome research—one in Santa Fe, New Mexico, on 3 May, and the other at Cold Spring Harbor, New York, from 10 to 14 May.

During these meetings, two teams—one led by John Sulston, Robert Waterston, and Bruce Roe, and the other by Michael Palazzolo and Robert Moyzis—firmed up plans to sequence chromosomes 22 and 16, respectively. By fall, they want to have data on their operations showing whether they can analyze large chunks of the human genome accurately and at low cost. In addition, a group interested in the X chromosome is meeting in mid-June and may organize a team to complete work on that chromosome. Anthony Carrano at the Lawrence Livermore National Laboratory is moving ahead on chromosome 19. Other teams in Japan and Germany are zeroing in on chromosomes X and 21.



New recruit. Bruce Roe joins a team sequencing chromosome 22.

"The bottom line," says David Kingsbury of Johns Hopkins University's genome data center, "is that the time has come to do some [large-scale] sequencing; we're not going to wait much longer" for improvements in technology. "The whole mentality of the field has undergone a substantial change in the past year ... towards a feeling that it's time to start doing it," says Francis Collins, director of the National Center for Human Genome Research (NCHGR).

This burst of sequencing activity heralds a new phase of the U.S. Human Genome Project. Until now, the project, funded jointly by NCHGR at the National Institutes of Health (NIH) and by the Department of Energy (DOE), has devoted most of its resources to producing the detailed genome maps intended to guide researchers to their ultimate goal: the complete sequence of all 3 billion base pairs in the human genome. But NIH began to shift attention last December to a new strategy proposed by two champion sequencers: Sulston, director of the Sanger Center at Cambridge University in the United Kingdom, and Waterston, director of Washington University's genome center in St. Louis (*Science*, 10 February, p. 783). The two manage automated labs that are sequencing the entire genome of the nematode *Caenorhabditis elegans*, grinding out more genomic data than anyone in the world—about 10 million DNA bases a year. This success led Sulston and Waterston to suggest a short cut.

Rather than determining the precise order of all 3 billion base pairs, they asked, why not settle for something less—say, 99% or 99.9% precision? This would mean leaving one uncertain base per 100 to 1000 bases sequenced. With this compromise and a centralized effort, they argued, it would be possible to save money and sequence the genome by 2001, 5 years ahead of target.

The initial response was muted. While disease researchers were delighted with a plan that promised to complete the genome in 5 years, others were skeptical. Some scientists didn't want to sacrifice precision, and many doubted that sequencing nematode DNA is comparable to sequencing human DNA. For example, the human genome contains longer and more frequent stretches of hard-to-assemble repeat patterns. Gene mappers were particularly dismayed, because the proposal would shift funds from mapping to sequencing sooner than expected.

Waterston's budget, projecting costs of as little as 10 cents per base, also raised some eyebrows. Many sequencers question that figure. J. Craig Venter, director of The Institute for Genomic Research in Gaithersburg, Maryland, an expert in high-speed sequencing who just reported the first complete sequences of two bacteria, *Mycoplasma genitalium* and *Haemophilus influenzae* (see p. 1273), finds it hard to believe the cost can be pushed below 30 cents per base. Waterston responds that he and his crew will be putting on "green eyeshades" this summer to refine their calculations.

Cost remains a critical issue. Even in the best of times, NIH and DOE would be hard pressed to support several large sequencing centers, as Waterston has proposed. But these are not good times. Congress is threatening to abolish DOE and cut NIH's budget next year (*Science*, 26 May, p. 1120). Nevertheless, both agencies are laying plans for new sequencing projects. NCHGR has in

vited applicants to apply by fall for awards of up to $750,000 per year to test new methods, and DOE is also getting ready to take a big leap into sequencing.

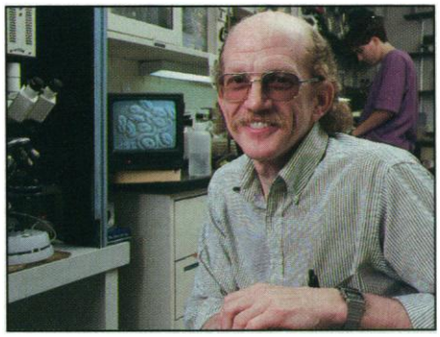
Indeed, that's why DOE called the meeting last month in Santa Fe. The agency wanted to bring together experts from DOE centers and other sites to talk about technical options for skimming through the genome and snatching useful data inexpensively ("low-pass" sequencing). Even though DOE funds may be cut, says David Smith, director of DOE's Health Effects and Life Science Research Division, the outfit that runs DOE's genome work, the agency is "going to be transferring a higher percentage of whatever resources we have" into sequencing. Smith says he hoped people at the Santa Fe meeting would arrive at a consensus about the relative value of low-pass versus more precise techniques, but they didn't. "There's a big range of opinions" about which methods are worth trying, Smith says, and he's mulling them over right now.

At one extreme, according to Santa Fe attendees, are proposals for very low-precision methods, such as that offered by Richard Gibbs of Baylor College of Medicine in Houston. Gibbs is in favor of skimming generich areas as long as it's merely a "down payment" that leads to complete data. "It's perfectly legitimate, I think, to survey a region, and if you don't like it, move on," he says, but "you must always justify your activity by showing you can go back and finish the job." Others, like Roe, would like to dissect the genome in detail because, he says, "it turns out that the difference between you and me" comes down to variations in single base pairs.

Moyzis, director of DOE's genome center at the Los Alamos National Laboratory, also advocates a low-pass approach. His scheme involves what he calls "sampling," in which patches of chromosomal DNA at regular intervals along the genome are sequenced with some redundancy, oriented, and linked with other patches, giving intermittently high precision over a large territory. This approach, he says, would "democratize" genetic studies by quickly giving researchers a complete picture of the genome with information on most genes and biologically "hot" zones. It will also feed directly into another ambitious DOE project at Lawrence Berkeley Laboratory (LBL), which is led by Palazzolo.

In the past, LBL has focused on sequencing the fruit fly genome and small stretches of human chromosome 5. Palazzolo says resources are now being redirected from chromosome 5 to 16, so that a team can start sequencing well-ordered clones delivered from Moyzis's group at Los Alamos. Unlike the Sulston-Waterston-Roe team, which plans to use random sampling and redundant sequencing, the Palazzolo-Moyzis team plans a "directed" strategy, with as little redundant sequencing as possible. Palazzolo thinks the costs for both methods are comparable, but claims that the DOE approach can easily be "tuned" to yield a precision of 99.95% or better.

Many alternatives were discussed at Cold Spring Harbor as well; no consensus emerged there, either. But there is a movement to compromise, even among sticklers for precision, such as Roe. While he prefers achieving a 99.99% level of precision, Roe concedes that would be "very expensive," and it's not clear "we can afford the Cadillac of genome sequencing." On the other hand, he regards anything less than 99% precision as "a dead end," because the data would be riddled with gaps. But Roe is willing to settle for 99.9%. Having secured that objective, he says he "shook hands" with Sulston and Waterston at Cold Spring Harbor and will join them in sequencing chromosome 22. "We're already doing it," says Roe, who says he has sequenced about 1 million bases.



TOM HEINE/WASHINGTON UNIV. SCHOOL OF MED.

Price chopper. Robert Waterson aims to sequence human DNA for 10 cents per base.

While the genome community may not agree on which method is best, they have reached consensus on one thing: It would be useful to get more data. "We're scientists," says Venter. Rather than engage in "religious" speculation, "I believe strongly in doing the experiment and letting the data tell you where to go." The data-gathering is now under way.

With so much at stake, scientists are elated and apprehensive about where these sequencing experiments will lead. Roe says, "We're on the verge of something very exciting" that will "set the tone of health care for the next century." But "our reputation hinges on this," and "we have to walk carefully and understand how to do it right."

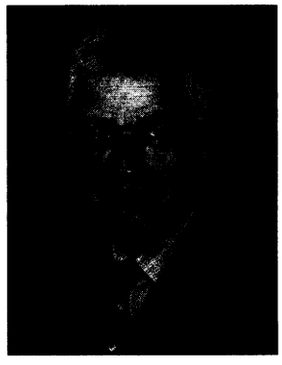
–Eliot Marshall

BUDGET RESOLUTION

Senate Restores NIH Funding Cut

Biomedical researchers won a significant victory last week as the Senate rescinded a proposed 10% cut in funding for the National Institutes of Health (NIH). Although this will be good news for some, not all researchers have reason to celebrate: NIH's good fortune may come at the expense of the rest of the domestic budget, including other science programs.

Senator Mark Hatfield (R–OR) led the effort to restore funding to NIH. His success was impressive: His amendment was the only significant change in the budget resolution accepted by the Senate, and it passed by a large margin (85 to 14). The vote returns $7 billion of the $7.9 billion that a draft resolution had removed from NIH's budget over the next 7 years, also adding back money for education, Medicare, Social Security, defense, and foreign aid (*Science*, 26 May, p. 1120). But most nondefense discretionary accounts would be "taxed" to pay for the adjustment, including general science and space (down $700 million over 7 years), energy (down $100 million), natural resources (down $700 million), agriculture (down $400 million), and transportation (down $1.3 billion).



Paper victory. Hatfield helps restore NIH funding—but it's only round 1.

On the Senate floor, Hatfield described this solution as "robbing Peter to pay Paul," adding that it was "the only way I could find to salvage and save NIH." He said his first choice, taxing defense and international programs to pay for health, appeared to have the support of only about 20 members, forcing him to adopt a formula that appealed to advocates of military funding.

The House and Senate must now reconcile differences in their budget resolutions, which are not binding on appropriators. With regard to NIH, the House budget plan calls for a 5% cut next year and a 6-year freeze; the Senate version now calls for a cut of roughly 1% a year.

The vote was applauded by a coalition that had mounted a fierce lobbying campaign on its behalf. "Sanity prevails. ... I couldn't be more pleased," said Sam Silverstein, president of the Federation of American Societies for Experimental Biology (FASEB). He sent FASEB members a memo lauding Hatfield and praising the membership for the "outpouring of faxes, phone calls, and other contacts."

NIH Director Harold Varmus, who called the original Senate plan "a prescription