level of resolution never before achieved an understanding of an animal that uses a nervous system to control behavior."

For worm biologists, the sequence will likely mean another revolution in how they do experiments. Says Chalfie: "It means that identification and cloning of genes—work that a lot of us spend a lot of time on—will already have been done. Instead of asking, Can we get the gene? we can ask, What is the function of that gene?"

To Sulston, the challenge is to learn how to read, or understand, the sequence. And biologists have a far greater chance of figuring it out in the well-studied worm, on which they can perform aggressive experiments, than they do in humans. Sulston and his colleagues are convinced that much of what they find in the worm will be relevant to human biology. Already, says Hodgkin, in the genes sequenced to date, worm biologists are encountering many "old friends"—conserved genes present in humans and other animals. He expects that soon the pattern will be reversed. "We will see them first in *C. elegans* and then go on to look for them in other animals."

Sulston agrees: "In a sense, one organism like this contains all of biology."

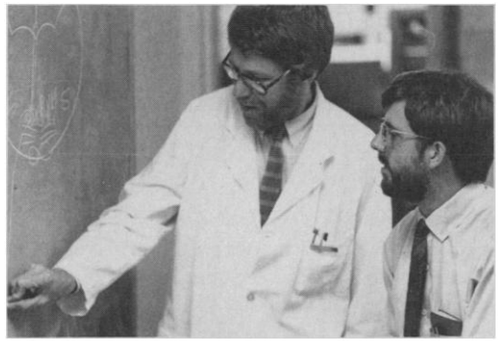
■ **LESLIE ROBERTS**

No Pain, No Gain?

Evolution has provided us with a nervous system that includes the endorphins, molecules that serve to reduce pain. Their evolutionary function is obvious (imagine a wounded hominid trying to escape a saber-toothed tiger). The evolutionary function of a system that enhances pain is less clear. Yet University of California at San Francisco researchers claim to have discovered just such a system, which, they propose, acts as a counterweight to the neurons that release endorphins.

These findings remain controversial, but if they are confirmed, they could have important implications for the treatment of drug addiction as well as for therapy in cases of chronic pain.

Howard Fields, leader of the research team, and his colleagues postulated the existence of the pain-enhancing system after studying the effects of morphine and induced morphine withdrawal on two sets of nerve cells in rats. Both are in the rostral ventromedial medulla, a brain region involved in pain modulation. One set is called "off cells," because their activity seems to shut off the experience of pain, possibly through the release of endorphins. The other set, which Fields dubbed "on cells," is active when rats respond to painful stimuli.



Painful discussion. *Howard Fields with Michael Rowbotham of the UCSF Pain Management Center.*

The San Francisco group reports in an upcoming issue of *Somatosensory and Motor Research* that in rats that had been lightly anesthetized, then injected with morphine, the soothing off cells were active but the pain-enhancing on cells were silent. In this state the rats did not respond to a mildly painful heat stimulus.

After morphine withdrawal was induced, however, the rats responded rapidly to the same type of stimulus, suggesting the presence of the hyperalgesia (increased sensitivity to pain) that is often reported in drug addicts going through withdrawal. During withdrawal, the soothing off cells were silent, while the on cells were active—and the higher the level of on cell activity, the faster the animal responded to the painful stimulus.

Fields and his colleagues were faced with the task of showing that the rapid response was due to on cell activity rather than simply to lack of activity on the part of the off cells. To do so, they inactivated the on cells that ordinarily responded during withdrawal. When those cells were put out of commission, the animals responded only slowly to the heat stimulus. According to Fields, this implies that the rapid reaction in withdrawal is due to "to some active process going on in the inactivated area," namely the firing of pain-enhancing on cells.

Some researchers think Fields has gone far beyond his data in extending his observations to propose a counterpart to the endorphin system. Several other labs have reported the existence of on cells, but just what role those cells play in the transmission of pain is the subject of a wide open debate.

"This stuff is so new you can't make a judgment about it," says Kenneth Casey, a neurophysiologist at the University of Michigan. Casey adds that the idea of a system that amplifies pain is a solid one, but "it is not clear that it is the on-off cells doing it."

Among those who have observed the on cells are Michael Behbehani, a neurophysiologist from the University of Cincinnati, and J. Peter Rosenfeld, a physiological psychologist from Northwestern University. Yet even they are not convinced that the existence of those cells alone explains pain-enhancing effects. "The story of the on-off cells is pretty clear," says Behbehani, "but there is some disagreement that it is as clear-cut as Howard Fields says it is."

Yet another reservation offered by some researchers is that Fields is observing a motor response rather than a sensory one. "He is looking at the spinal reflex," says Herbert Proudfit, a pharmacologist at the University of Illinois. "But I don't know what that says about the experience of pain in humans."

Undaunted, Fields has used his observations to propose a model of drug addiction in which morphine stimulates off cells, whose action is counterbalanced by increased on cell activity. On cell activity could lead to hyperresponsiveness to pain. As long as drug levels in the brain are high, the pain would be masked by the off cells. But as the drug levels decrease, sensitivity to pain would increase and the addict would need a new dose. Hence reducing the activity of on cells might reduce sensitivity to pain and help wean drug addicts from drugs. Chronic pain patients might also benefit if an on cell neurotransmitter could be identified and blocked.

It may be premature to ask whether there is an evolutionary rationale for a pain-enhancing system, but Fields offers a couple of "wild speculations." First, in an emergency, the body might need a way to override the pain-soothing effect of the endorphins. Second, "there is always going to be an evolutionary advantage to shortening reaction time," says Fields, giving the example of touching a hot skillet: pain enhancement could make it possible to pull a hand away before it gets burned.

■ **MARGUERITE HOLLOWAY**

Marguerite Holloway is a science writer based in New York.