Jeanloz sees no signs of such problems. As best as he and Li can tell by inspecting the lasered sample before conductivity measurements are made, the starting material is converted to mantle minerals right up to the electrode, but the electrode has not reacted with it. If asked what the problem might be, Jeanloz speculates that perhaps the Paris group's low-iron samples have some sort of contamination that increases conductivity.

Conductivity work by others has begun at lower temperatures and pressures that can be extrapolated to deep-Earth conditions, but results from these tests haven't changed the minds of either the Paris or Berkeley researchers. Wood and Johann Nell of Bristol have measured the conductivity of magnesiowüstite (which probably controls mantle conductivity) and find "excellent agreement with Poirier's data," according to Wood. Jeanloz, however, cites early work by Ho Kwang Mao and Peter Bell of the Geophysical Laboratory using an external furnace for final heating, as the French group does, that shows "good agreement" with his results. The decisive experiment, it would seem, has yet to be performed.

While the question of mantle conductivity persists, other disputes over results from the diamond cell rage on. The melting point of iron under lower mantle conditions ranges over 1000°C depending on who is doing the experiment, muddling estimates of the heat coming from the core and the temperature of the lower mantle. That in turn bears on whether the lower mantle is particularly hot, as required by a layered mantle, or is mixed with the colder upper mantle.

Removing mantle samples synthesized in diamond cells for further analysis has led to divergent results as well. Measurements of the expansion of perovskite with increasing temperature are central to the question of whether the lower mantle is dense enough to resist mixing with the rest of the mantle, but results have yet to converge (*Science*, 25 January, p. 382). The problem may be the instability of perovskite at pressures below those of the diamond cell. Even the location of iron atoms added to the crystal structure of perovskite—whether they substitute for silicon or magnesium—is in dispute. The culprit here may be samples containing something other than perovskite.

No matter what side researchers may be on in any given dispute, there is general agreement that the "macho technology" of the diamond cell, as one scientist calls it, needs to be operated under more controlled, reproducible conditions in a number of labs. Jeanloz's solution is simple enough. "What we need are more people doing these experiments." Any takers? ■ RICHARD A. KERR

Is Nitric Oxide the "Retrograde Messenger"?

New data suggest this gas may provide the key synapse-strengthening element in the brain that allows us to learn

NITRIC OXIDE, A SHORT-LIVED, HIGHLY REACTIVE gas, is one of the more bizarre messenger molecules used by cells. Dissolved in the aqueous cellular fluids, it slips right through membranes that would contain other molecules and is so reactive that it disappears within moments of its production. Yet it seems to play an important role in many parts of the body, including the brain. Four years ago it was shown to trigger blood vessel relaxation, and its discovery in the brain the following year left neuroscientists speculating about a number of roles it may play there. Now, in a collection of data that provided some of the hottest news at the neuroscience meeting in New Orleans earlier this month, comes evidence for a particularly exciting role: Nitric oxide may be a key chemical player in the storage of memories in the brain.

"If there is a presynaptic component of learning "then there has got to be a retrograde messenger."

—Charles Stevens

The idea that nitric oxide might be linked to memory storage arose because the molecule seemed perfectly suited to fill a long-vacant role: that of the "retrograde messenger." This messenger is an essential component of a hypothetical feedback loop that is required in one model of how learning may work. In the proposed scheme, a nerve cell on the receiving end of a message would send a "retrograde" messenger back to the sending cell, strengthening the connection between them and contributing to the formation of a long-term memory.

Among the properties that make nitric oxide appealing for such a job are the same ones that make it peculiar. An ability to slip right through cell membranes is a must, since there seems to be no other means of escape from the receiving cell, and a half-life measured in seconds ensures that the messenger's sphere of influence will be small—and precise. Nitric oxide seemed such a natural for the role, says Charles Stevens of the Salk Institute, that some insiders "were accepting that [it] was the retrograde messenger before there was even any evidence for it." Now the evidence is not only coming in, but it's showing up en masse from no fewer than four separate groups. But even this rich confluence of work hasn't removed all doubts, and fans of the hypothesis note that it remains far from established.

The concept of the retrograde messenger grew out of more than two decades of study of a phenomenon called long-term potentiation, or LTP, which seems to be one of the chief means by which memories are stored. LTP is triggered when a neuron receives several simultaneous signals. The signals trigger a class of glutamate receptors, called NMDA receptors, to let calcium into the cell. The calcium causes the synapses that delivered the simultaneous signals to be strengthened. That leads to "potentiation"—a bigger response in the receiving cell the next time signals are sent.

This intriguing feedback is central to some types of learning: Blocking the process, for example, erases spatial memory in rats. And that's why researchers are so eager to understand exactly how it works. Their findings have split the field and fueled a long and lively debate. One camp argues that the potentiation is due to an increase in the sensitivity of the receiving cell. But that view has been slipping out of favor in the last year, since data from both Stevens' lab and Richard Tsien's lab at Stanford suggested that at least some of the strengthening is due to an increase in the amount of neurotransmitter released by the sending cell (see *Science*, 29 June 1990, p. 1603).

If that view is right, it follows that something must carry a message from the postsynaptic (receiving) cell back to the presynaptic (sending) cell, telling the sender to increase its output. "As soon as you believe there is a component of LTP that is presynaptic, then there has got to be a retrograde messenger," says Stevens.

But nitric oxide wasn't the only candidate for this key brain molecule. Another early contender was arachidonic acid, chosen be-

cause it is made in many cell types and passes freely through membranes. Tim Bliss and his colleagues at the National Institute for Medical Research in London reported in 1989 that arachidonic acid did seem to strengthen synapses in the rat brain, but not fast enough to account for LTP. "If it is a retrograde messenger, it is not the messenger that turns on LTP immediately," Bliss says. "We realized that we needed to look for another messenger."

That was in 1989, just about the time John Garthwaite and his colleagues at the University of Liverpool reported that cultured brain cells make nitric oxide when stimulated with NMDA. Garthwaite suggested that nitric oxide might be the elusive retrograde messenger, but experiments by several labs provided little support, and nitric oxide passed out of the limelight until last spring, when Soloman Snyder's group at Johns Hopkins University cloned the nitric-oxide producing enzyme, NO synthase, and found that it was abundant in some parts of the brain (see *Science*, 28 June, p. 1788) and seems to participate in another NMDA-receptor-linked event, excitotoxicity, in which neurons die from overstimulation.

But while Snyder's work was in progress, the idea of nitric oxide as the retrograde messenger had merely stepped offstage for a while—and other labs were busily looking for a way to test that hypothesis. Now four of those groups are reporting evidence that it may be true. The first results were published several months ago, but it was the wealth of fresh data presented in New Orleans that has fueled excitement throughout the community. The first evidence came from a team headed by Georg Böhme, at the Centre de Recherches de Vitry-Alfortville, in Vitry-sur-Seine, France. They reported several months ago in the *European Journal of Pharmacology* that inhibitors of NO synthase block LTP in slices of rat brain. They also found that sodium nitroprusside, a chemical that releases nitric oxide, strengthens synapses in a manner resembling LTP.

At the neuroscience meeting, Daniel Madison and Erin Schuman of Stanford and Eric Kandel, Thomas O'Dell, Robert Hawkins, and Ottavio Arancio of Columbia confirmed the inhibitor findings of the French group and took the story several steps further. Both groups have papers in press—the Kandel team's in the *Proceedings of the National Academy of Sciences*, and Schuman and Madison in *Science*. They both found that they could block LTP not only with inhibitors of NO synthase but also by infusing the brain slices with hemoglobin, which binds nitric oxide. "Hemoglobin is this big protein that can't pass into cells," says O'Dell. That suggests the nitric oxide must diffuse out of cells to have its effect, evidence that it is an extracellular—and possibly retrograde—messenger.

Schuman and Madison found further evidence that the nitric oxide can travel between cells to exert its effects: Inducing LTP in one synapse can strengthen uninduced synapses nearby. "Our hypothesis is that nitric oxide is able to leak over from the neighboring cells," Madison explains.

The fourth team, Paul Chapman, Jane Haley, and George Wilcox of the University of Minnesota, has results in press in *Neuron* that confirm the inhibitor and hemoglobin studies of the Madison and Kandel labs. And in the kind of leapfrogging that characterizes this fast-moving field, they have taken yet another step—into living animals. They have preliminary findings that rats injected with inhibitors of NO synthase lose their ability to learn spatial tasks.

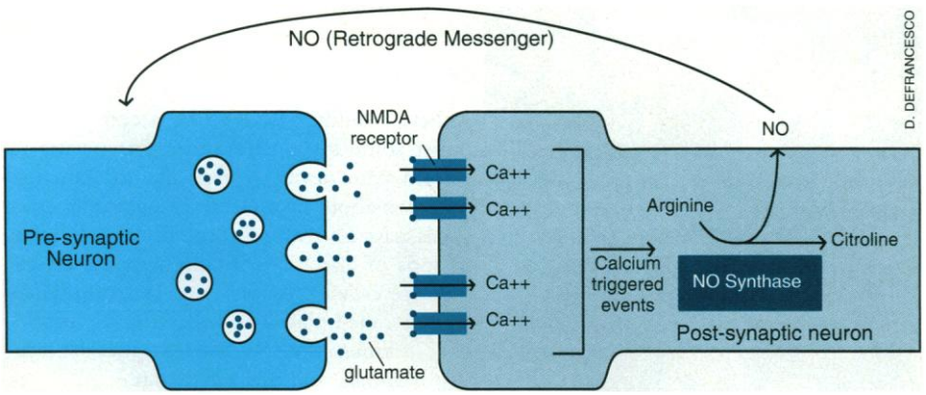
All this adds up to a fair amount of evidence pointing toward nitric oxide as the retrograde messenger. But the case isn't closed yet. One problem with all these experiments, says Hopkins' Snyder, is that they use inhibitory drugs to make their point. "All drugs do lots of things," he says, and the inhibitors could be having effects on something besides NO synthase. The most trustworthy experiment, Snyder and others agree, would be to show that application of nitric oxide itself to cells can strengthen synapses. But with a half-life of 5 seconds, nitric oxide is too short-lived to diffuse effectively into the brain slices in which LTP experiments are done. The French team's approach of using nitroprusside, which is longer-lived, is problematic due to the chemical's side effects.

The Kandel team tried a different tack—applying nitric oxide to cultured neurons. They saw an increase in the spontaneous release of neurotransmitter—a phenomenon also caused by conditions that trigger LTP. That's an "interesting observation," says Stevens, but he warns that the increase could be due to causes unrelated to LTP.

Looming over the whole debate about how best to test the nitric oxide hypothesis is one nagging worry: The enzyme that makes nitric oxide hasn't been found in the appropriate postsynaptic neurons, called pyramidal cells. If nitric oxide is required for LTP, "you would think [it] should be made by the pyramidal cells," says Snyder. Indeed, Madison and Kandel concede that the apparent absence of the enzyme in the pyramidal cells is their biggest worry.

In an interview last week, Snyder hinted at some new, unpublished results from his lab that may put those fears to rest. Postdoc David Bredt recently found that pyramidal cells stain with a dye that has been shown by Snyder's team to be selective for neurons that contain NO synthase. "It is conceivable that there is another NO synthase there," says Snyder, one that doesn't cross-react with his lab's probes. "It's still pure speculation," Snyder adds, as it is also possible that an unrelated enzyme could cause the staining. Nevertheless he says his group is currently trying to clone genes for other forms of the enzyme.

As this work proceeds, those in the field are trying to maintain an appropriate balance between excitement and caution. Even if nitric oxide does turn out to be involved in LTP, that doesn't mean that it is necessarily the retrograde messenger, warns Minnesota's Chapman. "It certainly has the properties one would look for in the retrograde signaller, but...its targets could [also] be other sites on the same postsynaptic cell, or on neighboring postsynaptic cells, or on glial (non-neuronal) cells," he says. "It's certainly very fascinating," adds Bliss, "but still an emerging story." As the story unfolds, the level of fascination will no doubt grow, since what is at stake is no less than the answer to a question that has intrigued human beings since the first questions were posed: How do we remember? ■ MARCIA BARINAGA



Retrograde hypothesis. *Nitric oxide made by the post-synaptic neuron may feed back to the pre-synaptic neuron, telling it to increase its output of neurotransmitters.*