

The Neurobiology of Depression

The search for biological underpinnings of depression is intensifying. Emerging findings promise to yield better therapies for a disorder that too often proves fatal

by Charles B. Nemeroff

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SUBTOPICS:

- Pressing Goals
- Genetic Findings
- The Norepinephrine Link
- Serotonin Connections
- Hormonal Abnormalities
- Support for a Model

SIDEBARS:

- The Symptoms of Major Depression
- Contributions from Imaging

ILLUSTRATIONS:

- Areas of the Brain
- Serotonin in Action
- Hormonal System

FURTHER READING

RELATED LINKS In his 1990 memoir *Darkness Visible*, the American novelist William Styron--author of *The Confessions of Nat Turner* and *Sophie's Choice*--chillingly describes his state of mind during a period of depression:

He [a psychiatrist] asked me if I was suicidal, and I reluctantly told him yes. I did not particularize--since there seemed no need to--did not tell him that in truth many of the artifacts of my house had become potential devices for my own destruction: the attic rafters (and an outside maple or two) a means to hang myself, the garage a place to inhale carbon monoxide, the bathtub a vessel to receive the flow from my opened arteries. The kitchen knives in their drawers had but one purpose for me. Death by heart attack seemed particularly inviting, absolving me as it would of active responsibility, and I had toyed with the idea of self-induced pneumonia--a long frigid, shirt-sleeved hike through the rainy woods. Nor had I overlooked an ostensible accident, á la Randall Jarrell, by walking in front of a truck on the highway nearby.... Such hideous fantasies, which cause well people to shudder, are to the deeply depressed mind what lascivious daydreams are to persons of robust sexuality.

As this passage demonstrates, clinical depression is quite different from the blues everyone feels at one time or another and even from the grief of bereavement. It is more debilitating and dangerous, and the overwhelming sadness combines with a number of other symptoms. In addition to becoming preoccupied with suicide, many people are plagued by guilt and a sense of worthlessness. They often have difficulty thinking clearly, remembering, or taking pleasure in anything. They may feel anxious and sapped of energy and have trouble eating and sleeping or may, instead, want to eat and sleep excessively.

Psychologists and neurobiologists sometimes debate whether ego-damaging experiences and self-deprecating thoughts or biological processes cause depression. The mind, however, does not exist without the brain. Considerable evidence indicates that regardless of the initial triggers, the final common pathways to depression involve biochemical changes in the brain. It is these changes that ultimately give rise to deep sadness and the other salient characteristics of depression. The full extent of those alterations is still being explored, but in the past few decades--and especially in the past several years--efforts to identify them have progressed rapidly.

At the moment, those of us teasing out the neurobiology of depression somewhat resemble blind searchers feeling different parts of a large, mysterious creature and trying to figure out how their deductions fit together. In fact, it may turn out that not all of our findings will intersect: biochemical abnormalities that are prominent in some depressives may differ from those predominant in others. Still, the extraordinary accumulation of discoveries is fueling optimism that the major biological determinants of depression can be understood in detail and that those insights will open the way to improved methods of diagnosing, treating and preventing the condition.

Pressing Goals

One subgoal is to distinguish features that vary among depressed individuals. For instance, perhaps decreased activity of a specific neurotransmitter (a molecule that carries a signal between nerve cells) is central in some people, but in others, overactivity of a hormonal system is more influential (hormones circulate in the blood and can act far from the site of their secretion). A related goal is to identify simple biological markers able to indicate which profile fits a given patient; those markers could consist of, say, elevated or reduced levels of selected molecules in the blood or changes in some easily visualizable areas of the brain.

After testing a depressed patient for these markers, a psychiatrist could, in theory, prescribe a medication tailored to that individual's specific biological anomaly, much as a general

practitioner can run a quick strep test for a patient complaining of a sore throat and then prescribe an appropriate antibiotic if the test is positive. Today psychiatrists have to choose antidepressant medications by intuition and trial and error, a situation that can put suicidal patients in jeopardy for weeks or months until the right compound is selected. (Often psychotherapy is needed as well, but it usually is not sufficient by itself, especially if the depression is fairly severe.) Improving treatment is critically important. Although today's antidepressants have fewer side effects than those of old and can be extremely helpful in many cases, depression continues to exact a huge toll in suffering, lost lives and reduced productivity.

The prevalence is surprisingly great. It is estimated, for example, that 5 to 12 percent of men and 10 to 20 percent of women in the U. S. will suffer from a major depressive episode at some time in their life. Roughly half of these individuals will become depressed more than once, and up to 10 percent (about 1.0 to 1.5 percent of Americans) will experience manic phases in addition to depressive ones, a condition known as manic-depressive illness or bipolar disorder. Mania is marked by a decreased need for sleep, rapid speech, delusions of grandeur, hyperactivity and a propensity to engage in such potentially self-destructive activities as promiscuous sex, spending sprees or reckless driving.

Beyond the pain and disability depression brings, it is a potential killer. As many as 15 percent of those who suffer from depression or bipolar disorder commit suicide each year. In 1996 the Centers for Disease Control and Prevention listed suicide as the ninth leading cause of death in the U.S. (slightly behind infection with the AIDS virus), taking the lives of 30,862 people. Most investigators, however, believe this number is a gross underestimate. Many people who kill themselves do so in a way that allows another diagnosis to be listed on the death certificate, so that families can receive insurance benefits or avoid embarrassment. Further, some fraction of automobile accidents unquestionably are concealed suicides.

The financial drain is enormous as well. In 1992 the estimated costs of depression totaled \$43 billion, mostly from reduced or lost worker productivity.

Accumulating findings indicate that severe depression also heightens the risk of dying after a heart attack or stroke. And it often reduces the quality of life for cancer patients and might reduce survival time.

Genetic Findings

Geneticists have provided some of the oldest proof of a biological component to depression in many people. Depression and manic-depression frequently run in families. Thus, close blood relatives (children, siblings and parents) of patients with severe

depressive or bipolar disorder are much more likely to suffer from those or related conditions than are members of the general population. Studies of identical twins (who are genetically indistinguishable) and fraternal twins (whose genes generally are no more alike than those of other pairs of siblings) also support an inherited component. The finding of illness in both members of a pair is much higher for manic-depression in identical twins than in fraternal ones and is somewhat elevated for depression alone.

In the past 20 years, genetic researchers have expended great effort trying to identify the genes at fault. So far, though, those genes have evaded discovery, perhaps because a predisposition to depression involves several genes, each of which makes only a small, hard-to-detect contribution.

Preliminary reports from a study of an Amish population with an extensive history of manic-depression once raised the possibility that chromosome 11 held one or more genes producing vulnerability to bipolar disorder, but the finding did not hold up. A gene somewhere on the X chromosome could play a role in some cases of that condition, but the connection is not evident in most people who have been studied. Most recently, various regions of chromosome 18 and a site on chromosome 21 have been suggested to participate in vulnerability to bipolar illness, but these findings await replication.

As geneticists continue their searches, other investigators are concentrating on neurochemical aspects. Much of that work focuses on neurotransmitters. In particular, many cases of depression apparently stem at least in part from disturbances in brain circuits that convey signals through certain neurotransmitters of the monoamine class. These biochemicals, all derivatives of amino acids, include serotonin, norepinephrine and dopamine; of these, only evidence relating to norepinephrine and serotonin is abundant.

AREAS OF THE BRAIN

Monoamines first drew the attention of depression researchers in the 1950s. Early in that decade, physicians discovered that severe depression arose in about 15 percent of patients who were treated for hypertension with the drug reserpine. This agent turned out to deplete monoamines. At about the same time doctors found that an agent prescribed against tuberculosis elevated mood in some users who were depressed. Follow-up investigations revealed that the drug inhibited the neuronal breakdown of monoamines by an enzyme (monoamine oxidase); presumably the agent eased depression by allowing monoamines to avoid degradation and to remain active in brain circuits. Together these findings implied that abnormally low levels of monoamines in the brain could cause depression. This insight led to the development of monoamine oxidase inhibitors as the first class of antidepressants.

The Norepinephrine Link

But which monoamines were most important in depression? In the 1960s Joseph J. Schildkraut of Harvard University cast his vote with norepinephrine in the now classic "catecholamine" hypothesis of mood disorders. He proposed that depression stems from a deficiency of norepinephrine (which is also classified as a catecholamine) in certain brain circuits and that mania arises from an overabundance of the substance. The theory has since been refined, acknowledging, for instance, that decreases or elevations in norepinephrine do not alter moods in everyone. Nevertheless, the proposed link between norepinephrine depletion and depression has gained much experimental support. These circuits originate in the brain stem, primarily in the pigmented locus coeruleus, and project to many areas of the brain, including to the limbic system--a group of cortical and subcortical areas that play a significant part in regulating emotions.

To understand the recent evidence relating to norepinephrine and other monoamines, it helps to know how those neurotransmitters work. The points of contact between two neurons, or nerve cells, are termed synapses. Monoamines, like all neurotransmitters, travel from one neuron (the presynaptic cell) across a small gap (the synaptic cleft) and attach to receptor molecules on the surface of the second neuron (the postsynaptic cell). Such binding elicits intracellular changes that stimulate or inhibit firing of the postsynaptic cell. The effect of the neurotransmitter depends greatly on the nature and concentration of its receptors on the postsynaptic cells. Serotonin receptors, for instance, come in 13 or more subtypes that can vary in their sensitivity to serotonin and in the effects they produce.

The strength of signaling can also be influenced by the amount of neurotransmitter released and by how long it remains in the synaptic cleft--properties influenced by at least two kinds of molecules on the surface of the releasing cell: autoreceptors and transporters. When an autoreceptor becomes bound by neurotransmitter molecules in the synapse, the receptors signal the cell to reduce its firing rate and thus its release of the transmitter. The transporters physically pump neurotransmitter molecules from the synaptic cleft back into presynaptic cells, a process termed reuptake. Monoamine oxidase inside cells can affect synaptic neurotransmitter levels as well, by degrading monoamines and so reducing the amounts of those molecules available for release.

Among the findings linking impoverished synaptic norepinephrine levels to depression is the discovery in many studies that indirect markers of norepinephrine levels in the brain--levels of its metabolites, or by-products, in more accessible material (urine and cerebrospinal fluid)--are often low in depressed individuals. In addition, postmortem studies have revealed increased densities of certain norepinephrine receptors in the cortex of depressed suicide victims.

Observers unfamiliar with receptor display might assume that elevated numbers of receptors were a sign of more contact between norepinephrine and its receptors and more signal transmission. But this pattern of receptor "up-regulation" is actually one that scientists would expect if norepinephrine concentrations in synapses were abnormally low. When transmitter molecules become unusually scarce in synapses, postsynaptic cells often expand receptor numbers in a compensatory attempt to pick up whatever signals are available.

SERATONIN IN ACTION

A recent discovery supporting the norepinephrine hypothesis is that new drugs selectively able to block norepinephrine reuptake, and so increase norepinephrine in synapses, are effective antidepressants in many people. One compound, reboxetine, is available as an antidepressant outside the U.S. and is awaiting approval here.

Serotonin Connections

The data connecting norepinephrine to depression are solid and still growing. Yet research into serotonin has taken center stage in the 1990s, thanks to the therapeutic success of Prozac and related antidepressants that manipulate serotonin levels. Serious investigations into serotonin's role in mood disorders, however, have been going on for almost 30 years, ever since Arthur J. Prange, Jr., of the University of North Carolina at Chapel Hill, Alec Coppen of the Medical Research Council in England and their co-workers put forward the so-called permissive hypothesis. This view held that synaptic depletion of serotonin was another cause of depression, one that worked by promoting, or "permitting," a fall in norepinephrine levels.

Defects in serotonin-using circuits could certainly dampen norepinephrine signaling. Serotonin-producing neurons project from the raphe nuclei in the brain stem to neurons in diverse regions of the central nervous system, including those that secrete or control the release of norepinephrine. Serotonin depletion might contribute to depression by affecting other kinds of neurons as well; serotonin-producing cells extend into many brain regions thought to participate in depressive symptoms--including the amygdala (an area involved in emotions), the hypothalamus (involved in appetite, libido and sleep) and cortical areas that participate in cognition and other higher processes.

Among the findings supporting a link between low synaptic serotonin levels and depression is that cerebrospinal fluid in depressed, and especially in suicidal, patients contains reduced amounts of a major serotonin by-product (signifying reduced levels of serotonin in the brain itself). In addition, levels of a surface molecule unique to serotonin-releasing cells in the brain are lower in depressed patients than in healthy subjects, implying that the numbers of serotonergic cells are reduced. Moreover, the density of at least

one form of serotonin receptor--type 2--is greater in postmortem brain tissue of depressed patients; as was true in studies of norepinephrine receptors, this up-regulation is suggestive of a compensatory response to too little serotonin in the synaptic cleft.

Further evidence comes from the remarkable therapeutic effectiveness of drugs that block presynaptic reuptake transporters from drawing serotonin out of the synaptic cleft. Tricyclic antidepressants (so-named because they contain three rings of chemical groups) joined monoamine oxidase inhibitors on pharmacy shelves in the late 1950s, although their mechanism of action was not known at the time. Eventually, though, they were found to produce many effects in the brain, including a decrease in serotonin reuptake and a consequent rise in serotonin levels in synapses.

Investigators suspected that this last effect accounted for their antidepressant action, but confirmation awaited the introduction in the late 1980s of Prozac and then other drugs (Paxil, Zoloft and Luvox) able to block serotonin reuptake transporters without affecting other brain monoamines. These selective serotonin reuptake inhibitors (SSRIs) have now revolutionized the treatment of depression, because they are highly effective and produce much milder side effects than older drugs do. Today even newer antidepressants, such as Effexor, block reuptake of both serotonin and norepinephrine.

Studies of serotonin have also offered new clues to why depressed individuals are more susceptible to heart attack and stroke. Activation and clumping of blood platelets (cell-like structures in blood) contribute to the formation of thrombi that can clog blood vessels and shut off blood flow to the heart and brain, thus damaging those organs.

Work in my laboratory and elsewhere has shown that platelets of depressed people are particularly sensitive to activation signals, including, it seems, to those issued by serotonin, which amplifies platelet reactivity to other, stronger chemical stimuli. Further, the platelets of depressed patients bear reduced numbers of serotonin reuptake transporters. In other words, compared with the platelets of healthy people, those in depressed individuals probably are less able to soak up serotonin from their environment and thus to reduce their exposure to platelet-activation signals.

Disturbed functioning of serotonin or norepinephrine circuits, or both, contributes to depression in many people, but compelling work can equally claim that depression often involves dysregulation of brain circuits that control the activities of certain hormones. Indeed, hormonal alterations in depressed patients have long been evident.

Hormonal Abnormalities

The hypothalamus of the brain lies at the top of the hierarchy regulating hormone secretion. It manufactures and releases peptides (small chains of amino acids) that act on the pituitary, at the base of the brain, stimulating or inhibiting the pituitary's release of various hormones into the blood. These hormones--among them growth hormone, thyroid-stimulating hormone and adrenocorticotrophic hormone (ACTH)--control the release of other hormones from target glands. In addition to functioning outside the nervous system, the hormones released in response to pituitary hormones feed back to the pituitary and hypothalamus. There they deliver inhibitory signals that keep hormone manufacture from becoming excessive.

Depressed patients have repeatedly been demonstrated to show a blunted response to a number of substances that normally stimulate the release of growth hormone. They also display aberrant responses to the hypothalamic substance that normally induces secretion of thyroid-stimulating hormone from the pituitary. In addition, a common cause of nonresponse to antidepressants is the presence of previously undiagnosed thyroid insufficiency.

HORMONAL SYSTEM

All these findings are intriguing, but so far the strongest case has been made for dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis--the system that manages the body's response to stress. When a threat to physical or psychological well-being is detected, the hypothalamus amplifies production of corticotropin-releasing factor (CRF), which induces the pituitary to secrete ACTH. ACTH then instructs the adrenal gland atop each kidney to release cortisol. Together all the changes prepare the body to fight or flee and cause it to shut down activities that would distract from self-protection. For instance, cortisol enhances the delivery of fuel to muscles. At the same time, CRF depresses the appetite for food and sex and heightens alertness. Chronic activation of the HPA axis, however, may lay the ground for illness and, it appears, for depression.

As long ago as the late 1960s and early 1970s, several research groups reported increased activity in the HPA axis in unmedicated depressed patients, as evinced by raised levels of cortisol in urine, blood and cerebrospinal fluid, as well as by other measures. Hundreds, perhaps even thousands, of subsequent studies have confirmed that substantial numbers of depressed patients--particularly those most severely affected--display HPA-axis hyperactivity. Indeed, the finding is surely the most replicated one in all of biological psychiatry.

Deeper investigation of the phenomenon has now revealed alterations at each level of the HPA axis in depressed patients. For instance, both the adrenal gland and the pituitary are enlarged, and the adrenal gland hypersecretes cortisol. But many researchers, including my colleagues and me at Emory University, have become persuaded that aberrations in CRF-producing neurons of the

hypothalamus and elsewhere bear most of the responsibility for HPA-axis hyperactivity and the emergence of depressive symptoms.

Notably, study after study has shown CRF concentrations in cerebrospinal fluid to be elevated in depressed patients, compared with control subjects or individuals with other psychiatric disorders. This magnification of CRF levels is reduced by treatment with antidepressants and by effective electroconvulsive therapy. Further, postmortem brain tissue studies have revealed a marked exaggeration both in the number of CRF-producing neurons in the hypothalamus and in the expression of the CRF gene (resulting in elevated CRF synthesis) in depressed patients as compared with controls. Moreover, delivery of CRF to the brains of laboratory animals produces behavioral effects that are cardinal features of depression in humans, namely, insomnia, decreased appetite, decreased libido and anxiety.

Neurobiologists do not yet know exactly how the genetic, monoamine and hormonal findings piece together, if indeed they always do. The discoveries nonetheless suggest a partial scenario for how people who endure traumatic childhoods become depressed later in life. I call this hypothesis the stress-diathesis model of mood disorders, in recognition of the interaction between experience (stress) and inborn predisposition (diathesis).

The observation that depression runs in families means that certain genetic traits in the affected families somehow lower the threshold for depression. Conceivably, the genetic features directly or indirectly diminish monoamine levels in synapses or increase reactivity of the HPA axis to stress. The genetically determined threshold is not necessarily low enough to induce depression in the absence of serious stress but may then be pushed still lower by early, adverse life experiences.

My colleagues and I propose that early abuse or neglect not only activates the stress response but induces persistently increased activity in CRF-containing neurons, which are known to be stress responsive and to be overactive in depressed people. If the hyperactivity in the neurons of children persisted through adulthood, these supersensitive cells would react vigorously even to mild stressors. This effect in people already innately predisposed to depression could then produce both the neuroendocrine and behavioral responses characteristic of the disorder.

Support for a Model

To test the stress-diathesis hypothesis, we have conducted a series of experiments in which neonatal rats were neglected. We removed them from their mothers for brief periods on about 10 of their first 21 days of life, before allowing them to grow up (after weaning) in a standard rat colony. As adults, these maternally deprived rats showed clear signs of changes in CRF-containing neurons, all in the

direction observed in depressed patients--such as rises in stress-induced ACTH secretion and elevations of CRF concentrations in several areas of the brain. Levels of corticosterone (the rat's cortisol) also rose. These findings suggested that a permanent increase in CRF gene expression and thus in CRF production occurred in the maternally deprived rats, an effect now confirmed by Paul M. Plotsky, one of my co-workers at Emory.

We have also found an increase in CRF-receptor density in certain brain regions of maternally deprived rats. Receptor amplification commonly reflects an attempt to compensate for a decrease in the substance that acts on the receptor. In this case, though, the rise in receptor density evidently occurs not as a balance to decreased CRF but in spite of an increase--the worst of all possibilities. Permanently elevated receptor concentrations would tend to magnify the action of CRF, thereby forever enhancing the depression-inducing effects of CRF and stress.

In an exciting preliminary finding, Plotsky has observed that treatment with one of the selective serotonin reuptake inhibitors (Paxil) returns CRF levels to normal, compensates for any gain in receptor sensitivity or number (as indicated by normal corticosterone production lower down in the axis) and normalizes behavior (for instance, the rats become less fearful).

We do not know exactly how inhibition of serotonin reuptake would lead to normalization of the HPA axis. Even so, the finding implies that serotonin reuptake inhibitors might be particularly helpful in depressed patients with a history of childhood trauma. Plotsky further reports that all the HPA-axis and CRF abnormalities returned when treatment stopped, a hint that pharmaceutical therapy in analogous human patients might have to be continued indefinitely to block recurrences of depression.

Studies of Bonnet macaque monkeys, which as primates more closely resemble humans, yielded similar results. Newborns and their mothers encountered three foraging conditions for three months after the babies' birth: a plentiful, a scarce and a variable food supply. The variable situation (in which food was available unpredictably) evoked considerable anxiety in monkey mothers, who became so anxious and preoccupied that they basically ignored their offspring. As our model predicts, the neonates in the variable-foraging condition were less active, withdrew from interactions with other monkeys and froze in novel situations. In adulthood, they also exhibited marked elevations in CRF concentrations in spinal fluid.

The rat and monkey data raise profound clinical and public health questions. In the U.S. alone in 1995, more than three million children were reportedly abused or neglected, and at least a million of those reports were verified. If the effects in human beings resemble those of the animals, the findings imply that abuse or neglect may produce permanent changes in the developing

brain--changes that chronically boost the output of, and responsiveness to, CRF, and therefore increase the victims' lifelong vulnerability to depression.

If that conclusion is correct, investigators will be eager to determine whether noninvasive techniques able to assess the activity of CRF-producing neurons or the number of CRF receptors could identify abused individuals at risk for later depression. In addition, they will want to evaluate whether antidepressants or other interventions, such as psychotherapy, could help prevent depression in children who are shown to be especially susceptible. Researchers will also need to find out whether depressed adults with a history of abuse need to take antidepressants in perpetuity and whether existing drugs or psychotherapy can restore normal activity in CRF-producing neurons in humans.

The stress-diathesis model does not account for all cases of depression; not everyone who is depressed has been neglected or abused in childhood. But individuals who have both a family history of the condition and a traumatic childhood seem to be unusually prone to the condition. People who have no genetic predisposition to depression (as indicated by no family history of the disorder) could conceivably be relatively protected from serious depression even if they have a bad childhood or severe trauma later in life. Conversely, some people who have a strong inherited vulnerability will find themselves battling depression even when their childhoods and later life are free of trauma.

More work on the neurobiology of depression is clearly indicated, but the advances achieved so far are already being translated into ideas for new medications. Several pharmaceutical houses are developing blockers of CRF receptors to test the antidepressant value of such agents. Another promising class of drugs activates specific serotonin receptors; such agents can potentially exert powerful antidepressive effects without stimulating serotonin receptors on neurons that play no part in depression.

More therapies based on new understandings of the biology of mood disorders are sure to follow as well. As research into the neurobiological underpinnings progresses, treatment should become ever more effective and less likely to produce unwanted side effects.

Related Links

[Artists and Depression](#)

[General Information Depression](#)

[National Foundation For Depressive Illness, Inc.](#)

Further Reading

BIOLOGY OF DEPRESSIVE DISORDERS, PARTS A AND B. Edited by J. John Mann and David J. Kupfer. Plenum Press, 1993.

THE ROLE OF SEROTONIN IN THE PATHOPHYSIOLOGY OF DEPRESSION: FOCUS ON THE SEROTONIN TRANSPORTER. Michael J. Owens and Charles B. Nemeroff in

Clinical Chemistry, Vol. 40, No. 2, pages 288-295; February 1994.

BIOLOGY OF MOOD DISORDERS. K. I. Nathan, D. L. Musselman, A. F.

Schatzberg and C. B. Nemeroff in Textbook of Psychopharmacology. Edited by A. F. Schatzberg and C. B. Nemeroff. APA Press, Washington, D.C., 1995.

THE CORTICOTROPIN-RELEASING FACTOR (CRF) HYPOTHESIS OF DEPRESSION: NEW FINDINGS AND NEW DIRECTIONS. C. B. Nemeroff in Molecular Psychiatry, Vol. 1, No. 4, pages 336-342; September 1996.

The Author

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