A Meeting of the Minds on the Genome Project?

In spite of some sharp exchanges, there was a lot of common ground when the project's organizers met their critics

San Diego, California—RESENTMENT OVER the rapid growth in the budget for the Human Genome Project and the intrusion of "big," or at least bigger, science into molecular biology got an airing at *Science*'s Genome II meeting here late last month. Genome project leaders James Watson and Charles Cantor invited two prominent critics, who gamely came to make their case before a less than receptive audience of molecular biologists. And while there was lots of heat—at least between NIH's Watson and Don Brown of the Carnegie Institution, who got into a shouting match before a group of reporters—what was striking was how close the two camps actually were.

The unexpectecd convergence of opinion at least partly reflected which critics were invited. Brown and Bernard Davis of Harvard Medical School are "distinguished skeptics who have to be taken seriously," said the Department of Energy's Cantor, suggesting that is not the case for some of the more rabid opponents of the project. Two of those, Martin Rechsteiner of the University of Utah and Michael Syvanen of the University of California at Davis, recently launched letter-writing campaigns urging that the project be killed, calling it mediocre science and terrible science policy (*Science*, 18 May, p. 804). By contrast, Davis and Brown argued not so much about scientific goals but how best to achieve them.

Davis had two gripes about the project. The first was what he called "fairness and distribution." While no one can prove that the genome project, now budgeted at nearly $90 million at NIH and $46 million at DOE, is in any way responsible for the current funding squeeze at NIH, its budget comes out of the same pot as everybody else's, he said. Davis then advised the genome officials that a little humility and an agreement to grow more slowly while their colleagues are suffering would go a long way toward restoring harmony.

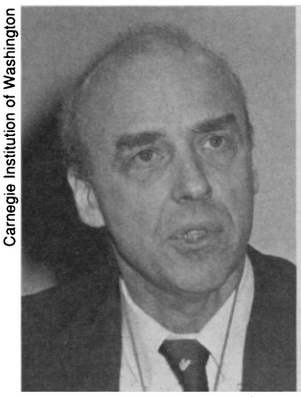
Davis' main target, however, was the plan for all-out sequencing of the human genome. Davis said he fully supports the first goal of the genome project, mapping the human chromosomes, and likewise thinks sequencing model organisms is a fine idea. But he can't see the value in working out every nucleotide base in the human genome, especially when 98% of it is of unknown function. What's more, he said, the experiments to figure out what this "junk" DNA does will likely be done in mice, not in humans.

But once it was impressed upon Davis that no one is contemplating all-out sequencing for at least 5 years—and even then only if the cost comes down—he backtracked substantially. In fact, he heartily endorsed the current plan to sequence the especially interesting areas of the genome, as reflected in a new project recently undertaken by DOE to map and partially sequence complementary DNAs, or expressed genes. "I don't want to say I have been converted," Davis told *Science*, "but there is much less disagreement than there was a year and a half ago."

To genome project proselytizers, Don Brown proved far more recalcitrant. While he said he agrees with the project's goals and is impressed with the quality of the science so far, he is fundamentally opposed to the "top-down" way it is organized, which is "overtargeted, overbudgeted, overprioritized, overadministered, and has to be micromanaged."

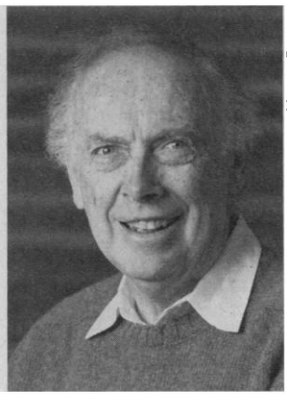
Brown's biggest objection is to targeted research, especially the creation of centers to carry out specific research tasks. NIH recently created four such genome centers (*Science*, 28 September, p. 1497). Throughout his talk, Brown waxed rhapsodic on the RO1, or investigator-initiated grant, system at NIH, "which supports quality science where it finds it. It has been the absolute pride of the biomedical enterprise and, in fact, of science, since World War II." His bottom line was that NIH should stick to what it does well—focus broadly on genetic disease, letting fertile ideas arise from the field—and leave DOE to run centers and handle the large-scale physical mapping and sequencing projects.

But the badly outnumbered critics barely got a fighting chance, as Watson launched a preemptive strike before they took the podium. "Saying that you support mapping without sequencing," as Davis had said in other forums as well, "is like saying I'll marry you but there will be no sex," blasted Watson. And, in anticipation of Brown's attack on targeted research, Watson dismissed as "pure nonsense" the view that NIH should support only "those people who don't promise anything but might come up with something interesting. The thing is not whether it is targeted but whether you have the wrong target. When Jonas Salk went off to get the polio vaccine, it was targeted."



Carnegie Institution of Washington

Arguing "religion." *Don Brown (left) bemoans any departure from investigator-initiated research, the "absolute pride of biomedical research." But to James Watson, the question is not whether it is wrong to target research "but whether you have the wrong target."*



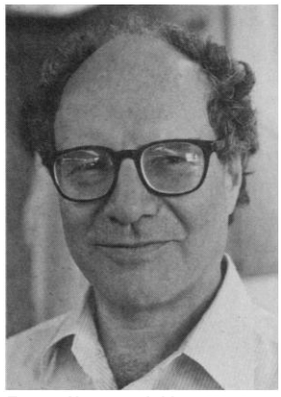
Margot Bennett

Other than those opening comments, Watson was uncharacteristically reticent during the rest of the morning session when Brown and Davis spoke. But at the subsequent press conference, when the critics reiterated their complaints, he could no longer contain himself, leaping up from the corner and telling Brown to quit being "mystical about RO1s. Most of them aren't that great anyway." Retorted a visibly angry Brown: "It is not appropriate for someone in the genome project to demean RO1s."

"That is pure crap," shot back Watson, to the dismay of *Science* editor Daniel Koshland, who was trying to moderate the panel and who had earlier urged Watson, perhaps not completely in jest, not to say anything controversial. Koshland then began trying to "interpret" Watson to the assembled reporters while Watson and Brown kept fighting. It was Watson, finally, who explained it best when he told the reporters, "You have to realize we are talking religion."

The rest of the audience may have been more polite, but they were hardly convinced

by the two critics. In fact, they seem somewhat perplexed about what they are complaining about. The genome project, a mere 1% of NIH's budget, is not responsible for the grant crunch, they say, and in terms of targeted research, as Watson pointed out, roughly half of NIH's budget overall is already targeted, so the genome project is clearly no exception.



Harvard University News Office

Paradigm shift. *Walter Gilbert argues that genome project critics are longing for a bygone era.*

In the end, it was Walter Gilbert, one of the scientists who pioneered DNA sequencing in the late 1970s, who tried to put the criticism in context in his talk in the closing session. Brown and Davis are essentially bemoaning the current state of molecular biology, he said, and in this they are not alone. Many professors complain that science has been gutted, that their students "use kits and look up how to do things in the Maniatis cookbook," said Gilbert, referring to the classic cloning manual. He thinks the critics are reacting to a change in molecular biology that they do not entirely understand, what Gilbert referred to as a "paradigm shift," and that they are confusing tools with science itself.

"The paradigm of molecular biology that Don Brown and Bernie Davis spoke from was that biology is a purely experimental science," in which you do experiments to isolate a gene, sequence it, and then go on to study it, said Gilbert. "In my mind, that paradigm is shifting," he said, in large part because of the genome project. Within 5 years, or 15 years, whenever the project is done, the first two steps will no longer be experimental, said Gilbert—instead, molecular biologists will look up the gene in their computers. Then they will ask a question, make a hypothesis, and do experiments. "Science will not be less experimental, but it will be different experiments. The classic biochemistry Brown talked about will no longer exist."

It's happened before and will happen again, he added. "Twenty years ago, every grad student working on DNA had to learn to purify restriction enzymes. By 1976 no grad student knew how to purify restriction enzymes, they purchased them. Historically, if you were a chemist you blew your own glassware. Today people simply buy plastic." To Gilbert and apparently the rest of the audience, which burst into applause, the current change is all to the good. But by the time Gilbert made his remarks, the critics had long since left.

■ LESLIE ROBERTS

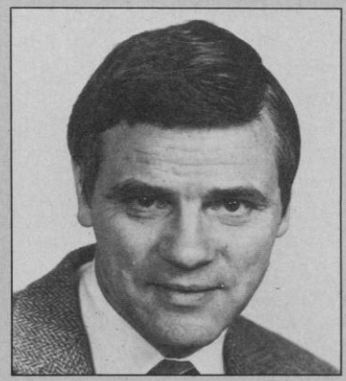
Hood Seems Likely to Head Berkeley Genome Center

If final negotiations go as anticipated, biologist Leroy Hood will soon become the director of the Human Genome Center at Lawrence Berkeley Laboratory (LBL), a post recently held by Charles Cantor. Hood, who has been at Caltech for 30 years and whose departure could prove a substantial loss for that university, will have a joint appointment with the University of California at Berkeley. His primary challenge will be to bring direction and focus to LBL's genome center, which has been floundering since its inception in 1988 (*Science*, 14 September, p. 1238).

LBL has already made Hood a written offer, but some formalities need to be tied up before the university follows suit. And there remains a major question about what will happen to the NSF-funded Science and Technology Center Hood created at Caltech. Nevertheless, insiders say that no snags are expected. Indeed, Department of Energy officials are so keen to have Hood that they have reportedly met all his demands for space and dollars—and, by all accounts, Hood drives a hard bargain.

LBL director Charles Shank has agreed to move out some of the current residents of the biology building, where the genome center now has the third floor, to make room for Hood's Caltech crew. The Hood lab now numbers 75 to 100, including about 50 Ph.D.'s, but not all of them will be making the move to Berkeley.

Hood also held out for tenured appointments in both UC's cellular and molecular biology department, where he will be a professor of genetics, and the chemistry department. The joint appointment will give him access to both genetics and chemistry graduate students, which he considers essential to his instrumentation work.



Hard bargainer. *Leroy Hood.*

The UC offer, when it comes, will also include 3000 square feet on campus for Hood's immunology group—twice the amount a full professor there typically gets. That caused quite a bit of grumbling among UC faculty until DOE agreed to kick in half of that allotment from its own space on campus. Even so, Hood will have to settle for less space than the 6000 square feet his immunology group now has at Caltech.

If Hood officially accepts, as everyone expects him to, the impact on Caltech will be enormous. Hood wants to take with him the Science and Technology Center he created at Caltech just 2 years ago—and that, by all accounts, remains the only complication. Funded by the National Science Foundation at $3.5 million a year, the center faces its rigorous third-year review in February 1992. If it does well, it will be guaranteed funds for a total of 11 years. The quandary for NSF officials will be whether to keep the center—which was awarded to the institution and not to Hood—at Caltech under a new director or allow it to be transferred to UC's chemistry department. Much of that will depend on how strong a case Caltech can make for keeping it there.

"Legally, it is a Caltech center," insists vice-provost David Goodstein, who says that the university will nominate a new director if Hood indeed decides to leave. "If the Science and Technology Center were to become portable, if NSF were to make such a mistake, then every director would have a price on his head." Meanwhile, he says, "you can be sure that Caltech is doing everything within reason to keep Lee Hood happy and content here." Whatever the outcome, Hood seems certain to stay put at Caltech until next summer at the earliest and perhaps until the review of his NSF center is completed. ■ L.R.