FIU and Carlo Laj of the Center for Studies in Weak Radioactivity and colleagues point out that the mantle is the natural place to look for a long memory. Like the molten metal of the outer core, the solid rock of the mantle flows—but at centimeters per year, not the tens of kilometers per year of the core. If some irregularity were to develop in the mantle that could put its stamp on the field, it would persist long enough to guide reversal after reversal.

What aspect of the mantle could be responsible? Speculation has centered on several possibilities. Variations in the electromagnetic conductivity of the lower mantle—perhaps due to iron picked up from the core—could distort the field and channel reversing poles. Or the mantle might leave its mark by encouraging a persistent flow pattern in the core. Some workers think the base of the mantle is patterned with bulges and hollows, which could redirect core flow, the way mountains affect weather patterns. Others suggest that unusually hot and cold patches on the base of the mantle could shape core circulation, the way deserts or mountaintops affect atmospheric circulation.

If the mantle guided the reversals of the past few million years by influencing core flow, it may be doing so still. Laj points to flow patterns in the liquid metal at the top of the core, inferred by Jeremy Bloxham and Andrew Jackson of Harvard University from historical magnetic measurements. The flow seems to follow the same paths the reversals traced: It appears to be feeble beneath much of the Pacific Ocean but relatively strong along north-south paths beneath the Americas and East Asia.

In fact, Laj sees a good correlation between an existing feature of the lower mantle—its temperature, which other researchers have determined from the velocities of seismic waves—and the paths of past reversals. Two great lobes of unusually cold rock arc beneath the Americas and East Asia, forming a broken ring at a depth of 2300 kilometers, 600 kilometers above the core-mantle boundary. Some geophysicists interpret this ring of cold deep mantle as a huge pile of former ocean floor that has sunk into the deep mantle through the deep-ocean trenches that rim the Pacific.

If discarded ocean plate really does affect the magnetic field, the surface motions of plate tectonics are linked not just to the mantle but, through it, to the core itself. That would lend a remarkable unity to the layered Earth. ■ RICHARD A. KERR

ADDITIONAL READING

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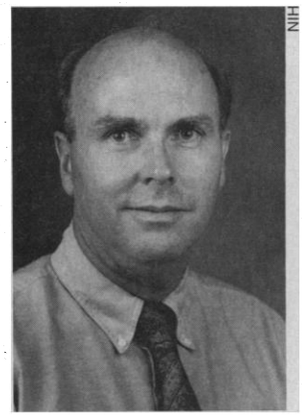
Gambling on a Shortcut to Genome Sequencing

Craig Venter says he can find all the human genes for a fraction of the cost of the Human Genome Project

ALMOST FROM THE START OF the Human Genome Project, a debate has been raging over whether to sequence the entire human genome, all 3 billion bases, or just the genes—a mere 2% or 3% of the genome, and by far the most interesting part. In England, Sydney Brenner convinced the Medical Research Council (MRC) to start with the expressed genes, or complementary DNAs. Brenner, who heads the MRC Molecular Genetics Unit in Cambridge, views sequencing the rest of the genome as "one of those problems we can and should leave to our successors."



NIH

Focusing on expressed genes. Craig Venter.

But the U.S. stance, from the outset, has been that the entire sequence is essential if we are to understand the blueprint of man. What's more, says James Watson, who directs the genome effort at the National Institutes of Health, existing tools for detecting cDNAs are so flawed that there is no chance of finding all of the genes without the full sequence. Lately, however, the U.S. stance has softened a bit, with both the Department of Energy and NIH venturing into cDNAs. Nonetheless, insists Watson, "cDNAs are not in any sense a replacement for genomic analysis. We feel that pretty strongly."

Now comes Craig Venter of the National Institute of Neurological Disorders and Stroke, who says that focusing on the expressed genes may be even more useful than expected (see p. 1651). It will provide much of the information being sought in the Human Genome Project—essentially, where and what the genes are—for a fraction of the cost, he claims. "It really moves the information from the genome project up by a decade or two." But if the reactions of his colleagues are any guide, the debate's not over.

Venter was convinced by the rapid progress being made in his ambitious new project to find and partially sequence every gene expressed in the human brain, thought to number 30,000. Venter, Mark Adams, and their colleagues started about a year ago, and so far they have partially sequenced, or "tagged," about 600 cDNAs, which are simply clones made from the messenger RNAs. Venter optimistically predicts he can wrap the whole thing up in a few years.

What persuaded Venter to try the cDNA approach was the enormous difficulty he and others were having in interpreting long stretches of DNA sequence. Last summer, hoping to turn up the Huntington's gene, Richard McCombie in Venter's group had sequenced a 60,000-base stretch from the region of chromosome 4 where it is thought to reside. Says Venter, "We found it is not trivial to find the genes, even if you have the sequence."

His new strategy—the "ultimate in simplicity"—offers a way around that problem, Venter says. It involves randomly selecting clones from cDNA "libraries," which theoretically contain all the genes that are switched on at a particular time in a particular tissue. Then the researchers sequence just a short stretch of each clone, about 400 to 500 bases, to create what Venter calls an "expressed sequence tag" or EST. The sequencing itself is trivial, says Venter, as it entails just one run on an automatic sequencing machine. The sequences of these ESTs are then stored in a database. Using that information, other researchers can then "recreate" that EST by using polymerase chain reaction techniques.

The ESTs contain enough information to enable investigators to search the databases for similar genes—the standard way to get a fix on what it is you have just found. The computer searches on the Venter group's first 600 clones turned up some intriguing similarities to known genes. But what is most exciting, says Venter, is that the clear majority of the expressed genes his group has identified have no match in the database. "They are new, totally unknown genes," says Venter. The ESTs also enable investigators to map the new clone to a particular chromosome, but the work is still slow and expensive, Venter says.

Venter calls his new effort "a bargain by

comparison to the genome project." His group alone can partially sequence 10,000 cDNAs a year, he says, at a cost of just 12 cents a base. "We can do it for a few million dollars a year, instead of hundreds of millions" to sequence the entire genome

All this doesn't mean that the cDNA approach is problem-free, Venter readily concedes. Indeed, a hefty share of the 600 cDNAs his group has pulled out of the libraries so far turned out to be garbage, he says, such as multiple copies of the same gene or ribosomal RNA genes. But Venter attributes these problems to the commercial cDNA library they were using and is optimistic about overcoming them. Even with improved libraries, admits Venter, it still might not be possible to find all the expressed genes, especially those that are active at only certain stages of development. But, he adds, "I won't feel we have failed if we get only 80% or 90% of the human genes."

Other sequencing experts question his optimism, however. "He ought to reduce that number," says John Sulston of the UK's Medical Research Council, who is sequencing the nematode genome and is also looking for cDNAs. While applauding Venter's effort, Sulston says, "I would bet quite a lot that it won't be 80% or 90%. I think 8% or 9% is more like it."

Nor is that Sulston's only gripe about a pure cDNA approach. It won't give you the gene control regions, he says. Nor can you learn about gene families. "The worm has about 100 collagen genes, which would be exceedingly difficult to collect as cDNAs, because you can't tell them apart. You would probably get one or two, but not the rest."

For a small experimental animal like the worm, says Sulston, there is no contest. "We want to know everything about it. To do so, we have to have the genomic sequence." He admits, however, that shortcuts look more appealing when you are talking about sequencing the human genome, which is far more difficult to interpret than the worm.

Venter, too, insists that he is not pushing cDNAs as an alternative to genomic sequencing but rather as a handy adjunct. "I firmly believe the other information is important to get. The cDNA approach does not eliminate the need for the Human Genome Project." Nonetheless, he just withdrew his grant application for large-scale sequencing to concentrate instead on cDNAs. ■ LESLIE ROBERTS

A Well-Rounded Worm

The millimeter-long roundworm Caenorhabditis elegans *is amassing a sizable research following. As more and more people have joined the confederation of research efforts loosely called the worm project (see* Science, *15 June 1990, p. 1310), the community's biennial meeting has outgrown the traditional watering hole at Cold Spring Harbor. This year, the researchers moved inland for the Eighth International* C. elegans *Meeting, held June 1–5 on Lake Mendota at the University of Wisconsin, Madison. More than 500 "worm people" turned out to absorb progress reports on the sequencing of the* C. elegans *genome, the study of its developmental pathways—and some newer topics as well.*

220 Kilobases and Counting

C. elegans, along with a bacterium, a yeast, and a mycoplasma, is serving as a proving ground for the Human Genome Project. But with 100 million base pairs, its genome dwarfs those of the other model organisms combined, and it is the only multicellular creature in the bunch. Sequencing the nematode at first seemed a daunting challenge to many researchers. Good news, Richard Wilson of Washington University in St. Louis told the meeting: Sequencing is running well ahead of schedule.

Wilson, Robert Waterston, and their Washington University co-workers are collaborating with John Sulston's laboratory at the Medical Research Council in Cambridge, England, to sequence the entire *C. elegans* genome by the year 2000. The pilot project, set up last August, aims to have 3 million bases finished in 3 years. Less than a year into the project, the two labs have already sequenced about 220 kilobases, well ahead of their first-year goal of 200 kilobases.

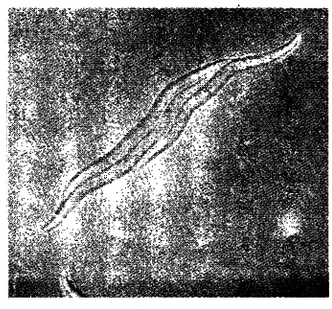
One key to their early progress: a nearly complete physical map of the *C. elegans* genome, consisting of large, overlapping pieces of cloned DNA known as cosmids, worked out by Sulston's laboratory. A second key: computer programs and refined sequencing reactions that have made possible a favorable sequencing strategy. The strategy combines random, or shotgun, sequencing, in which overlapping snippets of DNA from each cosmid are sequenced at random and the results assembled later, with more efficient but more costly directed sequencing, in which a cosmid is sequenced from beginning to end.

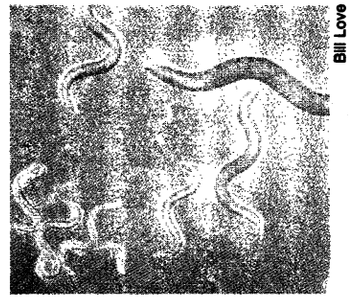
These innovations should be particularly pleasing to the managers of the Human Genome Project, who have been counting on this and other pilot programs to prove new strategies and technologies for making the sequencing cheaper and more efficient. When large-scale sequencing of the human genome begins, researchers hope to do it for 50 cents a base. Wilson estimates that his project is getting very close to that figure: the cost of their 3-year, 20-person effort, he says, will come out to 60 cents a base, including labor, equipment, and overhead.

Along the way, the researchers are learning some intriguing things about their subject. Among the finds so far: the presence of a functional tRNA gene within an intron, a stretch of DNA usually considered to be nothing more than filler. "As far as we know that's not been seen before," says Wilson. And the high number of genes found on the four cosmids sequenced so far—about 14 on each cosmid—has led researchers to double their estimate of *C. elegans*' total complement of genes, from between 5000 and 10,000 to more than 15,000.

The Education of *C. elegans*

Tap the side of its petri dish and *C. elegans* backs away. Tickle its tail—the usual instrument is an eyelash—and the tiny roundworm wriggles forward. Which way does it go if you touch the tail before tapping the dish? That depends on the worm's past experience, according to Catherine H. Rankin of the University of British Columbia.





Bill Love

Telltale worms. *A partially paralyzed strain of* C. Elegans (far left) *becomes motile again* (left) *when exposed to mutagenic chemicals*