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COVER: Basic research into the fundamental functions of the brain transformed our understanding of depression into a treatable, biological condition. Discoveries related to neurons and brain chemicals known as neurotransmitters (which act as messengers in the space between neurons) led to the development of new classes of drugs to combat depression.

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New Drugs Redefine An Old Problem

In 1988, the first member of a new drug family arrived on the United States pharmaceutical market with rock star pizzazz and excitement. Fluoxetine, trademarked as Prozac®, was featured on the cover of Newsweek (Figure 1) as a breakthrough drug and discussed with passion on radio and television, often by grateful users and sometimes by those concerned over its widespread use for a growing number of conditions. Today, Prozac remains the most widely prescribed antidepressant medicine in history, having been used by more than 54 million people in 90 countries.

Prozac also helped change the definition of depression. In the not so distant past, depression was regarded as an affliction of the human heart, mind and soul. When patients complained of persistent depression, so severe that they were unable to work, sleep, or enjoy once pleasurable activities, psychiatrists often suggested they were repressing anger toward others and turning it toward themselves or asked if they had felt unloved by their mothers. Friends and associates were more likely to tell the troubled person to “snap out of it.” Individuals suffering from depression often felt ashamed, stigmatized. With the availability of drugs that relieved symptoms of severe depression by acting upon a specific biochemical mechanism in the brain, depression became more commonly viewed as a medical problem like hypertension and diabetes, amenable to pharmaceutical interventions.

Prozac and the other Selective Serotonin Reuptake Inhibitor (SSRI) drugs that followed were not the first medicines to demonstrate success in treating depression, as this story describes, but they were the first class of antidepressants to be rationally designed based on new understanding of how the brain works to affect mood, especially the role and behavior of naturally occurring chemicals called neurotransmitters that deliver messages from nerve to nerve.

The SSRIs may also have been one of the first categories of drugs whose mechanism was widely discussed by the general public. If most people did not remember what SSRI stood for, much less know the discoveries that underlay every word in the long, cumbersome name, there was a widespread, shorthand understanding of how the drugs worked. It went like this: Individuals with depressive disorders have lower levels of the neurotransmitter serotonin in their brains. Selective Serotonin Reuptake Inhibitor drugs selectively focus on serotonin and inhibit its recapture or reuptake by the nerve cells, alleviating the serotonin shortage and leaving more of the mood-enhancing chemical outside the neuron and thus available for the brain’s use. Thanks to the new SSRI drugs, the phrase “chemical imbalance” entered the national consciousness and vocabulary as at least a partial
Depression: The Real Thing

When is feeling depressed a disease?
Everyone feels sad or blue at some time or other, especially after a loss or when confronting death or change, but individuals with a depressive illness are dealing with a very different situation: one that is persistent, severe, and debilitating. This depression is often referred to as endogenous, meaning it has no clear precipitating event. Without treatment, their symptoms can last for weeks, months, or years. With treatment, the great majority of those people, even with those whose depression is most severe, can be helped.

Like other diseases, depression comes in different forms.
- Major depressive disorder is severe enough to interfere with the ability to work, study, sleep, eat, and enjoy once pleasurable activities. Symptoms include a persistent sad, anxious, or "empty" mood; feelings of hopelessness, pessimism, guilt and worthlessness; loss of interest in hobbies and sex; fatigue; difficulty concentrating, remembering, making decisions; changes in sleep and appetite; thoughts of death or suicide; persistent physical problems that do not respond to treatment such as headaches, digestive disorders, and chronic pain; and others.
- Dysthymia is a chronic but less severe and less disabling form of depression, which, however, keeps a person from functioning well or feeling good over the long-term. Persons with dysthymia may also experience major depressive episodes at some time in their life.
- Bipolar disorder, or manic-depressive illness, is less common and is characterized by cycling mood changes, in which a person moves from a severe high (mania) to a severe low (depression). Although individuals may feel elated and energetic during the manic phase, their thinking, judgment and social behavior can cause serious problems and if left untreated, worsen to psychosis.

Who develops depression?
In any given year, almost 1 in 10 Americans, about 20.9 million adults, suffer from a depressive illness, according to the National Institute of Mental Health. Worldwide, from 5–8 percent of the population suffer severe depression, with up to 20 percent suffering from milder forms of the disease. Severe depression occurs in all ethnic, racial, and socioeconomic groups and can occur at any age, from childhood to old age. Women experience depression about twice as often as men, perhaps because of hormonal factors, perhaps because of the additional stresses often faced by women. Women are particularly at risk after the birth of a baby, with a full-blown depressive episode differing from the “blues” common in new mothers. While fewer men experience severe depression, they are four times more likely to commit suicide (although more women attempt it).

And why?
Major depression is now understood as a biological brain disorder involving a chemical imbalance in the neurotransmitters, chemical messengers that transmit signals between brain cells. (See The Chemical Flux: A neurotransmitter primer.) Although many depressive episodes occur spontaneously, some types of depression run in families, suggesting some people may have a genetic predisposition to developing depression. A major loss, change or chronic stress may trigger episodes of depression, as may certain illnesses and some medications.

This understanding of the role of biochemistry in depression is helping lift much of the stigma that accompanied the disease for so many years, causing some patients to keep their diagnosis a secret and other individuals experiencing symptoms to avoid seeking medical treatment altogether.
and biological explanation of severe depression, thus lifting much of the stigma and blame that had added to depressed patients’ woes.

Like all scientific breakthroughs, the development of the SSRI drugs was built on a scaffolding of earlier discoveries, some of them chance clinical observations, some of them excruciatingly detailed basic science results whose clinical significance would not be realized for decades. And like all such breakthroughs, the new drugs continue to raise more questions and opportunities as yet newer information and technology becomes available.

**What is Depression?**

Severe depression is sometimes referred to as the common cold of psychiatry. While that speaks to the number of people affected—approximately five to eight percent of the population worldwide, with up to 20 percent suffering milder forms of the disease—it makes too light of the impact of an illness that can rob a person of the ability to conduct and enjoy a normal life. (See “Depression: The Real Thing”.) Patients formerly hospitalized with depression are at high risk—over 10 percent—for suicide. More recent studies have found that patients with severe depression even have higher risk of developing heart disease and diabetes. In addition to the emotional and physical pain caused by depression, the economic cost in the United States alone is estimated at $70 billion annually, and The World Health Organization projects that by the year 2020, depression will be second only to heart disease as the leading cause of disability worldwide.

Fortunately, between 80 and 90 percent of those suffering from serious depression can be effectively treated, usually with drugs, often used in combination with non-pharmacologic options including counseling or psychotherapy and lifestyle changes including exercise. For those drugs, we owe alert clinicians and astute scientists who refused to be discouraged when research did not go in the directions they had first hoped.

*Figure 2: This engraving, titled Melencolia I, by German artist Albrecht Dürer depicts an early view of depression which was thought to be caused by an excess of black bile. The word melancholy comes from this belief, stemming from the Greek words *melan*, or black, and *cholia*, meaning bile. Image from the Wikipedia Commons.*

**Chance Discovery Meets Scientific Explanation**

The history of neuropharmacology (the study of drugs that affect the nervous system) mirrors the evolution of the understanding that mental disorders are diseases of the brain not, as believed in earlier centuries, a problem caused by evil spirits or the influence of the moon’s lunar cycles (hence the word lunacy). Or, in the case of depression, black bile (hence the word melancholia, from *melan*, meaning black, and *cholia*, meaning bile, Figure 2). But before such a transformation could take place, scientists had a lot of
What and why: Neurotransmitters are naturally-occurring chemicals held in an inactive form in tissues throughout the body, then liberated by the nervous system when needed to deliver messages telling cells what needs to be done. For one example, the hormone epinephrine (also called adrenaline) is produced in the adrenal gland and secreted or released into the bloodstream in response to physical or mental stress. In an instant, blood pressure goes up, the heart rate quickens, and energy-rich blood glucose is released into the blood, readying the individual for a "fight or flight" response to whatever is causing fear or injury. For another example, oxytocin is a peptide (a chain of amino acids chemically linked together) released within the brain, ovary, and testes. It stimulates contractions during birth, release of milk by mammary glands after the baby is born, and triggers maternal behavior. More recent studies suggest the protein even plays a role in emotional bonding between adults. More than 300 naturally occurring neurotransmitters are known.

How: The various types of neurotransmitters are produced or secreted in nerves (also called neurons) and stored in small membrane bags, or vesicles, at the end of the nerve. In response to a signal, the neurotransmitter is released from the nerve ending and begins to spread into the space or synapse between individual nerves. In the synapse, the neurotransmitter binds to receptors present on other nerves, and transfers the signal to the inside of that nerve. This is a little like a key fitting into a lock; however, any key will only fit a few locks. Receptors are very selective about which neurotransmitters they will let bind.

When the neurotransmitter is accepted by the nerve's receptor, information passes from the sending nerve to the receiving nerve and triggers a biological effect. The neurotransmitter's job is not always done after it delivers its message, as once thought. Instead, as Axelrod discovered, some neurotransmitters are destroyed by enzymes but others are retrieved, or taken (back) up, by the nerve cell that made it, enabling it to be used again. His discovery made it possible to select one specific neurotransmitter and inhibit its reuptake in order to increase the amount of that one neurotransmitter available in the brain, ready for use. When the reuptake of serotonin is inhibited, for example, the level of active serotonin in the brain is increased and the effect of the neurotransmitter is amplified. It is not fully understood why this increased level reduces the severity of depression. Some scientists believe it may work by correcting a too-efficient reuptake system in some individuals.
work to do in determining how the brain and nervous system function—and that these physical and biochemical processes could cross what was then perceived as a deep divide between body and mind.

In the first half of the 20th century, scientists painstakingly teased out a basic understanding of how the nervous system uses naturally occurring chemicals called neurotransmitters to travel from nerve to nerve, delivering messages throughout the body, telling cells what needs to be done to keep the body functioning. (See “Chemical flux: A neurotransmitter primer.”)

In the late 1940s and early 1950s, scientists began to identify specific neurotransmitters, such as norepinephrine (involved in the constriction of blood vessels and the increase in heart rate and blood pressure), dopamine (the chemical whose shortage is involved in Parkinson’s disease), and serotonin (soon to be recognized as deeply connected to depression). In the 1950s, scientists also became better able to measure levels of specific neurochemicals in the body and thus correlate these levels with behavior.

Despite these advances, the first drugs that appeared to ameliorate the symptoms of severe depression were found during chance observation of their antidepressive abilities when used for patients with very different diseases. When given to severely depressed patients, these drugs proved far from perfect but the fact that they worked at all for patients with depression was an enormous surprise.

**Thorazine: A Story Of Keen Observation**

Before beginning the story of the antidepressants, we need to take one step back. When the age of neuropharmacology began, drugs for depression were not first in line. The critical event in the foundation of drugs for mental illness took place in 1952, with the discovery of a drug effective against schizophrenia. Like so many scientific advances in this story, this one came from a search related to an entirely different disease.

At the height of European industrialization in the 19th century, German chemists manufactured a series of industrial dyes from coal tars, including one called methylene blue, the basic foundation of which was a chemical called phenothiazine. Decades later, in the 1930s, French scientists began synthesizing various phenothiazine compounds in a search for a new anti-malarial agent, the primary focus of the French pharmaceutical firm Rhone-Poulec at that time. Although methylene blue had shown some anti-microbial activity, it soon became clear it was of no use against malaria. It might well have sunk into obscurity had not the Pasteur Institute linked up with Rhone-Poulec. Scientists at Pasteur had been searching for antihistamine agents to diminish the effects of the hormone histamine (now recognized to play a key part in allergic responses, then believed to be involved in stress and shock reactions in response to blood loss or infections). The first ones they found had been too toxic for human use. The Rhone-Poulec scientists had recognized that while the phenothiazine compounds might not work for malaria, they also had antihistaminic properties. Their joint efforts led to development and marketing of some of the earliest antihistamine drugs, some of which are still in use today.

The new phenothiazine compounds were not only effective antihistamines, they also demonstrated clear sedative effects and some appeared to have beneficial effects in patients with Parkinson’s disease, suggesting the compounds played some role in overall nervous system functioning. In the late 1940s, Henri Laborit, a young French naval surgeon, began to use promethazine together with anesthesia, trying to minimize the risk of circulatory shock that anesthetics like ether and chloroform sometimes caused (the underlying basis of the then too-often true statement that the operation was a success but the patient died). An astute clinical observer, Laborit noticed that patients receiving promethazine became “calm and somnolent, with a relaxed and detached expression.” In 1951, while working in a hospital outside of Paris, he asked Rhone-Poulec if they could improve the effectiveness of phenothiazine. Much to
Laborit’s surprise, they handed over chlorpromazine, already developed and being used in clinical trials in a different French hospital.

Laborit was so impressed with the “beatific quietude” of his patients on chlorpromazine that he began urging his psychiatric colleagues at the military hospital to give it to psychiatric patients. They mixed it with the barbiturates and other sedatives various patients already were taking and agreed it might—or might not—be helping with their therapy. But when Pierre Deniker and Jean Delay, one of the leading figures in French psychiatry, gave chlorpromazine to patients who were psychotically agitated, usually manic, without mixing it with other drugs, the true significance of chlorpromazine for the treatment of psychosis became clear.

The company Smith-Kline & French (now GlaxoSmithKline) brought French clinicians to the United States to collaborate with American clinicians and chlorpromazine was soon introduced in the marketplace as Thorazine. Although at the time it was unclear how the drug worked, some patients who had been deluded and hallucinating for a decade emerged from their psychoses for the first time by taking Thorazine. In Europe and in the United States, the “miracle drug” and similar drugs that followed began to replace old, often-drastic treatments for schizophrenia, such as lobotomy, primitive electroshock and artificially induced insulin shock. Although the drug’s drawbacks would soon become apparent, (See “Troubles With Thorazine.”) Thorazine resulted in nearly half a million patients in the United States and many hundreds of thousands more in Europe being discharged from asylums, sent home—or into the streets—with a prescription in hand.

“Psychic Energizers”: Tuberculosis Leads To Unexpected Discovery and MAOIs

While clinicians now granted that, on the basis of Thorazine’s success, psychosis had a biological basis, they saw depression as a very different kettle of fish. Freudian theories about depression as a result of loss still held sway. Tranquilizers to blunt anxiety and unhappiness were widely prescribed, (especially to women, causing them to be referred to as “mother’s little helper”), but a drug to actually change symptoms of depression? Ready or not, these were on their way.

Thorazine was not the only neuro-psychiatric drug to have its origins in industrial chemistry. When ethanol and liquid oxygen began running low during the end of World War II, the Germans resorted to using a chemical named hydrazine to propel rockets. Large stocks of the chemical were left over when the war ended, and these were provided to civilian chemical companies, many of which were developing a pharmaceutical arm. In 1951, chemists at Hoffman-La Roche in New Jersey began to structurally manipulate hydrazine, synthesizing (forming a new compound from simpler elements or compounds) a compound named isoniazid, first produced in 1912 and then largely forgotten, and a then new compound named iproniazid. Found to be strongly active against tuberculosis (TB), both were soon pressed into use as therapies against this widespread problem.

Both drugs helped heal tubercular lesions in patients with TB, but clinicians noticed that the overall mood of patients taking...
Iproniazid seemed to change for the better. A 1953 Associated Press photograph showed patients dancing and clapping outside their TB sanitarium on Staten Island, New York, with a caption that read “A few months ago, only the sound of TB victims coughing their lives away could be heard here.” Researchers on both sides of the Atlantic began to ask why an anti-tuberculosis agent should have such positive mental “side effects.” After his own studies, psychiatrist Nathan Kline (Figure 3) pronounced the drug a “psychic energizer,” giving its users a “sense of joyousness and optimism.” In 1957, after papers at an international congress of psychiatry in Switzerland reported preliminary success in treating depression with iproniazid, some 400,000 patients were given the “TB drug” for their depression.

Iproniazid and similar compounds would soon be called monoamine oxidase inhibitors (MAOIs), because they work by inhibiting monoamine oxidase, the enzyme that destroys a class of neurotransmitters known as monoamines (biological chemicals that contain nitrogen bonded to hydrogen), thus increasing monoamine—including norepinephrine and serotonin—levels in the brain.

Despite its success, iproniazid vanished from prescription pads nearly as quickly as it had appeared. A small number of patients developed jaundice (a yellow staining caused by abnormally high blood levels of the bile pigment bilirubin), and while this almost certainly was related to the high prevalence of hepatitis in the general population rather than being a side effect, the manufacturer withdrew the drug.

But iproniazid’s sudden, widespread use for the treatment of depression had been a good measure of the pent-up demand for an effective drug to treat this condition. Other members of the MAOI family of drugs were quickly developed, some of which continue to have a place in treatment today. Yet simultaneous with the development of the MAOIs, other drugs with a different biological mechanism were discovered in the United States. These drugs, the tricyclic antidepressants or TCAs, quickly began to gain a competitive edge.

From Thorazine To Tricyclics

After the tremendous success of Thorazine (both clinically and economically), scientists hoped a structurally-related drug like imipramine, another antihistamine compound, might work even more effectively against psychosis.
It did not. However, a Swiss clinical psychiatrist, Ronald Kuhn, glimpsed imipramine's potential for treating depression. Knowing that some depressed patients responded to opium, he had been testing various antihistamines because of their similar sedating effect. After giving imipramine to several hundred severely depressed patients, Kuhn published a groundbreaking study in 1958. Patients began to "get up in the morning of their own accord," he wrote. "Their facial expressions become more vivacious...they once again begin to seek contact with the outside world...instead of being concerned about imagined or real guilt in their past, they become occupied with plans concerning their future...suicidal tendencies also diminish, becoming more controllable or disappearing altogether." Other psychiatrists soon confirmed his findings.

After many fits, starts, questions, and reservations, the pharmaceutical manufacturer Ciba-Geigy brought imipramine to market in several European countries in the late 1950s and in the U.S. in 1960. Tofranil®, its trademark, was the first of the tricyclic antidepressants (TCAs), called that because of the drugs' molecular structure of three rings of atoms. A year later, Tofranil was followed by another TCA—amitriptyline—under the market name Elavil®.

By the 1970s, the TCAs had become the World Health Organization's number-one recommended drug for depression, a first line status they would retain until the arrival of the SSRI drugs.

**Problems With Lack Of Selectivity**

Although the new drugs had given people with severe depression new hope, neither the MAOIs nor the TCAs were perfect. Only basic scientific research would reveal why this was so: the drugs altered the chemical flux of the brain indiscriminately, not selectively. As they altered neurotransmitters and other chemicals involved in depression, patients improved, yes. But as these drugs affected other chemicals, unwanted, troublesome, and sometimes life-threatening side effects were also created.

At first, no one could understand why some patients taking the MAOI drugs were experiencing migraine-like headaches and sudden bouts of dangerously high blood pressure. Then, thanks to observant clinicians, it became clear that the drugs interacted negatively with the substance tyramine, found in cheeses, wines, smoked or pickled meats, chocolate, caffeinated beverages, and other foods. These life-threatening side effects did not begin immediately following ingestion of food and could last longer than two weeks after patients stop taking the medicines. Moreover, the list of items containing tyramine was long, continually growing, and difficult to avoid, complicating treatment with MAOIs. This was especially true among patients whose depression sometimes caused them to care little whether they lived or died and therefore had trouble with purposefully staying clear of foods that could result in dangerous side effects. In addition to tyramine containing foods, other prescription and over-the-counter medicines can also set off severe problems, and the drugs can intensify the effect of alcohol and other drugs that slow down the nervous system, including medicines used during surgery, dental procedures or emergency treatment.

Like the MAOIs, the TCAs proved problematic. Although the biology would not become clear until later in this story, TCAs are what scientists sometimes refer to as "dirty" or nonselective drugs, meaning that they have prominent actions at sites in addition to the site that produces the intended therapeutic effect (Figure 4). For example, because TCAs block some of the actions of the neurotransmitter acetylcholine, they cause side effects like heart palpitations, dry mouth, blurred vision, constipation, and urinary retention.

Moreover, it was becoming obvious that individuals have marked differences in how quickly they can "clear" these drugs from their bodies, meaning excessive levels could accumulate in some patients' bodies even when given modest dosages. Since the early signs of toxicity mimicked those of depression, doctors sometimes increased the dosage, making the situation worse.
MAOIs and Tricyclic (TCA) drugs are less specific than SSRI drugs.

Monoamine oxidase is an enzyme that destroys neurotransmitters such as norepinephrine and serotonin. MAO inhibitor drugs block this action.

Serotonin specific channel

Norepinephrine specific channel

Tricyclic antidepressants prevent reuptake of several neurotransmitters, including serotonin, norepinephrine and acetylcholine.

Figure 4: Neurotransmitters are the chemical messengers that travel in the synapse (space) between neurons and are continually released and taken back up through specific transport channels. A lack of serotonin, one type of neurotransmitter, has been linked to depression, and antidepressants typically increase the amount of serotonin present in the synapse. Two classes of antidepressant drugs, the monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs), work by interfering with the normal release and reuptake of neurotransmitters. TCAs block the reuptake of multiple neurotransmitters while MAOIs prevent enzymatic destruction of multiple neurotransmitters. Unfortunately, because neurotransmitters play an important role as chemical messengers in many biological functions, MAOIs and TCAs can have undesirable side effects. This is in contrast to the SSRI drugs, which specifically interfere with reuptake of serotonin. Figure by Corporate Press.

But perhaps the worse disadvantage of the TCAs was the fact that for some individuals the lethal level could be as little as five times that of the therapeutic level. Furthermore, the TCAs tended to interact badly with alcohol. As with any drug, there was an interval of time between beginning treatment and experiencing meaningful improvement in symptoms. Because TCAs were being given to patients who already had a high risk of suicide and alcohol usage, these side effects proved to be especially dangerous. For years before the arrival of SSRIs, the TCAs were a leading cause of death by accidental overdose. For more than 20 years, clinicians were caught in a hard place, frequently choosing antidepressants for individual patients based on which side effects they could best handle.

But although the MAOIs and TCAs were being used, with some success, in patients with depression, the question remained: how did these new drugs actually work? And was there a way to keep the beneficial emotional effects while getting rid of the troublesome, life-threatening side effects? Only basic research could provide the answer, as new insight into the chemistry of the brain provided
Julius Axelrod: The Journey From Rejection to the Nobel Prize

The achievements of neuropharmacologist Julius Axelrod seemed unlikely at first. The son of Polish immigrants to New York City, Axelrod was rejected from every medical school to which he applied after graduating from college in 1933, perhaps because of the Jewish quota system then in place. He began working on a master's degree in chemistry at night while working in a laboratory. One night, an ammonia bottle exploded, causing him to wear an eye patch the rest of his life. He was a man who joked frequently, and he often joked that his patch was somewhat dashing. After the accident, he ploughed on, in a career reflected today in medicine cabinets across the developed world—and not just those of the millions who take one of the SSRI drugs for depression and other mental disorders.

As a young scientist at Goldwater Memorial Hospital in New York in 1946, "Julie," as his friends called him, participated in studies on then current non-aspirin painkillers. He helped identify the specific chemical in these medicines responsible for relieving pain and recommended that it be used in place of the medicines themselves, which were to blame for serious blood conditions in their users. Marketed under trade names like Tylenol, this chemical named acetaminophen became one of the most widely used painkillers in the world. It was Axelrod's first taste of real research, and he was hooked.

Moving to a job at the National Institutes of Health (NIH) Axelrod joined a group of scientists interested in brain chemicals. He was already a highly accomplished researcher when he decided he needed a Ph.D. to continue to advance. NIH gave him the time, and George Washington University agreed to accept his current research on neurotransmitters as his thesis. One year later, now Dr. Axelrod, he returned to the NIH's National Institute of Mental Health, where he became chief of the pharmacology section of the Laboratory of Clinical Sciences and established his own research program. One of his students, Solomon Snyder, later to play a pivotal role in the discovery of Prozac, remembers him as a generous mentor and a creative, intuitive scientist who once said "I don't like to do complex experiments...Picasso makes a single line, but it takes a lot of time and thought."

While at NIH, Axelrod conducted the research that transformed how scientists understood the regulation of neurotransmitters and for which, a remarkably short time afterward, he would be awarded the Nobel Prize in Physiology or Medicine. One of the two scientists with that inactivates the transmitter norepinephrine and in a different way than does the enzyme called monoamine oxidase (MAO). This discovery would help explain the mechanism of potent antidepressant drugs like imipramine, which do not change the breakdown of neurotransmitters by MAO.

Second, even more remarkably, he discovered that neurotransmitters are not always inactivated by breaking them down. Instead, they could be sucked back into the nerve from which each originated and used again. He called this novel mechanism reuptake.

Axelrod told a New York Times reporter that the decisive experiment (working with cats) "took a couple of hours (but that) working out all the details afterwards took three years."

Axelrod's discovery of reuptake further explained how neurotransmission functions. It also had important implications for how antidepressants might work by preventing reuptake and thus correcting a deficiency of a needed neurotransmitter in the brain. Norepinephrine appeared to be the missing ingredient but in 1963 Axelrod and others showed that imipramine also blocks reuptake of serotonin—then beginning to be seen as important in depression—in the same way as it blocks reuptake of norepinephrine.

At the Nobel Banquet in Stockholm in 1970, Axelrod thanked the Nobel Prize Committee for recognition of his and the other two men's work, noting that the award came at a time when too many people believed that basic research was "irrelevant or put to evil uses." Our work on chemical neurotransmission is of a very fundamental nature, he said, "but it also gives us insight in explaining such illnesses as mental depression, Parkinson's disease, hypertension and drug abuse (and) can also lead the way to the treatment of these terrible afflictions."

As indeed it has.
both the answers to these questions and the keys to the next generation of antidepressants.

The Path To Selectivity

The discoveries of Julius Axelrod provided a new model for understanding the metabolism and regulation of those chemical neurotransmitters mediating communications among neurons in the brain—and for explaining how the antidepressants and other drugs work. A biochemist and pharmacologist working at the National Institutes of Health (NIH), Axelrod had been studying drugs that induced altered states of consciousness, such as LSD, when Thorazine and other drugs to treat violent and psychotic behavior emerged in the early 1950s. Galvanized, he turned his attention to these.

Other scientists were on the same track, and Axelrod was particularly struck by work suggesting that mental illness might be caused by an imbalance of the hormone adrenaline, also called epinephrine. (See “Julius Axelrod: The Journey from Rejection to Nobel Prize.”)

Axelrod began studying the enzymes released from nerve endings along with norepinephrine, a neurotransmitter involved in communication in the sympathetic nervous system and almost identical in structure to epinephrine. One of these enzymes was monoamine oxidase, known since the 1950s to interfere with the action of neurotransmitters. In fact, the secret of the antidepres- sant drugs known as monoamine oxidase inhibitors lay in the drugs’ capacity to disable the monoamine oxidase (MAO) enzyme, allowing the neurotransmitters to continue to work.

Like most scientists of the period, Axelrod initially believed that monoamine oxidase destroyed the neurotransmitter once it had left the neuron that produced it, crossed the synapse (or space) between neurons, delivered its instructions to the neuron lying across the synapse, and thus completed its original task. But experiments by a colleague indicated that even when the enzyme monoamine oxidase was inhibited that norepinephrine was still inactivated, suggesting it was removed from the system in some other way. Perhaps this mysterious disappearance accounted for the fact that scientists could only account for about 3 percent of epinephrine in the body at any given time. Where was the rest?

By chance, a fellow NIH scientist had ordered radioactive norepinephrine for a different experiment, one involving schizophrenia, and agreed to share some with Axelrod. When Axelrod injected the radioactive norepinephrine in laboratory animals (Figure 5), he could find it in organs rich in sympathetic nerves such as the heart, spleen, salivary and adrenal glands. But what he really wanted was to know where it went within the nerves.

What occurred to Axelrod was that the neurotransmitter was being taken back up in the nerve endings where it was stored. It would be impossible to actually
Once the neurotransmitter has done its job, it has one of two fates: destruction or reuptake.

**Destruction:** Some neurotransmitters are destroyed by enzymes.

**Reuptake:** Some neurotransmitters are recaptured by the neuron that released them, repackaged into vesicles, and used again.

*Figure 6:* As Julius Axelrod discovered, once a neurotransmitter has completed its job as chemical messenger, it is either destroyed by enzymes like monoamine oxidase or recaptured by the neuron that released it. This *reuptake* of neurotransmitters prevents a nervous signal from propagating for too long and allows reuse of these chemicals, but can also cause a neurotransmitter deficit, as seems to occur in the case of depression. *Figure by Corporate Press.*

see where it was at that magnitude of detail, of course, so in order to find out if this novel idea could be true, he devised an ingenious experiment. First, he and his colleagues gave laboratory animals enzyme inhibitors to assure that monoamine oxidase would not be the cause of any degradation or removal of norepinephrine. Next, they disabled the sympathetic nervous system on one side of the animals' bodies but not the other. (The sympathetic nervous system is the part of the nervous system that operates without intervention of conscious thought, including the “fight or flight” reactions that humans and other animals experience when suddenly faced with a threat.) Then, and only then, the scientists administered the radioactive norepinephrine.

Sure enough, the results showed that on the side of the body where the sympathetic nerves had been destroyed, there was no accumulation of radioactivity. On the side of the body where the nerves were still intact, however, the radioactive norepinephrine was clearly present. Clearly, uptake into the sympathetic nerves accounted for the inactivation of the neurotransmitter. When Axelrod began to explore actions of drugs, he found that cocaine, amphetamine, and other drugs also could block this uptake process. Their next experiments demonstrated, first, that stimulat-
ing a nerve caused a release of norepinephrine and, second, that when norepinephrine was infused into a part of the body rich in sympathetic nerve endings, that it ended up in those nerves.

In 1961, Axelrod announced that neurotransmitters do not stop working when they cross the synapse between the two nerves and arrive at the post-synaptic nerve. Instead, the neurotransmitter is recaptured or taken back up—the word used by scientists is “reuptake”—by the original, pre-synaptic nerve that released it so that the neurotransmitter can be released and used again when needed (Figure 6).

Reuptake? This was a daring, dazzling new concept, one that changed scientists’ understanding of how neurotransmitters performed, one that would make possible the selectivity of the SSRI drugs. Using Axelrod’s discovery of neurotransmitter reuptake, scientists now knew where another 95 percent of norepinephrine was located at any given time. The vast majority of this and other neurotransmitters were in a continuous state of flux and transit.

In 1962, Axelrod and his post-doctoral researcher Richard Wurtman conducted another series of experiments that showed how tricyclic drugs block neurotransmitter reuptake, leaving more neurotransmitters available for the nerves’ use. Two years later, Axelrod and Solomon Snyder, then a postdoctoral student, concluded that different types of antidepressants work in different ways, some inhibiting the MAO enzyme so that it cannot destroy the neurotransmitter, thus increasing its availability, some blocking the reuptake of neurotransmitters, also increasing their availability.

For the first time, scientists could understand how drugs behaved in relation to norepinephrine and other neurotransmitters and why these behaviors should affect mood. For example, cocaine prevented the reuptake of both norepinephrine and dopamine back into the pre-synaptic nerve endings. As a result, the high availability of these neurotransmitters in the brain causes a temporary high.

And for the first time scientists saw how it would be possible to design a drug that would focus, selectively, on only one neurotransmitter at a time.

Basic Biology To Drug Design: The SSRI s

Understanding the reuptake mechanism described by Axelrod suggested that one could design and engineer a drug—not just wait for fortuitous discovery—that would act only upon the neurotransmitters that created the desired effect relative to depression and leave alone the neurotransmitters that would, if altered, cause unwanted side-effects.

The neurotransmitter of choice also was becoming clear. Medical evidence linking serotonin to depression included the finding of lower concentrations of the neurotransmitter in the cerebrospinal fluid of depressed patients, particularly those who tried or succeeded in committing suicide. Serotonin levels were also lower in the brains of those who had died from suicide than in the brains of those who died suddenly from accident or heart attacks. Treatment with precursors of serotonin showed antidepressant effects. As more and more evidence for the role of decreased levels of serotonin in depression began to emerge, the search began for something that would inhibit the reuptake of serotonin, thus increasing the level affecting the brain.

Thanks to rapidly emerging techniques such as nuclear magnetic resonance, crystallographic analyses and other physical methodologies, scientists now could analyze compounds’ molecular structure: the three-dimensional arrangement of the atoms that determine properties of a substance including its biological activity. Many of these techniques originated with scientists working at universities and research institutions that had the expensive and specialized equipment needed to perform such structural studies, and that instrumentation often came from a special program funded by NIH.

In academic and commercial laboratories, scientists were already hard at work, synthesizing new compounds to create drugs of various kinds, using new techniques of molecular engineering to combine and
From Across The World, A Team Of Scientists Meet In New Jersey: Three American Success Stories

Ray Fuller, Bryan Molloy and David Wong could not have had more different origins, but their fascination with science and scientific discovery brought them together at the Eli Lilly Company. There, their knowledge of the molecular structure of compounds—and their ability to make variations of those compounds to achieve desired effects—resulted in the creation of the first selective serotonin reuptake inhibitor drug: fluoxetine, trademarked as Prozac.

Ray Fuller, the chief of the team assigned to build this better drug, always described himself as a little boy who grew up wearing overalls on a farm in an area of Illinois without electricity, telephones, or indoor plumbing. He never expected to go to high school, having met very few people who had done so, but when he was in the 7th grade of the town’s one-room schoolhouse, his parents moved to a bigger town in order to give their sons more opportunities. After graduation, Fuller moved on to Southern Illinois University where, he says, “eventually learned how to study—though not immediately—through the persistence of my professors.” While working to help pay his way through school, Fuller worked at various positions in a local state mental hospital. During this job he developed an intense interest in the brain—and the conviction that a better understanding of the central nervous system could lead to new treatments for mental illness.

Bryan Molloy was born and grew up in Scotland, where he received his bachelor’s and PhD in chemistry before beginning postdoctoral work in the US and England, then joining Eli Lilly as a senior organic chemist. Being part of a process that brought benefits to so many was rewarding but, as he once told a grateful patient, the search for fluoxetine also was “great fun” and a true “intellectual high.”

As a young boy in Hong Kong, David Wong was already fascinated by chemistry, so much so that his parents encouraged him to move to the United States to study. After receiving a bachelor’s, master’s, and doctoral degree in biochemistry in rapid succession, followed by postdoctoral training, Wong shocked his mentors by leaving academics and taking a job in the pharmaceutical industry. At Eli Lilly, he also took a bold step, initiating studies of the uptake processes in monoamines (the earlier drugs) without asking permission.

For their work on fluoxetine, the team received one of the most coveted awards for drug development, the Pharmaceutical Manufacturers Association’s Discoverers Award. In recognition of the tremendous impact of their discovery on people with depression, the co-inventors of Prozac also were honored by NARSAD, a patient and donor supported organization dedicated to supporting innovative scientific research to find the causes, better treatments and cures for severe mental illnesses.

delete parts of the molecular structure of compounds to enhance desired effects. In the 1960s, for example, at the American pharmaceutical company Eli Lilly, Bryan Molloy was focused on creating new compounds for heart disease, particularly those in which acetylcholine regulated heart action. Another Eli Lilly scientist, pharmacologist Ray Fuller, persuaded Molloy to turn his attention to drugs for depression, especially those that would work without affecting acetylcholine, thus avoiding the TCAs’ troubling side effects. Like so many scientists before him, Molloy focused on antihistamines. He began to tinker with the molecular structure of diphenhydramine, one of the oldest antihistamines, marketed under the trade name Benadryl for treatment of hay fever, allergies, the common cold, bee stings, poison ivy and other of life’s irritations. He created a series of analogues: structural derivatives of a compound that can differ by as little as a single element.

David Wong, a chemist at Eli Lilly, also was ready to shift his area of research, then focused on antibiotics, to neurochemistry. He had been particularly fascinated by new work suggesting that serotonin played a major role in mood regulation.

In 1971, Solomon Snyder, one of Axelrod’s former postdoctoral students and now one of biological psychiatry’s superstars, received an award from the
American Society for Pharmacology and Experimental Therapeutics. The prize carried with it the obligation to give a lecture at Eli Lilly and Snyder decided to talk about work being done in his laboratory at Johns Hopkins University. He and colleagues had just developed a method that allowed them to discriminate nerves’ uptake of serotonin, norepinephrine and dopamine. In this method, brain cells were centrifuged and the nerve endings separated out. Astonishingly, the nerve endings in this extract continued to take-up neurotransmitters to which they were exposed, giving researchers a relatively fast and clear way to see how various compounds might block these neurotransmitters. Wong and Molloy were amazed. They joined forces in the laboratory headed by Ray Fuller. Using Snyder’s method, Wong began testing Molloy’s new compounds, more than 250 of them, looking for a compound selective for serotonin (See “Three American success stories”).

Over the summer of 1972, one of those versions—fluoxetine—was found to be the most potent and selective inhibitor of serotonin reuptake while inhibiting very little else. It was 200 times more active in inhibiting the uptake of serotonin than of norepinephrine, and it did not affect either histamine or acetylcholine.

The discovery of fluoxetine (Figure 7), which came to be known by its trade name Prozac, and its effect on serotonin reuptake was announced in 1974. It would take another 13 years before it was shown clearly that fluoxetine would work in humans with severe depression and be approved for treatment of depression by the FDA.

The pharmaceutical licensing environment had changed greatly since the arrival of the earlier antidepressants on the market. In 1962, alarmed by the often striking birth defects that occurred in babies of women who had taken the sleeping pill thalidomide while pregnant, the U.S. Congress had instructed the Food and Drug Administration to conduct extensive tests in animals, then in humans, before allowing any new drug to be approved for market. (Thalidomide had been marketed in Germany without adequate testing.) Furthermore, all new drugs had to be tested against placebos: substances with no recognized medical effect but that sometimes alleviated symptoms in users who believed they might be receiving “real medicine.”

While Eli Lilly pondered whether it should begin the expensive and time-consuming process of testing fluoxetine, a Swedish pharmaceutical company, Astra, began marketing its own drug, an antihistamine...

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Figure 7: The chemical structure of fluoxetine, marketed under the name Prozac, allows it to specifically block serotonin reuptake in neurons and is chemically very similar to antihistamines such as diphenhydramine, better known as Benadryl. Image from Wikipedia Commons.
derivative named zimelidine. This drug, under the trade name of Zelmid®, blocked reuptake of serotonin (but not norepinephrine) and relieved depression. Licensed by Merck for distribution in the United States, it was withdrawn when several patients developed Guillain-Barre syndrome, a paralysis that can be lethal. Without this unexpected complication, the new “miracle drug” soon to be proclaimed in headlines might have been Zelmid, not Prozac. With this complication, however, the market was wide open.

Eli Lilly began moving forward. Fluoxetine made it through numerous clinical trials, demonstrating it could improve symptoms of depression in the majority of patients, clearly outperforming placebo, and working at least as well as earlier drugs but—very important—without their complications and side-effects.

Under the brand name Prozac, fluoxetine was approved for clinical use by the FDA on December 29, 1987. Early in 1988, Eli Lilly introduced it for the treatment of depression as a once a day medication with minimal side effects. Six years later, the FDA also approved the drug for the treatment of obsessive-compulsive disorder. Approval for use treating other medical conditions would follow. Over a relatively short period of time, five different new SSRIs were launched successfully in multiple countries around the world, each developed by a different company.

**Figure 8:** Unlike previous anti-depressant treatments, selective serotonin reuptake inhibitors (SSRIs) drugs specifically prevent only serotonin from being recaptured through reuptake mechanisms. This results in more serotonin available in the synapse (space between neurons), which has an antidepressant effect. Because SSRIs are specific to serotonin, they have fewer side effects than predecessors that affected multiple neurotransmitter receptors. Figure by Corporate Press.
This was testimony to the shift from a serendipitous discovery process—noting what worked—to one of rational drug development, a three-step process in which:

• the enzyme or receptor involved in a disease is identified,

• the molecular structure of that enzyme or receptor is identified, and

• a molecule is designed and synthesized so that it will bind tightly to that enzyme or receptor, changing its behavior in the desired manner.

As basic scientists are fond of noting, when they can understand the cause of a problem, then they know how to begin to fix it.

While Many Cheered, Others Worried

One of the “miracle” aspects of the new SSRIs was their relative lack of side effects. Because of their design, largely blocking the reuptake of only one specific neurotransmitter and not interfering with the action of others, the SSRIs had few of the side effects of the TCAs (Figure 8). As a result, patients could begin treatment, on day one, with a therapeutic dose level, as opposed to earlier generation antidepressants, which had to be initiated at lower, less therapeutic dosages, then slowly increased, so that the patient had time to develop some tolerance to the unwanted side effects. Unlike previous antidepressants, Prozac did not interfere with ongoing or new psychotherapy; in fact, patients often appeared better able to take advantage of it. But perhaps the most important difference was that, while the early SSRIs did have some side effects for some patients, notably sleep disturbance, sexual dysfunction, and weight gain, the new drugs were seldom lethal in overdose, whether accidental or intentional.

But others worried that the SSRIs’ relative lack of side effects was a two-edged sword in that it meant clinicians felt freer to prescribe it to less severely ill people, perhaps even to some who wanted to change their personality rather than treat an illness. Then, several lawsuits claimed that the drugs were responsible for some well-publicized cases of violent and suicidal behavior. A political hearing in the early 1990s was so emotional that the chair decided to wear a bulletproof jacket. Many of these patients involved in these early cases were found to have had earlier problems, and a review of studies published between 1960 and 2004 found that overall suicide rates have dropped steadily since Prozac and other antidepressants hit the market. Professional groups, including the American Psychiatric Association, argue that untreated and undertreated depression carries a far greater suicide risk. Nonetheless, disagreement still exists about how widely antidepressants in general should be used, especially in children and adolescents. Placebo-controlled clinical trials have shown that children and adolescents on antidepressants (SSRIs and other types of medications) do have a two-fold increased risk of suicidal thinking.

The Promise Of The Future, Building On The Past

Although SSRIs quickly rose to the top of the charts, the older drugs did not go away (Table 1). For example, TCAs are still believed to be more effective for patients with melancholic and psychotic depression, and the availability of an arsenal of different drugs meshes well with science’s growing ability to subdivide the types of depression. In fact, 21st century medicine is moving rapidly in the direction of individualized, personalized care, no longer clumping all patients with a specific diagnosis together for the same treatment, but instead using genetic and other information to identify specific groups of patients that would benefit from taking one drug more than another, individualizing drug dosage, and identifying those more likely to experience adverse drug effects. Individuals are also sometimes placed on more than one antidepressant, the combinations and dosages changing as symptoms change. Even more often, pharmacological treatment is combined with other, non-pharmacological treatments. Although Freudian psychoanalysis for depression has become markedly less popular, newer psychotherapies, such as
<table>
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<tr>
<th>CATEGORY OF MEDICATION</th>
<th>SOME COMMON BRAND NAMES</th>
<th>CHEMICAL NAME</th>
<th>HOW IT WORKS</th>
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<tr>
<td>Antipsychotic</td>
<td>Thorazine</td>
<td>Chlorpromazine</td>
<td>Through many receptor blocking mechanisms as well as preventing reuptake of neurotransmitters</td>
</tr>
<tr>
<td>Antidepressant—Monoamine oxidase inhibitor (MAOI)</td>
<td>Marsilid, Iprozid, Ivronid, Revival, Propiniazida</td>
<td>Iproniazid</td>
<td>Blocks the destruction of neurotransmitters by the enzyme monoamine oxidase</td>
</tr>
<tr>
<td>Antidepressant—Tricyclic antidepressants (TCA)</td>
<td>Tofranil, Elavil</td>
<td>Imipramine, Amitriptyline</td>
<td>Blocks the reuptake of multiple neurotransmitters, including norepinephrine, serotonin, and dopamine</td>
</tr>
<tr>
<td>Antidepressants—Selective serotonin reuptake inhibitors (SSRI)</td>
<td>Prozac, Paxil, Zoloft</td>
<td>Fluoxetine, Paroxetine, Setraline</td>
<td>Specifically blocks the reuptake of serotonin</td>
</tr>
</tbody>
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Note: List is not comprehensive and is not intended to be endorsing any products.

cognitive-behavioral therapy, found a new ally in drugs that make people better able to focus on solving problems that may have worsened or been worsened by their depression. In addition, patients increasingly are “prescribed” exercise as it has become clear that a regular exercise routine can have profound biological and psychological effects.

As always true in science, discovery of the biochemical processes involved in depression—and how chemicals could alter those processes to alleviate symptoms—both solved some mysteries and brought new ones to light. The recognition that there are genetic vulnerabilities to mental disorders has led to the search for specific genes that confer risk for depression and a better understanding of how this vulnerability interacts with specific types of environmental factors. The recent sequencing of the human genome and the tabulation of variants of human genes have set the stage to make this possible. Finding these gene variants will allow scientists to identify the brain circuits whose functions they affect and then create new drugs to normalize those brain functions. The field of psychiatric pharmacogenomics (the intersection of psychiatry, pharmacology, and genomics), although in its infancy, represents “personalized medicine” at its best—allowing us to refine individual treatment, and optimize development of new drugs.

Another hot new technology neuroscientists are now using is brain imaging. The human brain was once considered to be a black box. Today, emerging technologies such as functional magnetic resonance imaging allow scientists and clinicians to look at brain regions active in certain kind of mental processes and to see differences in different groups of people, such as those with and those without depression. It then should be possible to correlate this knowledge with what is being discovered about genetic variation and create better, more personalized treatments.

Continued understanding of the biological basis of depression and the fundamental neuroscience of the brain will one day lead to more and perhaps improved treatments for depression. Like the scientists and clinicians of the past who worked to develop today’s breakthrough treatments, which have allowed many suffering from depression to resume a much higher quality of life, today’s researchers are making the discoveries that will lead to the antidepressants of the future.
Biographies

Sylvia Wrobel, Ph.D. writes frequently about science and medicine and was the author of the first Breakthroughs in Bioscience article in the FASEB Journal.

David B. Bylund, Ph.D. is a professor in the Department of Pharmacology and Experimental Neuroscience at the University of Nebraska Medical Center. His research focuses on the regulation and development of alpha-2 adrenergic receptor subtypes in the brain in relation to various disorders, including depression and Attention Deficit Hyperactivity Disorder (ADHD). In particular, Dr. Bylund’s lab is examining differences in regulation of these receptors in response to antidepressant treatment in adults versus children, as well as looking at potential genetic basis of ADHD. Dr. Bylund has served on numerous editorial boards, including the Editor of Pharmacological Reviews, the series editor for The Receptors, Associate Editor for the Journal of Pharmacology and Experimental Therapeutics, and the Executive Editor for xPharm, a comprehensive web-based pharmacology database. He has published over 160 papers and is currently the PI on three NIH grants, two of which are related to juvenile depression. The third is for a short course in integrative and organ system pharmacology.

Suggested Reading

Listening to Prozac is well subtitled “A Psychiatrist Explores Antidepressant Drugs and the Remaking of the Self.” In this classic first published in 1993, author Peter D. Kramer discusses how, as a psychiatrist accustomed “to seeing patients’ personalities change slowly, through painfully acquired insight and hard practice,” he began to see some “personalities altered almost instantly, by medication,” becoming, as one patient told him, “better than well.” Spending time with patients who responded to Prozac transformed his views about what makes people the way they are, what is “inborn, biologically determined,” and what is “slowly acquired, history laden.” He called this realization, experienced both by himself and his patients, “listening to Prozac.” In addition to discussing how Prozac had “entered into our struggle to understand the self,” this lively book also provides an overview of how the new drugs were created (the description of the work in the Eli Lilly laboratories in this article is largely based on Kramer’s account) and gives numerous case histories of people who benefited from antidepressant drugs. Penguin Books.

Better than Prozac: Creating the Next Generation of Psychiatric Drugs traces some of the early discoveries that led to drugs for anxiety, depression, obsessive compulsive disorder, panic disorder and other conditions. The author, distinguished neurobiologist and psychiatrist Samuel H. Barondes, explains how new understanding of molecular mechanisms that produce specific patterns of mental symptoms creates targets for the “next generation” of drugs. He also discusses what newly identified genetic susceptibility genes, whether for Alzheimer’s or schizophrenia, tell scientists about these mechanisms. Intended for the lay reader, his explanations are clear and supported by patient histories. Oxford University Press, 2003.

First hand accounts from those who have suffered severe depression bring home its harrowing realities, pain and exhaustion—and enable those who suffer from it to realize they are not alone. For this reason, journalist Mike Wallace, humorist Art Buchwald, and Pulitzer Prize-winning author William Styron, perhaps best known for novels such as Sophie’s Choice, were among a few of the famous people who often spoke publicly of their own battles with depression. Styron wrote movingly of his own illness in Darkness Visible: A Memoir of Madness (Random House, 1990). Psychiatrist Kay Redfield Jamison wrote the classic textbook on bipolar disorder, also known as manic depression. She also wrote about her own struggle with the disease in An Unquiet Mind: A Memoir of Moods and Madness (Vintage Books 1995), and has more recently written about the connection between emotional illness and creativity.

For up-to-date information on depression and treatment, or for help in locating services in your area, visit the National Institutes of Mental Health webpage at www.nimh.nih.gov. The Harvard Medical School—InteliHealth website includes regularly updated information about depression. Go to www.intelihealth.com and select depression under medical conditions.

Acknowledgement:

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