demanding standard." Everyone seems to concede that point, but there is no agreement on just how demanding a performance standard should be. Landsea and Knaff offer an empirical model of their own—dubbed the El Niño–Southern Oscillation Climatology and Persistence (ENSO-CLIPER) model—as a reasonable benchmark. Developing ENSO-CLIPER took the two of them just a few weeks, Landsea says, and it runs on a workstation in about a microsecond. "If you can't do better than ENSO-CLIPER," he says, "the state of El Niño forecasting is still pretty primitive." Indeed, none of the 12 models tested—six dynamical and six empirical—beat it when forecasting 8 months ahead, and only two empirical models and one dynamical model improved on it out to 11 months and longer, the dynamical model just barely.

The bottom line. An El Niño far stronger than forecast wreaked havoc in Peru.

The reception for the models' regrading is mixed. "I think it's fair," says meteorologist Stefan Hastenrath of the University of Wisconsin, Madison, who forecasts climate in drought-prone northeast Brazil but does not forecast El Niños. "It has to be a little more demanding. I don't think the profession, much less the public, is served by overblown claims." Huug van den Dool, who supervises NCEP's long-range U.S. climate forecasts at the Climate Prediction Center (CPC) in Camp Springs, also thinks "it was an overstated conclusion that the big models were scoring big. [Landsea and Knaff] upped the bar a little, which I sympathize with."

Meteorologist Anthony Barnston of Columbia University's International Research Institute for Climate Prediction in Palisades, New York, (who was until recently at CPC) agrees that "we don't have a whole lot to crow about yet concerning dynamical models," but he thinks comparing them to ENSO-CLIPER "is a little bit too harsh," pointing out that ENSO-CLIPER is relatively sophisticated for an empirical model. Vernon Kousky of CPC, who produces official El Niño advisories, also sees ENSO-CLIPER as too high a standard. The complex dynamical models "are marginally useful," he says. "They help confirm what we're seeing. We hope they will be better in the future."

The future is where modelers are now looking. "Empirical prediction is a dead end," says dynamical modeler J. Shukla of the Center for Ocean-Land-Atmosphere Studies in Calverton, Maryland, whereas "dynamical prediction has a lot of future." Empirical models will get only marginally better as decades of El Niño history accumulate, he says, whereas faster computers, better observations, and more complete models will surely advance dynamical models more rapidly. Adds Nicholls: Dynamical models "will only improve from here."

–RICHARD A. KERR

NEUROSCIENCE

New Brain Cells Prompt New Theory of Depression

Growing evidence from laboratory and animal experiments and brain imaging suggests that a slowdown in brain cell growth may be linked to depression

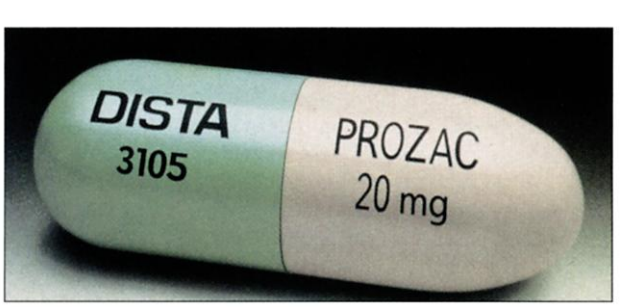
Depression can be a crippling disease. Its sufferers become trapped in a cycle of exhausting gloom, in which even eating seems like a chore. Drugs such as fluoxetine (Prozac) have helped millions, but patients are notoriously susceptible to relapses, and often the symptoms worsen with each episode. No one knows what causes depression, although many neuroscientists blame an imbalance of brain chemicals, so-called neurotransmitters, especially those that affect the brain's pleasure responses.

Now a few neuroscientists are converging on a radical, but complementary, theory: that depression may be caused by a lack of new cell growth in the brain. Even a few years ago, that notion, now being promoted by neuroscientist Barry Jacobs of Princeton University, among others, would have been met with ridicule. And indeed, it remains highly speculative today. But the recent discovery that the brain keeps producing neurons into adulthood (*Science*, 27 March 1998, p. 2041) has given it at least one leg to stand on.

Work by several neuroscientists over the past 2 years has shown that growth of new cells in the adult human brain occurs in an area called the hippocampus, best known for its role in learning and memory but also a suspect in mood disorders. And a different line of research has recently revealed that the hippocampus is smaller than normal in many depressed patients. What's more, several of the most effective antidepressants seem to increase brain cell growth, according to animal experiments and some preliminary observations in people.

Put those insights together, says Jacobs, and it starts to look as if disruptions in the cycle of new brain cell growth might be a primary cause of depression. Others say that although a lack of new cells may not cause the sleep disturbances, lack of appetite, and feelings of overwhelming sadness that characterize the disease, the evidence is persuasive that the two processes are linked. "There has been no convincing biological theory for depression," says Jacobs. And the idea that waxing and waning patterns of brain cell growth might account for cycles of depression "could explain at least as much of the biological data as anything else out there."

Those biological data come from several sources. Scientists studying depression have been stymied for years because no one could find any obvious changes in the brains of depressed patients. "We don't have the luxury of knowing where we ought to be looking" for damage, says Helen Mayberg, a neurologist at the University of Toronto. "We have no plaque or tangle or Lewey



Secret of a best seller? Prozac-like drugs encourage brain cell growth in animals.

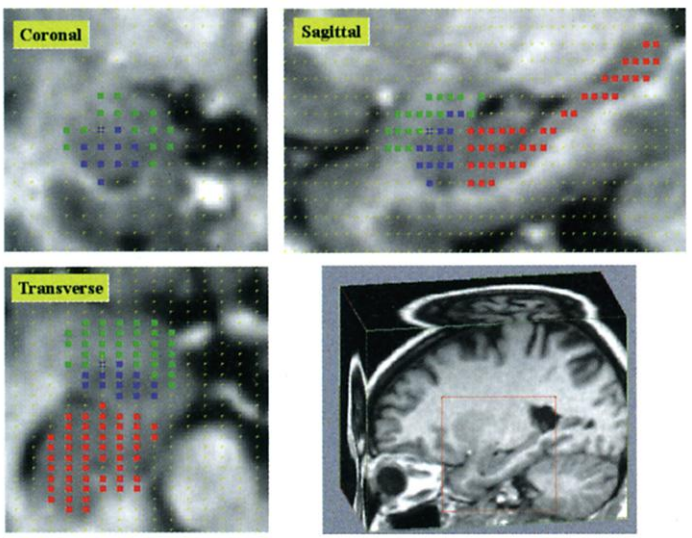
CREDITS: (TOP TO BOTTOM) O. PAREDES/AP PHOTO; ELI LILLY CO.

body or spongiform degeneration," as in other neurological diseases. Many scientists have assumed that depression results from changes on a molecular scale—an imbalance in chemical messengers that communicate among brain cells.

In 1996, Yvette Sheline of Washington University School of Medicine in St. Louis and her colleagues reported evidence that changes may be occurring on a larger scale as well. As reported in the *Proceedings of the National Academy of Sciences* (*PNAS*), their magnetic resonance imaging (MRI) studies revealed that the hippocampi of 10 depressed patients were on average 12% to 15% smaller than those of controls of the same age, height, level of education, and handedness. At least two follow-up studies in the past year, involving 40 patients and matched controls, have found consistent results. "It is absolutely clear that really prolonged major depression is associated with loss of hippocampal volume," says Stanford University neuroscientist Robert Sapolsky.

Examinations of the brains of deceased patients who had suffered from depression suggest that a similar phenomenon may occur in other parts of the brain as well, according to work by Grazyna Rajkowska, a neuroscientist at the University of Mississippi Medical Center in Jackson. She and her colleagues reported in *Biological Psychiatry* last year that the brains of 23 people who suffered from either major depression or bipolar disorder—alternating cycles of mania and depression—have smaller and less densely packed neurons and fewer glial cells (a type of neuronal support cell) in the prefrontal cortex, an area of the brain thought to be involved in emotion and cognition.

Many neuroscientists suspect that these cell losses in both the hippocampus and prefrontal cortex are related to the effects of stress on the brain. Stress is a frequent trigger for depression, and evidence has been building for years that stress, whether from acute trauma such as a car accident or chronic pressure on the job, is not good for brain cells. Stress causes an increase in hormones called glucocorticoids, which raise the heart rate, boost the immune system, and suppress energy-intensive systems such as reproduction. Such changes are clearly advantageous for a mammal trying to escape from a predator but are not beneficial over, say, 30 years of chronic stress, says Sapolsky. Decades of animal studies have shown that stress-related glucocorticoids cause cell atrophy and death in certain areas of the hippocampus. More recent studies, notes Jacobs, suggest that stress and glucocorticoids inhibit new cell growth in the hippocampus as well. Specifically, Princeton University neuroscientist Elizabeth Gould, using a chemical called BrdU that marks newly divided cells, has found that exposing monkeys to chronic stress blocks the new neuron growth found in control animals.



CREDIT: Y. SHELINE/WASHINGTON UNIVERSITY SCHOOL OF MEDICINE

Growing evidence. Some neuroscientists suspect that cell growth and death in the hippocampus (colored red) may affect depression.

Intriguingly, several effective depression fighters may have the opposite effect. Prozac, for example, increases the amount of serotonin in the gaps between brain cells, and serotonin, Jacobs notes, is a well-known promoter of cell growth during fetal development. It seems to have similar effects in adult animals as well. In work in press at the *Journal of Neuroscience*, neuroscientist Ronald Duman of Yale University and his colleagues have found that rodents given any of three different classes of antidepressant drugs (including Prozac) or electroshock therapy all have significantly more newly divided cells in the hippocampus. This suggests, Duman says, that increased neurogenesis is a common effect of antidepressant treatment.

A more natural antidepressant—exercise—may also encourage brain cell growth. Exercise has been shown to increase the level of serotonin in the brain and can often help patients shake off mild depressive symptoms. Neuroscientist Fred Gage of the Salk Institute for Biological Studies in La Jolla, California, and his colleagues reported last year in *PNAS* that rodents with access to a running wheel (on which they ran an average of nearly 5 kilometers per day for several months) had more than twice as many cells marked with BrdU as did mice with no running wheel.

The mood stabilizer lithium also seems to trigger growth of brain cells in humans. In work published last week in *The Lancet*, Husseini Manji of Wayne State University School of Medicine in Detroit and his colleagues reported that patients who suffer from bipolar disorder experienced a slight but measurable increase in brain gray matter volume after 4 weeks on lithium, as detected by MRI. The team is now trying to determine whether the increase is concentrated in a particular area of the brain.

All these results are suggestive, agrees Mayberg, but she is not yet convinced. "Do I think failure of neurogenesis is the cause of depression? I don't think there's any direct evidence to support that," she says. "We have several intriguing coincidences. The task now is to see whether they're causally linked or working in parallel with each other." As several scientists point out, there is little evidence that the hippocampus is a primary player in mood. And the shrinking observed in the hippocampus during depression may be a sort of collateral damage rather than a cause of depression, says Mayberg.

But Jacobs thinks that the connection is more direct. Depressed patients often report memory problems, he notes, and one of the first signs of Alzheimer's disease—which attacks the hippocampus—is depression. There are known links between the hippocampus and the amygdala and the prefrontal cortex, the two regions of the brain that are thought to control emotion and have long been suspected in depression. It's possible, he says, that a dearth of new neurons—triggered by a stress-induced spike in glucocorticoids—could disrupt those connections and lead to depression. But he agrees that cause and effect are difficult to separate.

"It is all highly speculative, and yet it is based on some pretty interesting observations," says neuroscientist Bruce McEwen of Rockefeller University in New York City, who has studied the effects of stress on the hippocampus. "It's a fascinating possibility that in some of these psychiatric disorders, you might be able to rescue the brain" by designing new drugs to encourage the regrowth of lost neurons. But it will take a lot more basic research—and a lot more debate—before doctors will be able to attempt such a rescue.

—GRETCHEN VOGEL