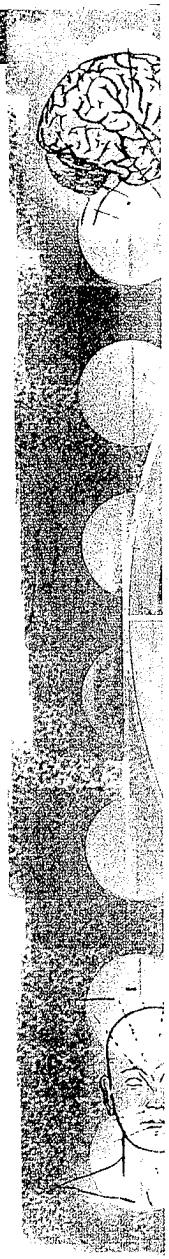
FROM HARVARD MEDICAL SCHOOL

Depression may look like a single disease, but the underlying causes vary, and so do the ideal treatments. BY MICHAEL CRAIG MILLER, M.D.

Managing Every Shade Of Blue

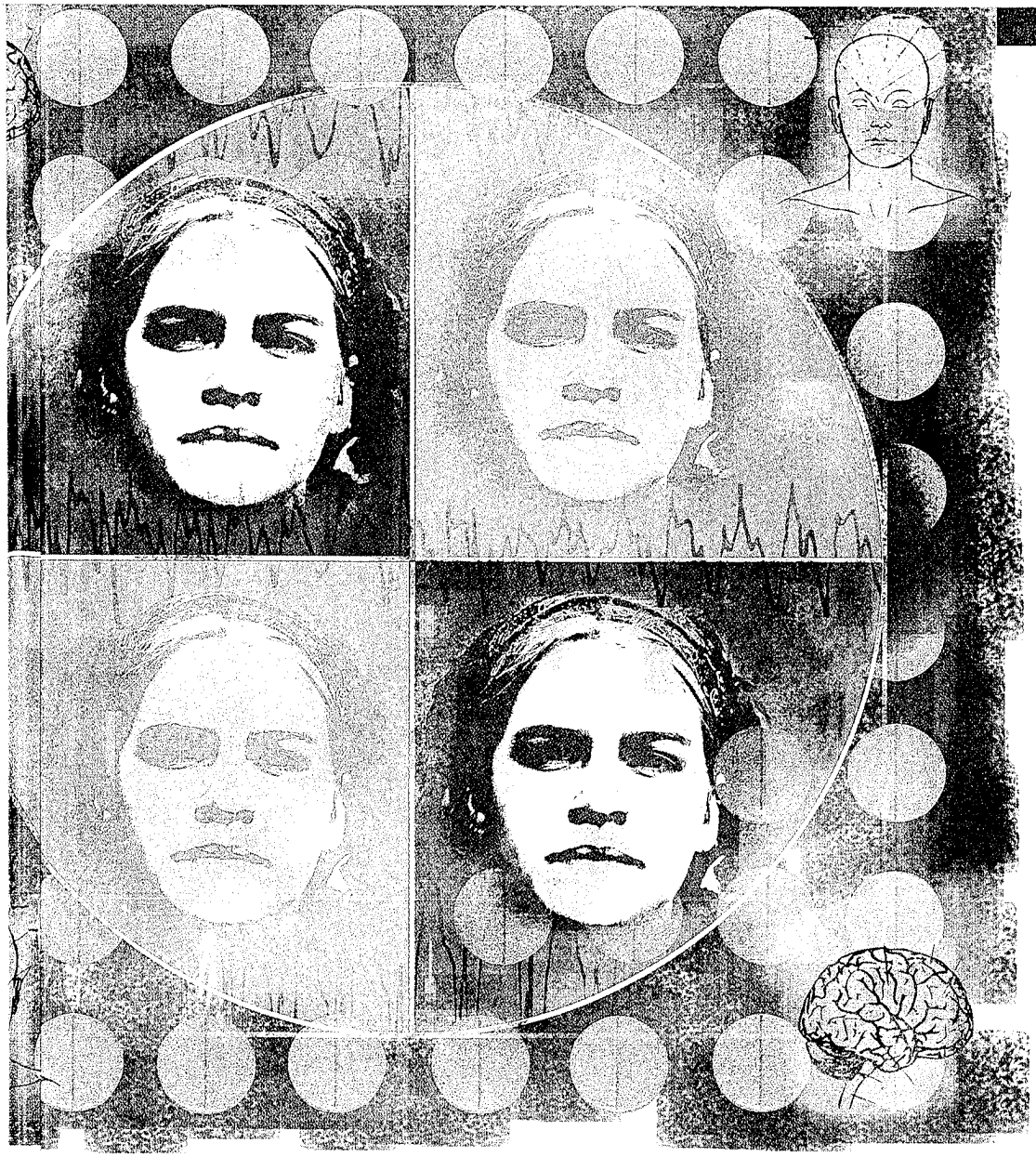


IMAGINE BEN AND RON, TWO MEN IN THEIR 50s who met in law school and have been friends ever since. They have a weekly tennis date, and their families sometimes vacation together. Both are successful litigators, but both have grown depressed in midlife, and their symptoms are out of the same textbook. The smallest problems irritate them. They lie awake worrying over the day's events. Nothing gives them pleasure. Everything feels like an effort. Ben tries an antidepressant on his doctor's advice, and within weeks the weather clears. His energy returns and he feels less irritable. He sleeps better, too. But when Ron tries the same pill, all he gets is nausea and a headache. His internist refers him to a psychiatrist, who prescribes three different drugs before finding one that offers any relief.

How could two such similar men have such different outcomes? Because Ben and Ron don't really have the same illness. Depressed people may share a common cluster of symptoms, but that doesn't mean they share the same internal abnormalities. Mood is affected by dozens of genes. And as our genetic endowments differ, so do our depressions. Researchers are now pinpointing the genes involved in the condition and elucidating their functions. If this work fulfills its promise, future patients will receive different medicines for different types of depression—and doctors may monitor their responses with molecular tests as well as office visits. That new era is still years from the clinic, but the science is evolving rapidly.

The most immediate priority is to target today's drugs more effectively. Researchers are pursuing that goal one "snip" at a time. Those snips, or SNPs, are single nucleotide polymorphisms—small variations in the DNA sequence that can have big consequences. An example is the SNP code-named G1463A. People with G1463A produce very low levels of serotonin, a neurotransmitter that helps regulate mood. This aberrant SNP shows up more often in people who have major depressive disorder than in those who don't. And depressed people with G1463A are relatively resistant to antidepressants like Prozac and Zoloft (the so-called SSRIs), which act on serotonin. If Ron's doctor could have tested him for G1463A—a feat that isn't practical today but may be tomorrow—the result might have signaled the need for a substitute antidepressant.

ILLUSTRATION BY PLINKO FOR NEWSWEE



Another goal is to understand how, exactly, biology makes certain people vulnerable to depression. The reigning theory holds that genes affect our risk of depression by shaping our responses to stress. Studies are now confirming that phenomenon and illuminating the mechanisms involved. Two years ago researchers found that people were more likely to become depressed in response to stress if they have a particular variant of a gene that influences the movement of serotonin across nerve-cell membranes. Subsequent studies have linked the same gene to alcohol abuse, anxiety disorders and resistance to antidepressants. It turns out that the amygdala, the part of the brain that reacts to threat, is more reactive in people with this gene.

A third challenge is to find better, faster ways of gauging depressed patients' responses to treatment. When you take a cholesterol-lowering drug, your doctor can measure your progress by taking a simple blood test. We can't yet measure a person's response to an antidepressant that way. But what scientists have discovered about a protein called beta-arrestin-1 hints at what may soon be possible. This protein interacts with neurotransmitter receptors found in the brain and in circulating blood cells. In a recent study, antidepressants boosted beta-arrestin-1 levels in the brains of laboratory rats. In a human study, the same scientists found that beta-arrestin-1 levels were low in the blood cells of depressed patients but that levels returned to normal after treatment with an antidepressant. As we learn more about this protein, it could become an important diagnostic tool.

The move toward personalized psychiatry isn't confined to the laboratory. While lab scientists analyze genes and proteins, clinical researchers are beginning to classify patients according to their most prominent symptoms. The inability to experience pleasure may be one kind of depression, preoccupation with death another. They are also searching for other markers of depression, such as changes in the level of stress hormones or a change in patterns of sleep. Any scheme that separates depression into distinct shades of blue could help doctors and patients make better treatment decisions.

The ultimate ambition is nothing less than learning how the brain regulates mood. As we unravel the process—linking genes to proteins, and learning how proteins affect nerve circuits and mental function—we will get ever closer to a true understanding of depression. From there it's a short step to imagining treatments that can repair specific links in the chain. Technology alone won't create human fulfillment. No matter how sophisticated the tools and treatments become, good mental-health care is also about helping people cultivate a sense of well-being, durable relationships and satisfying work. Targeted antidepressants will not take the place of support, counseling and psychotherapy. But for the Rons of the world—and there are millions of them—better drugs and diagnostics could be an important first step.

MILLER is editor in chief of the Harvard Mental Health Letter. For related health information, go to health.harvard.edu/newsweek.

Mind Matters

Researchers are now decoding depression at the molecular level. Some new tools:

G1463A

A variation at this point in your DNA sequence causes low levels of serotonin, making you less responsive to drugs like Prozac.

The Stress Gene

People with a particular mutation in the serotonin transporter gene are more likely to become depressed in response to stress.

Beta-Arrestin-1

Depressed patients have unusually low levels of this protein. Measuring it may enable doctors to monitor the effects of treatment.