

SIXTY-ONE YEARS AGO, in a Staten Island hospital complex, doctors testing a new drug on tuberculosis patients observed a strange side effect: While the drug, known as an MAO inhibitor, was no miracle cure for the hospital's debilitated residents, it seemed to have an energizing, almost magical effect on their mood. One report noted that patients were "dancing in the halls tho' there were holes in their lungs."

The early history of what would come to be known as antidepressants is dominated by such stories of serendipity, and many pharmaceuticals prescribed for depression today are, by and large, descendants of these decades-old happy accidents. Newer drugs replaced old ones because they were safer, not more effective, explains William Potter, senior advisor to the director of the National Institute of Mental Health.

Now, as psychiatry inches toward a more refined understanding of the neurochem-

istry of depression, the course of drug discovery is changing. Roughly half of all clinically depressed patients fail to respond to available antidepressants—all of which target one neurotransmitter or another—and the lack of relief provides an important clue: Depression is not a monolithic disease, but a set of symptoms that can spring from a variety of causes. A treatment may work, scientists are finding, only when it is tailored to the type of depression found in a particular patient.

"Today's antidepressants seem to change the brain only slowly and indirectly," explains Olivier Berton, a neuroscientist at the University of Pennsylvania. Because doctors knew that some early antidepressants boosted serotonin, they hypothesized that the neurotransmitter may be linked to depression. But a person's outlook doesn't start to shift until a month after beginning serotonin-altering drugs like Prozac, even when they work. The delay suggests another process is involved.

Enter neural plasticity. Researchers have long observed the growth of new brain cells following antidepressant use. It may be that the sluggishness and stunted outlook that characterize depression at



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HOW THE FUTURE OF ANTIDEPRESSANTS IS DIVERGING FROM ITS SCATTERSHOT PAST. **by Amy Maxmen**

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bottom reflect a failure to generate new nerve cells, and yet the role of serotonin in neurogenesis is indirect, at best. The chain of reactions that link them remains largely unknown.

Recently, however, new research has begun to point to substances in the brain that act closer to the scene of neurogenesis, suggesting more logical drug targets. In June, researchers reported one important step in *Nature Medicine*. After mice took Prozac-like antidepressants, the levels of a fat molecule in the brain called ceramide plummeted. Ceramide normally stalls brain cell growth; by blocking ceramide, the drugs presumably jump-started neural regeneration. New drugs that inhibit ceramide could work faster than drugs that act on serotonin because they are more directly linked to neurogenesis, the authors suggest.

Others are entirely abandoning approaches related to serotonin. Researchers know that individuals who are obese or who take immune-altering medications may not respond to antidepressants. What such people have in common is chronic inflammation, explains Emory University psychiatrist Andrew Miller. He believes that inflammation is a particular path to depression that stems from a beneficial adaptation. Depression is often characterized by what are called sickness behaviors—withdrawal from others, loss of appetite, lethargy. These are typical responses to physical injury and infection, and—in the short term—may foster recovery. Such responses become a problem, Miller says, only when the inflammation is chronic. Then the depressive behavior endures.

Earlier this year, Miller investigated whether a drug currently used to tame inflammation in rheumatoid arthritis might help people who found no relief in antidepressants and failed to respond to talk therapy. The drug indeed helped depressed patients with excess inflammation and did little for those without.

Depression that stems from trauma can also be especially resistant to con-

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ventional antidepressants. Scientists believe that trauma may cause epigenetic changes—lastingly modifying molecules that turn mood- and behavior-related genes on or off. The upshot may be that those who experience trauma early in life may be unable to bounce back from later hardship the way other people can.

Penn's Berton recently studied trauma-induced depression in mice. Bullying—one type of trauma, easily modeled in animals—typically causes a meeker mouse to act asocial, refrain from favored foods, and scare easily—behaviors analogous to those of depressed humans. But when Berton blocked a particular protein in the bullied mice, they showed no such symptoms. Berton is now collaborating with a pharmaceutical company to develop a drug that blocks the same protein. Other researchers are also experimenting with drugs that block different proteins that may act as on/off switches for the genes affected by trauma.

“For a long time, people focused only on serotonin, and that inhibited new avenues of investigation,” Berton says. Now that the variety of mechanisms underlying depression is becoming clearer, a one-size-fits-all approach may soon be a thing of the past.