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.

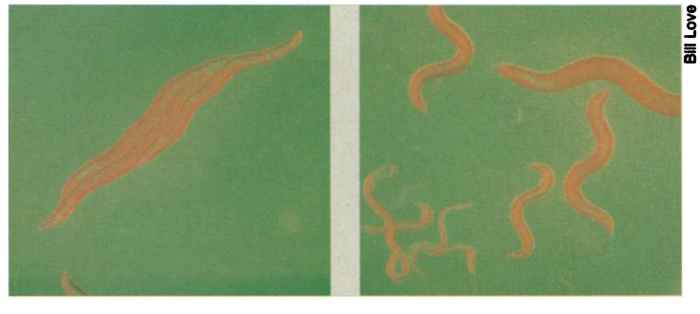
One key to their early progress: a nearly complete physical map of the *C. elegans* genome, consisting of large, overlapping pieces of cloned DNA known as cosmids, worked out by Sulston's laboratory. A second key: computer programs and refined sequencing reactions that have made possible a favorable 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*

In some of the first studies of learning in *C. elegans*, Rankin and other researchers are finding a surprising amount of plasticity in its nervous system. "It's not simply hardwired," she says. And that's a tantalizing finding for researchers interested in the cellular and molecular roots of learning, because the roundworm comes with something no other organism has: a complete wiring diagram of its 302-neuron nervous system, worked out in the mid-1980s.

So far, Rankin has concentrated on pinning down the kinds of learning the worm is capable of. She has found that the "touch" and "tap" reflexes ordinarily inhibit each other: touch a worm's tail before tapping its dish and it won't back away from the tap. But after repeated, innocuous tail touches, a worm becomes habituated to them. A further tail touch no longer inhibits its response to a tap. The more experience a worm has with tail touches, the more the inhibition is diminished. "The inhibition is plastic," says Rankin. In other words, it is subject to the worm's past experience.

Habituation is considered to be one of the simplest forms of learning. But Norman Kumar, who works in the laboratory of Derek van der Kooy at the University of Toronto, showed meeting attendees that *C. elegans* is also proving adept at higher forms of learning—specifically classical conditioning, in which an animal learns to associate two different stimuli. In a Pavlov-style experiment, Kumar divided his small subjects into two groups feeding on *E. coli*—the nematode version of the chow that Pavlov fed his dogs—mixed with sodium or chloride ions. Those who got the sodium solution were then exposed to chloride without the appetizing *E. coli*, while their counterparts were exposed to sodium alone.

Kumar then tested for learning by putting the worms between gradients of the two ions, with no food present. After one round of training almost 70% of the worms moved toward the ion that had been paired with *E. coli*. When the worms had been starved for 5 hours before their training, the percentage that learned which ion went with food rose to almost 80%. And the worms remembered their lessons: A statistically significant preference for the food-associated ion lasted at least 7 hours.

The worm even seems capable of developing a conditioned aversion. When the *E. coli* was replaced with garlic extract, the worms avoided the paired ion. ("There may or may not be homology in vampires," Kumar deadpanned to the meeting.)

In the wake of these experiments, the Rankin team and Kumar *et al.* are starting to combine their results on learning with the wealth of existing knowledge about *C. elegans*' genetics and cellular development. The Toronto group is proceeding with studies of mutant strains that are deficient in certain kinds of learning, while Rankin's lab is examining what happens to learning when particular neurons in the worm's touch circuitry are knocked out by laser pulses. Rankin says that *C. elegans* promises nothing less than "the possibility of understanding the role of each cell in learning."

Roundworm as Canary?

C. elegans, darling of developmental biologists, neurobiologists, and sequencers, is making its debut in another field: ecotoxicology. Susan Anderson, an environmental toxicologist at Lawrence Berkeley Laboratory, and her collaborators are exploring the use of *C. elegans* to monitor the genetic effects of environmental contaminants.

Biomonitors are sorely needed for environmental chores such as cleaning up toxic waste sites or monitoring wildlife habitat. Some currently available methods, such as looking for chromosome aberrations in wild-caught fish, are cumbersome and unstandardized; others, based on bacterial assays, are hard to extrapolate to higher animals.

Anderson thinks *C. elegans*, an easy-to culture, multicellular animal, offers the potential of assays that would be standardized, convenient, and much easier to apply than bacterial screens. Worm-based bioassays would also be versatile: the worm normally lives in soil but can also survive in water, creating the possibility of one monitor for air, water, soil, and sediment samples. "The very significant thing is that you could use *C. elegans* in so many media," says Anderson. "There really isn't anything else like that."

Her group has developed an assay based on a mutant *C. elegans* strain. The mutant worms are paralyzed, but genetic changes triggered by exposure to a mutagenic chemical result in motile progeny. The workers are now testing the motile-worm assay on sediment samples from San Francisco Bay.

Many chemical contaminants become mutagenic in mammals only when the animal's own metabolism chemically activates them. To extend the roundworm assay to such substances, Anderson's group is studying the effectiveness of mixing rat enzymes into a sample before exposing the worms to it. "If we get a good range of metabolic activation," says Anderson, "I'm convinced that the test can be very widely applied." ■ CHRISTINE MLOT

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Can Earth's Internal

When the first deep-sea hot springs were discovered off the Galápagos Islands in 1977, their biological importance was immediately apparent. They were oases of lush life, of worms and crabs and giant clams, in the otherwise sparsely inhabited abyss. More important, they turned out to be an entirely new kind of ecosystem, one sustained not by the sun's energy but by chemicals spewed out by the vents.

In the decade and a half since that dramatic discovery, countless other vents have been spotted along the globe-girdling system of mid-ocean ridges, and biologists and geophysicists have been probing the secrets of the volcanic springs and the ecosystem they sustain. Physical oceanographers, who study the circulation of the ocean itself, have been slower to get into the act. After all, ocean currents, like most ocean life, are generally thought to be driven by energy from the sun rather than from Earth's interior. But new evidence suggests that in parts of the ocean depths, heat coming out of the vents may be more important. Escaping in buoyant plumes, it may churn the abyssal waters in vast, sluggish gyres.

"People have never thought much about the physical effects of vents," says Stephen C. Riser of the University of Washington, one of the oceanographers who have collected the new evidence, which he and his colleagues announced at a recent meeting of the Oceanography Society in St. Petersburg. "But if vents generate their own flow field, it would be a ready [means of] mixing all sorts of chemicals and biology into the deep sea."

Like many of the most interesting ideas in modern physical oceanography, this one can be traced to Henry Stommel of the Woods Hole Oceanographic Institution. In 1981 Stommel, who had laid much of the groundwork for the modern understanding of ocean currents in the 1950s and 1960s, learned of a remarkable discovery made by Scripps Institution oceanographers. On a transect across the East Pacific Rise, a mid-ocean ridge dotted with hydrothermal vents, John Lupton and Harmon Craig had detected an immense plume of water laden with excess helium emanating from the ridge around 15 degrees south of the Equator, at a depth of around 2500 meters. The plume vanished immediately to the east of the ridge, but to the west Lupton and Craig tracked it more than 2000 kilometers. Clearly, the researchers concluded in a paper published in *Science*, the helium plume was acting as a tracer of the ambient