DEPRESSION:
BEYOND SEROTONIN

New research is challenging the assumption that the world's most common mental ailment is *just* a chemical imbalance in the brain.

By Hara Estroff Marano

> Death was now a daily presence, blowing over me in cold gusts. Mysteriously and in ways that are totally remote from normal experience, the gray drizzle of horror induced by depression takes on the quality of physical pain. But it is not an immediately identifiable pain, like that of a broken limb. It may be more accurate to say that despair, owing to some evil trick played upon the sick brain by the inhabiting psyche, comes to resemble the diabolical discomfort of being imprisoned in a fiercely overheated room. And because no breeze stirs this caldron, because there is no escape from the smothering confinement, it is entirely natural that the victim begins to think ceaselessly of oblivion.
>
> —William Styron

Melancholy is a fertile muse. No sooner had William Styron become the poet laureate of depression after describing his bout with madness in *Darkness Visible* (Random House, 1990) when all manner of confessions followed. Mike Wallace. Art Buchwald. Dick Cavett lined up to disclose their own struggles with the disabling disorder. It quickly became acceptable, even chic, to publicly confide vulnerability to depression.

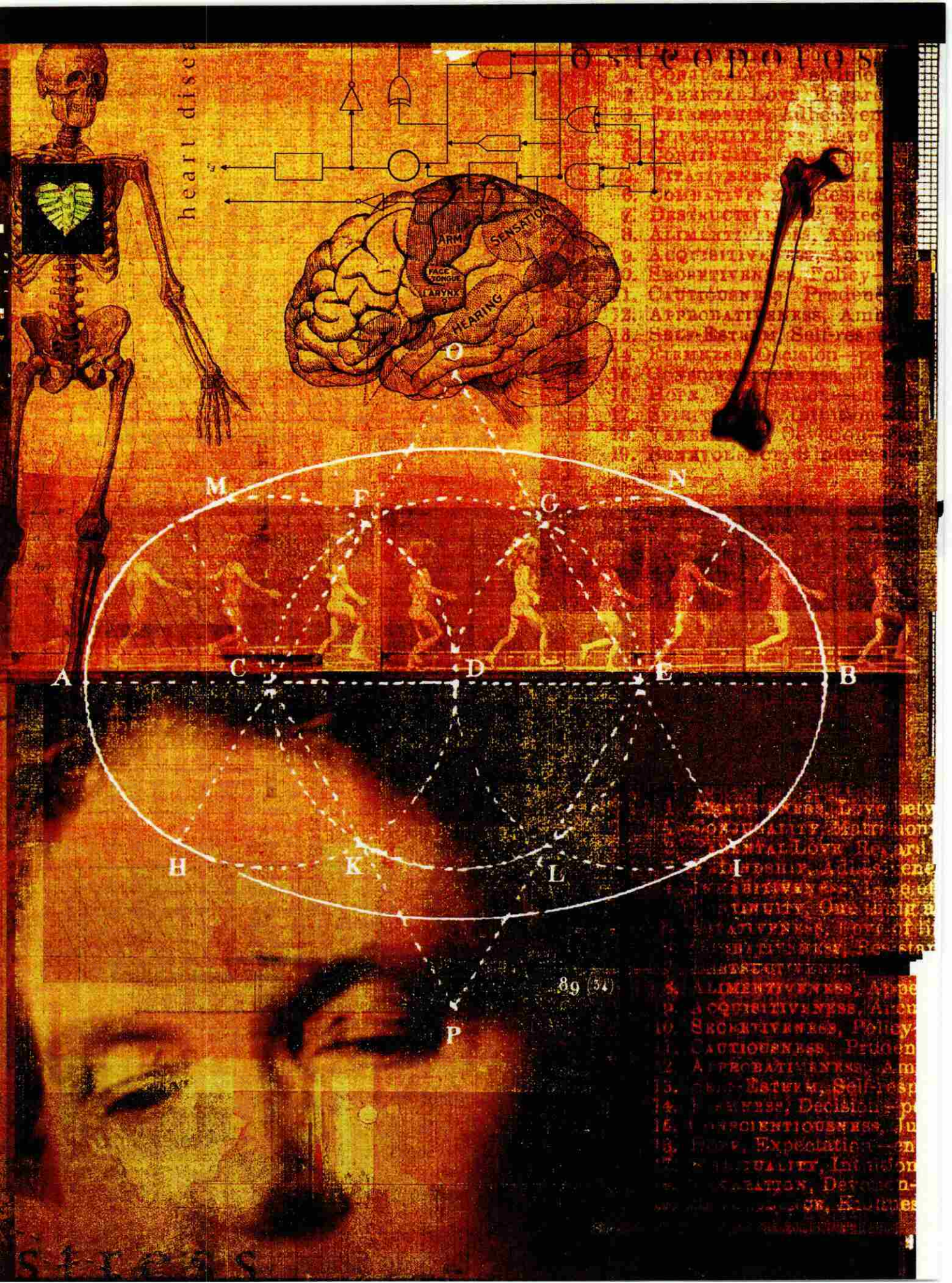
At the same time, the world was being made safe for depression, or at least public revelations of it, by another development, the 1988 advent of the so-called SSRIs—Prozac, Paxil and related drugs believed to specifically combat depression by beefing up serotonin and other neurotransmitters that ferry signals between nerve cells. The wild success of psychiatrist Peter D. Kramer's thoughtful *Listening to Prozac* (Viking, 1993) generated not only new respect for the effectiveness of Prozac but new appreciation of the disorder it was intended to treat. There followed hundreds of new book titles on depression, over 100 on Prozac alone, surely making it the most heralded drug on the planet. Depression chic cannot be dismissed as a passing fad because, it turns out, how the disorder is defined and popularized deeply shapes what patients are willing to do about it.

Despite the flood of Prozac prose, depression itself has remained, as Styron saw it, a mystery. One of science's cruel ironies is that it can explain bizarre rare conditions, but common afflictions like depression—Western countries' second most disabling ailment (after heart disease) and the world's fourth—elude understanding. That, however, is changing.

In the last three years, refined imaging techniques have begun providing an unprecedented look into the neurobiology of depression, showing what goes on in the brains of patients as they process positive and negative experiences. Though in its infancy, the work is already forcing a radically revised view of depression, one that promises new treatments for the future. Among the findings:

- Regarding depression as "just" a chemical imbalance wildly misconstrues

Illustrations by Terry Miura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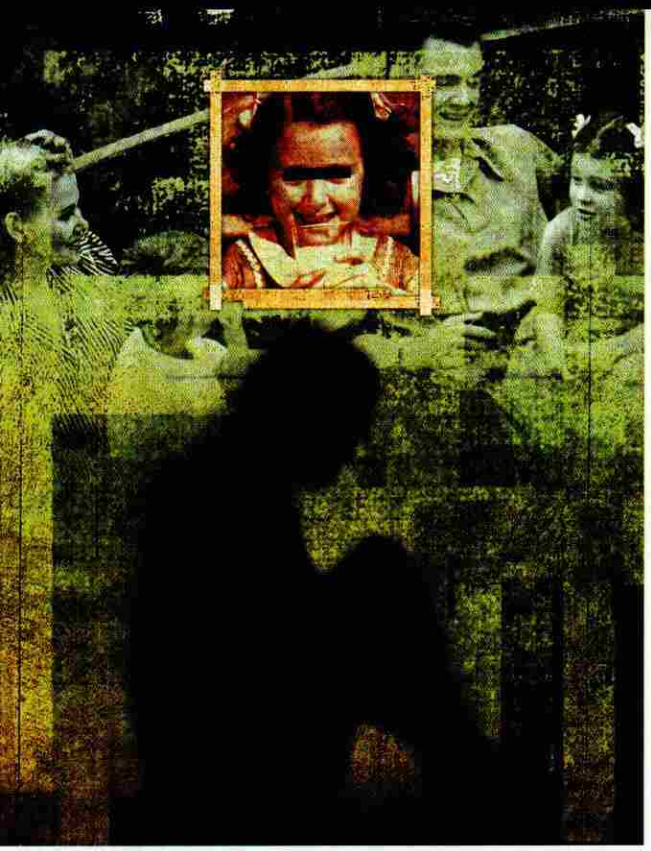


the disorder. "It is not possible to explain either the disease or its treatment based solely on levels of neurotransmitters," says Yale University neurobiologist Ronald Duman, Ph.D.

The newest evidence indicates that recurrent depression is in fact a neurodegenerative disorder, disrupting the structure and function of brain cells, destroying nerve cell connections, even killing certain brain cells, and precipitating cognitive decline. At the very least, depression sets up neural roadblocks to the processing of information and keeps us from responding to life's challenges.

•Human emotions take shape in a neural circuit involving several key brain structures, including the hippocampus, the amygdala, and the prefrontal cortex. In depression, faulty circuitry fails both in generating positive feelings and inhibiting disruptive negative ones.

•Stress-related events may kick off 50% of all depression and early life stress can prime people for later depression. Ongoing research in animals and in people demonstrates that early strain can alter nerve circuits that control emotion, exaggerating later responses to stress and creating the neurochemical and behavioral changes of depression. In other words, the deeper researchers probe the brain, the more they validate the psychoanalytic view that early adverse life events can create adult psychopathology.

•Depression is not just a disorder from the neck up but a disorder involving many body systems. It both leads to heart disease in otherwise healthy adults and magnifies the deadliness of existing cardiac problems. What's more, it accelerates changes in bone mass that lead to osteoporosis. "The lifetime risk of fracture related to depression is substantial," researchers have declared in the *New England Journal of Medicine*.

•Just as nerve cell connections can be destroyed in depression, perhaps they can be rebuilt. The common denominator in effective antidepressant treatments, including electroshock, may be their ability to stimulate the sprouting of neurons in key brain regions, literally the forging of behavioral flexibility. A neurochemical pathway newly identified promises to revolutionize therapy by suggesting ways to do this better and faster.

•The adult brain has a degree of plasticity that is astonishing researchers. "The big news is the structural plasticity of the adult brain, the remodeling of neurons," says neurobiologist Bruce McEwen, Ph.D., of Rockefeller University. "The idea that there are long-lasting, even permanent, changes in structure and function that can affect the way brains process information is the most important part of what we're doing in the lab. We thought that after birth, the brain is a stable organ like a computer that just works away, and no more new nerve cells are produced. The emphasis was on chemical imbalances, as if the circuitry itself was fairly stable. All these changes—cell loss, atrophy of connections—that's very new, and still catching people by surprise."

Uniting Mind and Brain

To understand depression we have to confront the mind/body dilemma head on. Although we often arbitrarily divide the mind from the brain and regard "mental illness" as strictly mental, mood disorders are not disembodied ailments. If depression proves anything, the mind and the brain are one. There are nerve circuits in the brain that color psychological events positively and negatively, that lead us to to see rewards and pleasures or merely emptiness and hopelessness, and then to negotiate the world by engaging it or withdrawing from it.

Such nerve circuits connect widely with other brain areas and they malfunction in depression, spreading the malaise into every fiber of being. What sets the

The Natural History of Depression

Likelihood that a person will develop major depression or dysthymia in his/her lifetime: **6.1%**
Likelihood that a person will suffer some depressive symptoms in his/her lifetime: **23.1%**
Average age of first onset of major depression: **25-29**
Average duration of all depressive episodes: **20 weeks**
Percent of patients who recover within a year after onset of symptoms: **74%**
Likelihood of a second or more episodes of major depression: **80%**
Likelihood of a second or more episodes of minor depression: **100%**
Median number of major depressive episodes during a patient's lifetime: **4**
Percent of patients whose depression takes a chronic unremitting course: **12%**
Incidence of depression in women vs men: **3.62 vs 1.98** per 1000 per year
Female: male ratio of depression incidence in cultures with low rates of alcoholism: **1:1**
Rank of unipolar major depression in the world league of disabling diseases in 1990: **4**
Rank of unipolar major depression among disabling diseases in westernized countries: **2**
Rank of depression among disabling diseases the world over, projected, in 2020: **2**

malfunction in motion may be environmental circumstances, such as childhood neglect, or an internal physical fact, such as a faulty gene controlling a brain enzyme. Or, likely, a mixture of both.

Circuit Riding

Depression appears to hold the very soul hostage, with total lack of energy, disturbed sleep, loss of interest in food and sex, inability to experience pleasure, difficulty concentrating and thinking clearly, impaired short-term memory, self-blame, and inability to see alternatives. But the disorder's full-blown misery arises in just a few distinct centers in the brain. These hubs have discrete channels of communication with each other, their messages sent out over long filamentous arms extending from the cell bodies in one center to those in another.

One seminal spot in the circuitry of depression is the prefrontal cortex (PFC), the brain area just behind the forehead, which acts as the executive branch of emotions. According to Richard Davidson, Ph.D., professor of psychology and psychiatry at the University of Wisconsin, two of the PFC's most important functions are restricted to one side or the other. His studies show that the left side of the PFC is crucial to establishing and maintaining positive feelings, while the right is associated with negative ones. Depressed people appear to have a power failure of the left PFC. The failure shows up both in electrical studies of brain response and PET scans indicating decreased blood flow and metabolism. The depressed just don't activate the machinery to process positive emotions or respond to positive stimuli.

Specifically, the left PFC is instrumental in producing what Davidson calls "pre-goal attainment positive affect," what you and I call eagerness, the emotion that arises as we approach a desired goal. The depressed can't mentally hang on to goals or stay attuned to rewards. Result: lowered capacity for pleasure, lack of motivation, loss of interest.

But the left PFC doesn't just activate positive feelings. Davidson finds that it is also crucial in inhibiting negative emotion that gets in the way of focusing on positive goals. In this, the left PFC draws on its links to the amygdala, an almond-shaped structure in the center of the brain that pumps out negative feelings.

By placing subjects in a functional magnetic resonance imager to measure brain activity while showing them emotionally laden pictures—photographs of starving children, for example—Davidson has graphically confirmed what many scientists have suspected: that the amygdala scans incoming experience for emotional significance, puts a flag on negative feelings such as fear, and sends out notice of threat, information we could not survive without.

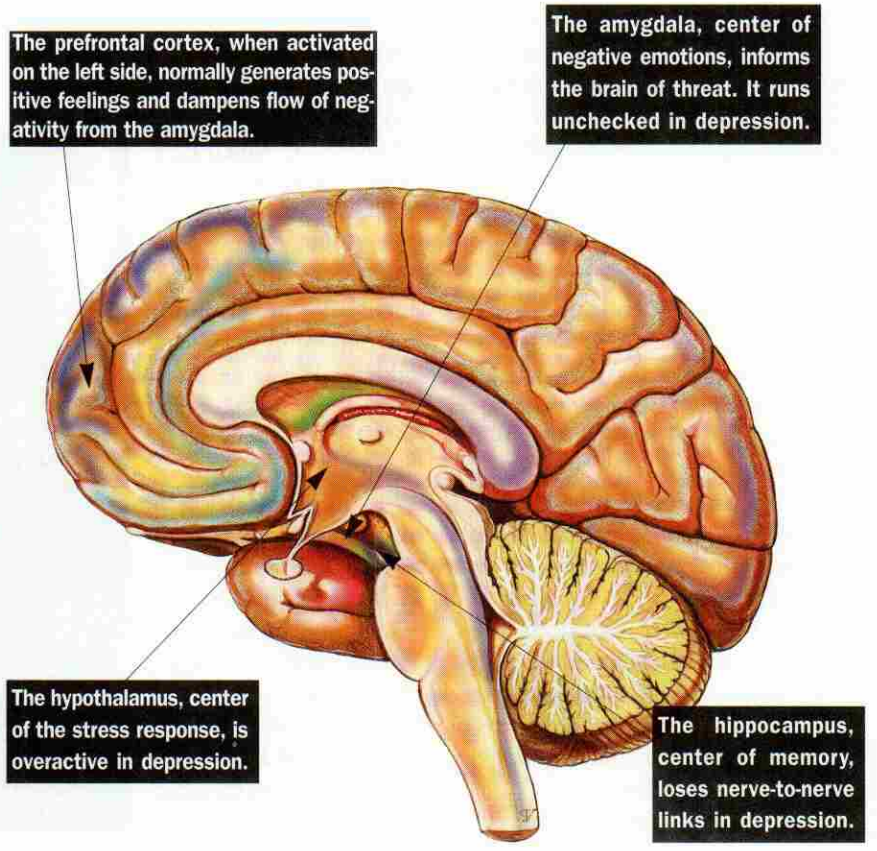
If the PFC masterminds depression by failing to activate, the amygdala controls the severity of depression by its negative output. Along with the University of Pittsburgh's Wayne C. Drevets, M.D., Davidson has found that blood flow in the amygdala is greater the more depressed a person is. Moreover, studies show that the amygdala is highly active during states of helplessness, as when people face an insoluble problem. Amygdala activity also determines how firmly a negative event is held in memory.

Ordinarily, as the left PFC turns on, it simultaneously shuts off the amygdala and dampens the flow of negative emotions from it. But among the depressed, the general failure of activation of the left PFC leaves the amygdala running unchecked, overwhelming them with dread, fear and other negative feelings.

Individuals normally differ in the degrees of neural activation of the left and right sides of the PFC in response to emotional messages. That difference may help account not only for a person's vulnerability to depression, Davidson says, but also for variations in personality. A peppy left PFC underlies extraversion, while a relatively more active right PFC is linked to inhibition and anxiety.

It isn't clear how asymmetries in prefrontal activity get established to begin with. "Although these characteristics of brain function are very stable in adults," Davidson says, "they are much less so in children." That suggests to him that activation levels of this circuit are set early in life, certainly by puberty.

One clue may be that differences in



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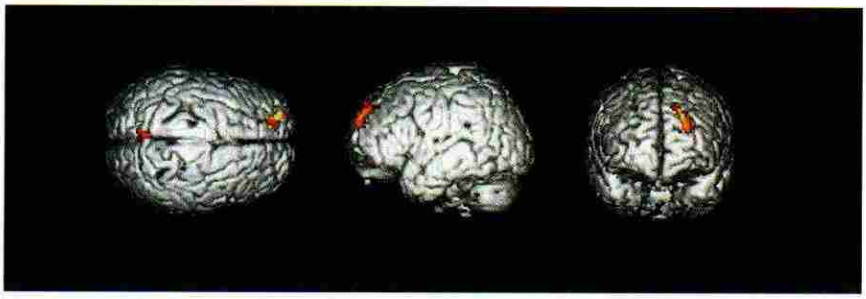

Improved mood is tracked by magnetic resonance imaging of brain. In acute depression (far left), left prefrontal cortex minimally activates in response to emotional pictures. After drug treatment (right), patient experienced symptom remission—and increased activation of left prefrontal cortex.

PFC activation go hand in hand with differences in brain levels of the stress-related hormone cortisol. When the left PFC is highly active, not only do people have a sunny outlook, but levels of cortisol are low. Cortisol patterns suggest that stress had a hand in there somewhere.

No Glee Over Glia

Barely two years ago, Wayne Drevets, then at Washington University, discovered that depressed persons not only have altered PFC activity, but their prefrontal cortex is actually smaller than in the nondepressed. It is one thing to find abnormalities in the way the brains of the depressed function—but *structural* abnormalities? *Anatomical* ones?

Drevets found that depressed patients have a drastically smaller volume of a section of the left PFC that sits about two and a half inches behind the bridge of nose and is called the ventral anterior cingulate. Drevets calls it the subgenual prefrontal cortex because it sits beneath the genua, or knee, of the corpus callossum, the Continental Divide of the brain. The little site was 40% smaller in the depressed.

The subgenual cortex is vastly important: it is one of the few cortical regions connecting to the hypothalamus, a deep-brain structure that instigates the body's stress response. The subgenual cortex also helps orchestrate the body's hormonal response to stressful stimuli.

Taking their cue from Drevets' findings, colleagues at Washington University began searching for what could account for the cortical shrinkage. They examined tissue that, at autopsy, had been collected from the brains of normal individuals and those with bipolar or unipolar depression.

At a recent meeting of the Society of Neuroscience, graduate student Dost Ongur reported startling findings. He had expected to see a decrease in the number of neurons, what he calls "the business end of the brain in terms of processing information and generating actions." Instead he found a dramatic loss in the number of glia, small cells that perform important—maybe critical—housekeeping functions for the more patrician neurons. The loss of glia was seen only in those with a family history of depression.

Glut of Glutamate

The glia are known to nourish neurons by assuring a steady supply of glucose, their preferred food. They also protect neurons by stabilizing levels of the neurotransmitter glutamate. Glutamate is the main transmitter in the cortex that activates cells. But too much glutamate can overstimulate neurons, causing collapse of the branches by which they communicate with other cells.

The glia also play a big role in the development of the serotonin neurotransmitter system, which, everyone now knows, also functions abnormally in depression. "It could be," Drevets says, "that some defect in the neural development of the prefrontal cortex could be the initial abnormality in depression that starts a cascade of changes in other systems."

It may also be that the action of antidepressant drugs on serotonin is less important than their action on glutamate. Researchers know that one effect of antidepressants is to reduce the sensitivity of receptors in the PFC for glutamate. "Suddenly," says Drevets, "that makes sense. Agents that desensitize the frontal cortex to glutamate may be compensating for the loss of glial cells."

Of course, that still leaves the possibility that a serotonin deficit in other parts of the brain could induce other depressive symptoms. But that's exactly the point; not only is serotonin not the whole story of depression, neurotransmitters may not even be the main story.

Changes in the structure of the brain—losses of cells—are relatively permanent types of alteration. So far, there's no evidence that such changes, once they occur (and it's not clear when in the lifetime course of depression they set in) are reversed with drug or other therapy. And

that may account for the propensity of depression to recur. "What's less clear," Drevets says, "is why there are periods when the illness remits, then returns."

Nature, Nurture, Neuron

One of the most debilitating features of depression is the inability of the afflicted to see out of their rut, to imagine alternative ways of being and doing. "In depression," says Ronald Duman, associate professor of psychiatry and pharmacology at Yale, "there's a loss of appropriate adaptability."

Ordinarily, the neurons of the brain have an ability to change and adapt by sprouting new dendritic spines, tiny fibrous protrusions that are the primary receiving end of connections between nerve cells. By literally opening new neural pathways, this sprouting is what allows us to learn and remember, to change our behavior, to meet new challenges, to adapt to new circumstances. Scientists call this capacity neuronal plasticity.

Duman has tracked the inside operations of nerve cells and found evidence that the depressed have a deficit in specific nerve growth factors, the substances that make possible the sprouting of new nerve cell connections. One in particular is brain-derived neurotrophic factor. BDNF strengthens synaptic connections in the hippocampus (a center of learning and memory) and enhances the growth of neurons that respond to serotonin

Duman's studies also show, yet again, that how antidepressant agents are believed to work and what actually accounts for their effectiveness may be two different things. Long-term antidepressant treatments—including electroshock—do increase receptors for serotonin at the cell surface. But, Duman found, they also do something else inside the neuron that may be more important. They kick off a cascade of molecular steps that winds up amplifying a neuron's own production of BDNF—and the sprouting of new connections. Moreover, they do this in parts of the brain that have been linked to depression, such as the hippocampus. The real power of antidepressants, then, may be summed in two words: neuronal plasticity.

Skirmish or Siege?

Depression is a chronic illness with recurring episodes. So should we deploy antidepressants battle by battle, or order them in for the long war?

By Christina Frank

When Sheila Singleton, 45, filled her first prescription for an antidepressant, she assumed it would also be her last. "I thought OK, when the pills work and I get myself straightened out, I'll go back to taking nothing but my vitamins," she says. Seventeen years later, Singleton still pops a pill every day. During the brief intervals when she's gone off medication, or when the ones she was on stopped working, the depression returned with a vengeance.

Among the newer antidepressants, options range from SSRIs (selective serotonin reuptake inhibitors) such as Prozac, Paxil, and Zoloft, to those—Wellbutrin and Effexor, for example—that target different or combined neurotransmitters. Most satisfied patients claim they provide highly effective relief with few side effects.

But there is one notorious downside: roughly 70% of SSRI users are plagued by sexual difficulty. "It's a big problem," acknowledges Donald Klein, M.D., professor of psychiatry at Columbia University and director of research at the New York State Psychiatric Institute. "There are no hard data on how many people actually discontinue treatment due to the sexual side effects; it largely depends on how they are handled by the specific doctor. Zoloft, for example, is short-acting and can be stopped for a couple of days, restoring sexual function for that period. Adding Wellbutrin to an SSRI is another way to restore libido. But not all doctors may try these adjustments; they may just say that's the price you have to pay."

Another fly in the psychiatric salve is that that these drugs have been officially approved only for short-term use—six to 12 months—yet are routinely prescribed for indefinite periods, in order to prevent future depressive episodes. It's not that the drugs are contraindicated for long-term use, it's just been impossible to conduct long-term studies. Americans move or drop out.

"So you have this disparity between the length of time for which the medications are approved and the length of time you might have to take them in order to have a good interval without depression," says Peter D. Kramer, M.D. "No one has really bridged that gap and figured out just what is appropriate for long-term treatment. It does seem that recurrences are prevented. On the other hand, do the medications lose their effectiveness? Are there long-term side effects? These are just not known."

What is known is that although many individual depressive episodes can be temporarily "fixed" by antidepressants, the drugs are not curative, no more than insulin cures diabetes or antihypertensives cure high blood pressure. The demon almost always returns at some point.

"We're increasingly recognizing something our European colleagues, who've been able to do longitudinal studies on depression, have known for some time: That major depression is predominantly a recurrent illness," says Fred Goodwin, M.D., professor of psychiatry at George Washington University, former director of the National Institute of Mental Health, and host of *The Infinite Mind* on National Public Radio. "Eighty percent of people who have had one episode will eventually have another one, one year or many years down the road."

So why not just stop the medication after one episode is cured and wait until the next one hits before resuming treatment? Kramer points to a phenomenon known as kindling: the more episodes you have, the worse they get—and the less stress it takes

The molecular cascade Duman has exposed opens up a whole new realm of possibilities for improving treatment of depression. It may be possible to create therapies that more directly and more strongly augment BDNF output. At the same time, the molecular pathway of BDNF production suggests new target points for a more rapid-acting treatment.

Duman's evidence that neuronal plasticity is at stake in depression fits with imaging studies showing that structural changes are taking place in the brains of the depressed. The two strands of information suggest a way that depression might originate. In a word: stress.

New Stress on Stress

"There is elegant work showing that stress, whether environmental or social, actually changes the shape, size and number of neurons in the hippocampus," says Duman. "There are studies showing that stress decreases levels of BDNF. It's a really hot area of research just now." And right at its epicenter is Bruce McEwen, Ph.D., director of the neurobiology lab at New York's Rockefeller University and head of a MacArthur Foundation workgroup on socioeconomic status and health.

McEwen is studying what happens in the adult brain, specifically the hippocampus, of animals undergoing repeated stress. Imaging studies have found that this area, like the prefrontal cortex and the amygdala, shrinks in people with recurrent depression. Prolonged stress, research has shown, kills hippocampal cells, precipitating cognitive decline.

McEwen himself has documented that several kinds of stress—the psychosocial stress of being a subordinate among group-living animals, the stress of being physically restrained—can cause hippocampal cells to atrophy and retract their dendrites. Others have seen the same effects in animals subjected to the stresses of social isolation and, in infancy, to deprivation of maternal care. McEwen has also found that stress can suppress nerve cell growth in a part of the hippocampus recently shown capable of renewing nerve cells in *(continued on page 72)*

to trigger them. Anecdotal evidence also suggests that going on and off medications may increase the dose needed next time to achieve the same benefit as last time. In the long run, stopping and starting doesn't reduce overall drug exposure.

Untreated, some depressive episodes eventually resolve themselves, on average, says Goodwin, in less than a year, though there is considerable variation from person to person. What antidepressants do is speed recovery by eliminating symptoms and enhancing motivation and energy.

Klein points out that of 100 depressed patients given any antidepressant, only 66 will show improvement. However, half of these positive responses are a placebo effect. Thus, only a third of patients are truly responding to the specific drug.

In Klein's estimation, the vast majority of sufferers—85% to 90%—can find substantial relief with one or a combination of drugs within six to eight weeks, assuming they faithfully follow the prescribed drug regimen ("total compliance" in medical jargon). Most people with depression, he says, can find relief with the first or second antidepressant they try. Only about 10% to 15% of patients, unipolar and bipolar, are truly resistant to treatment.

A study of 161 outpatients, recently reported in the *Journal of the American Medical Association*, demonstrated that long-term treatment with sertraline (Zoloft) prevents recurrence of chronic severe depression. In the study, conducted for 76 weeks, 50% (42) of 84 placebo-treated patients experienced recurrence of significant depressive symptoms, versus only 26% (20) of 77 patients given sertraline.

When determining who is a candidate for long-term drug therapy (lasting more than one year), doctors consider frequency of and length of time between episodes, severity of depressive symptoms, risk of suicide as well as family history of mood disorders. One of the most debated treatment dilemmas today is how to handle the persistent low-grade depression known as chronic dysthymia: does it merit long-term medication, or medication at all? Jesse Rosenthal, M.D., chief psychopharmacologist at Beth Israel Medical Center in New York City, suggests that the personal price paid by the chronically dysthymic can be as great as that paid by people with major depression, in terms of damaged relationships, poor work performance and overall low energy.

Still, it's not as simple as just putting everyone who is depressed on long-term drug therapy. Some patients will run into so-called "poop-out"; the medications simply stop working after a while. There are no official data on the antidepressant poop-out rate, but experts estimate it at about 20%. According to Klein, poop-out is highly unlikely to occur before three or four months of treatment; after that, there is no saying whether or when it will. "Poop-out is not uncommon, but it's not the expectation" says Goodwin. "It is possible to keep taking these drugs indefinitely at the same dose and maintain the same level of relief."

Another unknown is what's behind poop-out—whether it is true pharmacologic failure or a worsening of the disease, a relapse that overrides medication. Other factors that can dent a medication's apparent effectiveness are aging (which tends to worsen or change depressive symptoms), substance abuse, a co-existing medical illness and noncompliance, a big problem.

Rajinder Judge, M.D., clinical research physician for Prozac at Eli Lilly, estimates that just 50% of patients actually take antidepressants properly. "They miss doses or just stop on their *(continued on page 72)*

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adult life. He's trying to nail down what is cause and what is effect.

"So far," McEwen says, "all we know is that atrophy of these brain structures is seen in people who have a long history of recurrent depressive illness. It may be that those changes cannot be reversed."

But they may be preventable earlier in the course of depression, by use of an appropriate drug, before repeated bouts of depression kill off brain cells. "We've begun to look at this," reports Yale's Ronald Duman. "And we have found that antidepressant treatments are in fact able to induce the genesis of neurons."

FREUD 1, NEUROBIOLOGY 1

For many neurobiologists, behavioral plasticity is only half the new story on depression. The other part is the degree to which early experience can establish a lifelong pattern of brain activity. New research both in animals and in people demonstrates that stress early in life permanently sensitizes neurons and receptors throughout the central nervous system so that they perpetually overrespond to stress.

At the most recent meeting of the Society for Neuroscience, for example, psychologist Christine Heim, Ph.D., reported that sexual abuse in girls before puberty creates hyperactivity of the stress-hormone system headquartered in the brain's hypothalamus. And that likely makes them subject to depression as adults. "This is the first human study to report persistent changes in the reactivity of the hypothalamus-pituitary-adrenal axis among adult survivors of early trauma," she points out.

> "If you're 45, in perfect health, and depressed, you're 50% to 100% more likely to have a heart attack."

Heim so far has studied eight depressed women with a documented history of childhood abuse, seven women who also experienced childhood abuse but who do not have depression, and seven women who were never exposed to such early life stress and who have never been depressed. At Emory University, she tracked the chemical footprints of stress reactivity, in both brain and body, in all 22 women after applying mild stress—having them make a brief speech and do mental math in front of an audience.

Normally, when a threat to physical or psychological well-being is detected, the hypothalamus steps up production of corticotropin-releasing factor (CRF). This induces the pituitary gland to secrete ACTH, which in turn instructs the adrenal glands to pour out cortisol. Early trauma, Heim found, leads to chronic overactivation of the system. CRF, studies show, acts on various brain sites to create symptoms of depression.

All of the women who experienced early trauma reacted to the experimental stress with elevated stress hormones. The levels were highest in those with current major depression.

Such studies are leading researchers to a new model of depression, one they call the diathesis-stress model. Simply put, some inherited factor—a flawed gene for BDNF, individual differences in

Skirmish or Siege?

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own," she says. It is not uncommon for patients to drop their medications after four months, although prevention of relapse is believed to warrant longer treatment. Some find the side effects too pesky. Others become overconfident because they feel so much better. "Once you recover," Judge explains, "you don't want to be reminded of those dark days and the only thing reminding you is this little pill."

Whatever the cause of poop-out, it can almost always be remedied by upping (or sometimes even reducing) the dose, or changing or adding medications. Whereas older medications—so-called tricyclic antidepressants and monoamine oxidase (MAO) inhibitors—can be dangerous at high doses, amounts of the SSRIs can be doubled and then doubled again without harm, according to Peter Kramer. "Sometimes the patient ends up on a more complicated regimen to get the same effect," he says. "Or sometimes it's a matter of taking a person off one drug and reintroducing it later. One way or another, it is mostly possible to get people back to where they were."

While Kramer is a proponent of antidepressants, he also expresses some skepticism, especially where dosing and long-term side effects are concerned. "My sense is that we're giving Prozac at too high a dose. Many people can do well with 10 mg, but 20 mg to 80 mg is common. Also, there's suspicion that the SSRIs may affect memory in the long run; it's hard to be sure because depression itself impairs memory."

And what role does good old-fashioned psychotherapy play these days? A recent mega-analysis of 595 patients with major depressive disorder, reported the *Archives of General Psychiatry*, concluded that the best treatment plan involves a combination of psychotherapy and drug therapy.

But there are many kinds of therapy and not all are equally effective. Goodwin advocates a here-and-now approach of behavioral and cognitive techniques.

Furthermore, he says, even patients prescribed medication alone need psychological attention. Knowledgeable clinicians "can miss things like poor compliance, life stresses and substance abuse that can interfere with the medicine's working."

Depression, Donald Klein asserts, is among the most medically treatable illnesses. Accepting that short-term treatment may not be a possibility for most is perhaps the next hurdle to get over. "I now know that there is no cure," says Sheila Singleton. "I will have depression for the rest of my life and I'll take medication the rest of my life."

PFC activity—creates the biological vulnerability for major depression. Then some early stressful experience—such as parental neglect or physical or sexual abuse—sets up the brain to permanently overreact to environmental pressures. Then even small degrees of later stress provoke an outpouring of stress hormones, such as CRF and cortisol, throughout the brain (and body). These hormones act directly on multiple sites to produce the behavioral symptoms of depression—the vegetative state, the sleep disturbances, the cognitive dullness, the loss of pleasure. They push the amygdala into overdrive, churning out the negative emotions that steer the depression's severity and add a twist of anxiety. To boot, they magnify the effects of the neurotransmitter glutamate so that it overstimulates neurons until their dendrites collapse and shrink up.

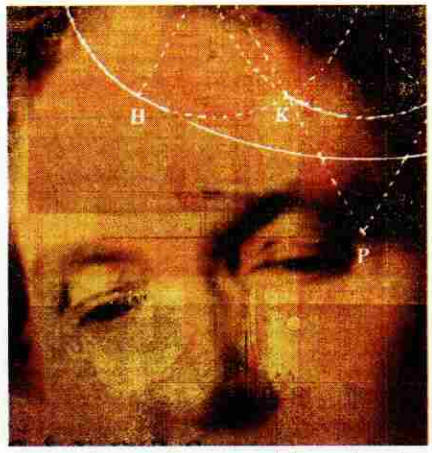
The moral of the story: early life experience counts. Not because it creates oral fixations or such. But because it shapes wiring patterns in the brain and sets the sensitivity level of the molecular machinery behind nerve-cell operations.

It's Not All in the Head

While disparate biological changes suggest that there are different types of depression—some arising spontaneously from within, others reflecting heightened reactivity to life events—all depression is more than an affliction from the neck up. It is a whole-body disorder.

At Columbia University, where he is professor of psychiatry, Alexander Glassman, M.D., was studying the cardiac effects of antidepressant drugs when reports began to trickle in confirming what he had suspected: depression makes heart disease particularly deadly. But it wasn't clear what role cigarettes played; the depressed are apt to smoke, and smoking leads to heart disease.

So Glassman teamed up with epidemiologists following more than 2,000 people for over a decade. In 1993 the group reported that, even after they controlled for smoking, depression essentially multiplies the malignity of heart disease, substantially increasing the risk of sudden death within the next year. The



report dropped an even bigger bombshell; it warned that healthy people struck by depression are more likely than people without the ailment to develop heart disease 10 years down the road. Just because they once got depressed.

"There are two things we can say without any hesitancy," says Glassman. "If you're 45, in perfect health, and depressed, you're somewhere between 50% and 100% more likely to have a heart attack than if you weren't depressed. That's big. And if you have a heart attack and then get depressed, whether you simply get some symptoms of depression or the full diagnosis, over the next 18 months you are three and a half times more likely to die. That's even bigger."

There are roughly 500,000 heart attacks a year in the U.S. And 20% of heart attack victims develop depression.

What put the head and the heart on a collision course are blood platelets, which play a key role in the ability of blood to clot. Platelets turn out to be stickier in those who are depressed. At Emory University, Dominique Musselman, M.D., has shown that the platelets of depressed people are hair-trigger responsive to activation signals, aggregating when they should be flowing.

A decade ago, the thinking was that heart attacks occurred when cholesterol-laden plaques formed on coronary artery walls and, over time, grew large enough to block blood flow in the artery. Today it's known that heart attacks occur only when a crack develops in the artery lining that covers the slow-growing plaque. Then platelets are suddenly drawn to the site, where they adhere to the exposed

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artery wall and rope in even more platelets. Clotting occurs within minutes, choking off blood flow to the heart.

BONES OF CONTENTION

The somatic changes of psychological depression go bone deep. Literally. The hormonal abnormalities that mark the disorder, particularly elevated body levels of cortisol, also rob the skeleton of calcium. The result: osteoporosis on a speeded schedule.

Researchers at the National Institutes of Health have found that depressed premenopausal women develop bones as porous as those of postmenopausal women. And the leaching of bone mineral persists, despite treatment with antidepressants. Led by David Michaelson, M.D., the team reported that bone mineral density was, on average, 6% lower in the spine among 24 depressed women than among 24 controls. And in the hip, it was 10% to 14% lower among the depressed—decrements that set women up for hip fractures.

"Once lost," Michaelson observes, "bone density is difficult to regain." It takes years, plus a modicum of physical activity and a calcium-rich diet. But it probably never returns to normal in depression, since the disorder tends to recur—and depressed people tend to be physically inactive and eat poorly.

It's not that chronic depression doesn't create a huge psychological burden. But it's becoming increasingly clear, says Columbia's Glassman, that "depression is an illness with very real and dangerous physical concomitants."

SICK, NOT SAD?

The new corporeality of "mental" illness is perhaps most daringly embodied in the work of Bruce Charlton, M.D., a research psychiatrist in the department of psychology at the University of Newcastle in England. Depression, Charlton provocatively contends, doesn't just have physical concomitants; it is wholly a physical disorder, one that is misinterpreted by the brain. Sickness is read as sadness.

The low mood is a secondary response, a product of physical malaise, the same malaise—the lack of energy, slowed movement, lack of pleasurable appetites (including sex), inability to concentrate—one gets when, say, the flu strikes. "The trouble with malaise is that you don't necessarily know you've got it, and you blame yourself for your condition of low performance," he says. But it is the body's way of withdrawing (think of a wounded animal) to conserve energy and minimize risk, an "evolved pattern of behavior" mediated by the immune system. "Major depressive disorder," he says, "is sickness behavior inappropriately activated and sustained."

How antidepressants are said to work and what actually accounts for their effectiveness may be two different things.

Charlton subscribes to the model of emotions put forth by the University of Iowa's Antonio Damasio, M.D., that feelings are the brain's representation of what's going on in the body. But, he says, sadness and happiness are "catch-all names given to aversive and gratifying states, end products of more primary emotions."

Still, the prevailing body state, the malaise, colors all incoming perceptions and stamps them "aversive" as they are encoded in memory. Recall, then, summons up malaise, as does thinking about the future. To the extent the malaise continues, patients are stuck, unable to even imagine anything that makes them feel motivated and energetic. Bleakness! Despair! Depression!

In this view, antidepressants, notably the tricyclics, possibly Prozac, work to the degree that *(continued on page 76)*

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they are analgesics! "Antidepressants do not make people happy," Charlton insists. They treat the state of unpleasantness. "Their effect on mood is no more remarkable than the fact that it is easier to be happy without a headache."

Charlton joins a rising chorus in disputing the way antidepressants are said to work. British psychiatrist David Healy, a card-carrying psychopharmacologist, contends in his book *The Antidepressant Era* (Harvard, 1998) that these agents are falsely presented as specific to depression. And the idea that depression is a single specific disorder was created largely by drug companies with a product—antidepressants—to sell. He argues that depression is even more than a disorder of the whole body; it's a disorder of the whole person, existential or social distress marked by unhappiness and hopelessness. It is cast into physical symptoms precisely because they have been made fashionable, sanctioned and publicized by today's medical-industrial complex.

Flexibility Regained

Whatever pathways depression takes through the brain and the body, it is still experienced by sufferers as a disorder of the whole person, which is why its pain has always been so hard to locate. As a result, how depression is seen by psychologists and psychiatrists, how they explain it to you and me, and how patients understand their own disorder—all influence what symptoms patients complain of. And what they are willing to do about them.

Fashions in thinking about depression make a difference to recovery. "We have looked at clients' theories of why they are depressed," reports psychologist Michael Addis, Ph.D., of Clark University. "Their theories are predictive of the outcome of treatment."

"Medication is one way of helping patients broaden their perspective," says psychiatrist Peter Kramer.

What is available to clients as explanation is the very stuff psychologists and psychiatrists talk about. The culture has become both more psychological-minded and more biological-minded. As a result, Addis has heard clients say things like, "My doctor said this is a chemical imbalance, so why are you talking to me about doing pleasurable activities?" He admonishes professionals: "We don't know what our theories mean to individuals. We say 'chemical imbalance.' A patient thinks, 'I'm damned.' Our theories are not neutral."

Which is why Peter Kramer, who prescribes both psychotherapy and drug therapy, ponders "which is the umbrella concept?" Is the brain a biological organ and psychotherapy another way to influence the brain? This is the view that psychiatry is moving towards. Or is drug therapy an adjunct to psychotherapy? "This is my model," he says. "Medication is one way of helping patients broaden their perspective." In other words, it's a way to restore what makes people most human—our remarkable capacity to adapt to life's ever changing demands. ✉

Solution to Puzzle

(puzzle appears on page 88)