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Why Are So Many Women Depressed?

Women may be more sensitive—physiologically, at least—to certain changes in the environment. And this responsiveness might help explain the high rates of depression in their ranks

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The symptoms of depression range from uncomfortable to debilitating: sleep disturbances, hopelessness, feelings of worthlessness, difficulty concentrating, fatigue and sometimes even delusions. Most of us have watched a relative or friend struggle with depression—and many of us have experienced it ourselves. Even so, few people realize just how common depression is, how severe it can be or that it is most prevalent among women. In 1990 the World Health Organization found depression to be the leading cause of "disease burden" (a composite measure including both illness and death) among women, noting that it affects almost 20 percent of the female population in the developed world. Epidemiological studies indicate that 12 percent of U.S. women—compared with only 6 percent of U.S. men—have suffered from clinically significant depression at some time in their lives.

The big question, of course, is why such a gender gap exists. Over the years various explanations have surfaced to account for the fact that, from one study to the next, depression is between two and three times more common among women than it is among men. Some mental health workers have pointed to psychology, arguing that women are better trained to recognize their feelings and seek help, so they come to the attention of health professionals more often than men. Others have suggested that oppression—in the form of physical or sexual abuse, harassment or discrimination—is to blame. Others still have attributed the increased rates of depression among women to the female reproductive system and the menstrual cycle.

Medications known as selective serotonin reuptake inhibitors (SSRIs), which are often most effective when used in conjunction with psychotherapy, were approved for treating depression in the late 1980s. These drugs, which include Prozac, Paxil and Zoloft, act on the brain by regulating the neurotransmitter serotonin.

But it isn't that simple. Data from a variety of studies show that depression clearly has psychological, environmental and biological roots. Modern neuroscience is beginning to teach us how these roots can become intertwined and reinforce one another. In other words, an increased risk for depression in women might stem from genetics, the effects of stressful events or social pressures, or some combination of all three. Neuroimaging of the brain's circuitry by PET and MRI scans reveals that psychological phenomena such as anger and sadness have biological underpinnings; we can now see circuits of brain cells becoming activated when these emotions arise.

Similarly, neuroimages demonstrate that environmental and psychological experiences can alter our brain chemistry. For example, Lewis R. Baxter and his colleagues at the University of California at Los Angeles found similar changes on the PET scans of patients with obsessive-compulsive disorder who responded to treatment, regardless of whether the patients were treated with medication or with behavioral therapy.

To figure out why depression is more common among women, scientists have to study how genetics and environment divide the sexes—and how the two conspire to produce the symptoms we describe as depression. It is difficult work, and progress is necessarily slow. But what is coming into focus is that certain environmental factors—including stress, seasonal changes and social rank—may produce different physiological responses in females than they do in males. These findings, which I will outline, are small pieces in what is proving to be an incredibly complex puz-

Psychotherapy has long proved valuable in alleviating symptoms of depression. More than 80 percent of all depressed patients now respond to therapy or medication, or a combination of the two.

zle. Laying them out at this stage does not begin to explain depression's double standard. Nevertheless, it could help scientists develop more effective treatments for depressed individuals—both women and men—in the meantime.

Stress and Cortisol

Many scientists have wondered whether there is some quirk in the way depression is inherited, such that a depressed parent or grandparent is more likely to pass on a predisposition for the disorder to female than to male descendants. Based on studies that trace family histories of depression, the answer to that question appears to be no. Women and men with similar heritage seem equally likely to develop the disorder. Simply tracing family histories, though, without also considering environmental influences, might not offer a complete picture of how depression is inherited.

Indeed, Kenneth S. Kendler and his colleagues at the Medical College of Virginia found in a study of 2,060 female twins that genetics might contribute to how women respond to environmental pressures. The researchers examined twins with and without a family history of depression; some twins in both groups had recently undergone a trauma, such as the death of a loved one or a divorce. The investigators found that among the women who did not have a family history of depression, stressful events raised their risk for depression by only 6 percent. But the same risk rose almost 14 percent among the women who did have a family history of depression. In other words, these women had seemingly inherited the propensity to become depressed in the wake of crises.

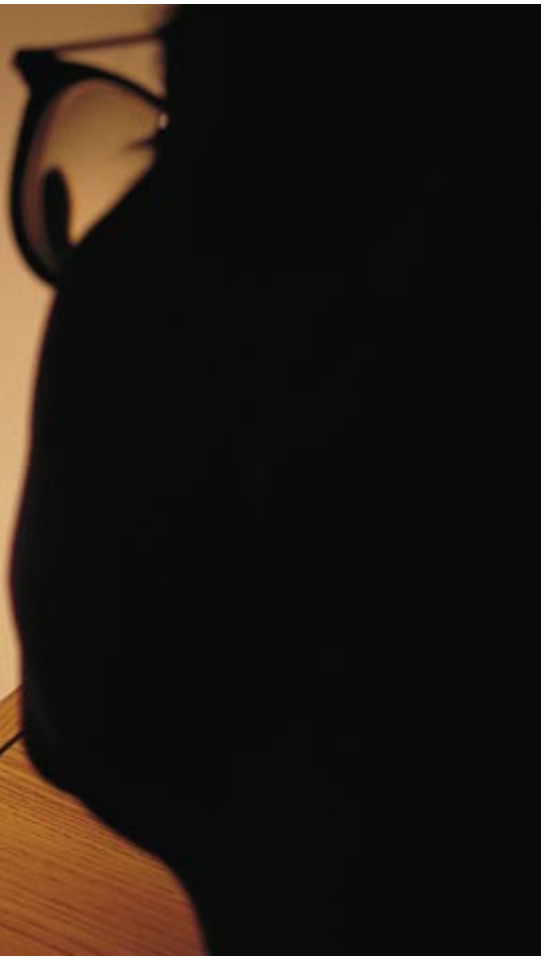
A similar study has not been done in men, leaving open the question of whether environmental stress and genetic risk for depression interact similarly in both sexes. But research is being done to determine whether men and women generally experience similar amounts and types of stress. Studies of key hormones hint that they do not. Hormones are not new to depression researchers. Many have wondered whether the gonadal steroids estrogen and progesterone—whose cyclic fluctuations in women regulate menstruation—might put women at a greater risk for depression. There are at least two ways in which they might do so.

First, because of differences between the X and Y chromosomes, male and female brains are exposed to different hormonal milieus in utero. These hormonal differences may affect brain development so that men and women have different vulnerabilities—and different physiological reactions to environmental stressors—later in life. Indeed, animal experiments show that early hormonal influences have marked behavioral consequences later on, although the phenomenon is of course difficult to study in humans.

Second, the fact that postpubertal men and women have different levels of circulating gonadal steroids might somehow put women at higher risk for depression. Research shows girls become more susceptible to depression than boys only after puberty, when they begin menstruating and experience hormonal fluxes. Even so, scientists have never been able to establish a direct relation between emotional states and levels of estrogen and progesterone in the blood of women. For example, Peter J. Schmidt and David R. Rubinow of the National Institute of Mental Health recently reported that manipulations of estrogen and progesterone did not affect mood, except in women who suffer from severe premenstrual mood changes.

It now appears, however, that estrogen might set the stage for depression indirectly by priming the body's stress response. During stressful times, the adrenal glands—which sit on top of the kidneys and are controlled by the pituitary gland in the brain—secrete higher levels of a hormone called cortisol, which increases the activity of the body's metabolic and immune systems, among others. In the normal course of events, stress increases cortisol secretion, but these elevated levels have a negative feedback effect on the pituitary, so that cortisol levels gradually return to normal.

Evidence is emerging that estrogen might not only increase cortisol secretion but also decrease cortisol's ability to shut down its own secretion. The result might be a stress response that is not only more pronounced but also



NAJLAH FEANNY *SABA*

longer-lasting in women than in men.

For example, Nicholas C. Vamvakopoulos, George P. Chrousos and their colleagues at the National Institute of Child Health and Human Development recently found that increased levels of estrogen heighten the activity of the gene for human corticotropin-releasing hormone (CRH). This gene controls the secretion of CRH by a region of the brain called the hypothalamus. CRH makes the pituitary gland release adrenocorticotropic hormone (ACTH), which circulates in the blood and eventually reaches the adrenal glands, where it prompts the secretion of cortisol. Thus, estrogen can, by increasing CRH secretion, ultimately boost cortisol secretion. And Elizabeth A. Young of the University of Michigan and others have shown that female rats are more "resistant" to cortisol's negative feedback effects than are either male rats or spayed female rats. She has also shown that women have longer-lasting cortisol responses during the phase of the menstrual cycle when estrogen and progesterone levels are high.

It is unclear whether depression is a cause or a consequence of elevated cortisol levels, but the two are undoubtedly related. Over the past few decades, a number of studies have shown that cortisol levels are elevated in about half of all severely depressed people, both men and women. So the idea is this: if estrogen raises cortisol levels after stress or decreases cortisol's ability to shut down its own secretion, then estrogen might render women more prone to depression—particularly after a stressful event.

Light and Melatonin

Despite their importance, estrogen and cortisol are not the only hormones involved in female depression, and stress is not the only environmental influence that might hold more sway over women than men. Recent findings by Thomas A. Wehr, Norman E. Rosenthal and their colleagues at the National Institute of Mental Health indicate that women might be more responsive physiologically than men to changes in exposure to light and dark. These investigators have had a long-standing interest in seasonal affective disorder (SAD), or so-called winter depression (although it can occur in the summer as well), and the role that the hormone melatonin might play in the illness. Similar to the gender ratio in other forms of depression, SAD is three times more common in women than in men.

Melatonin has been a prime suspect in SAD because organisms (including humans) secrete it only when they are in the dark and only when the body's internal clock (located in the hypothalamus) believes it is nighttime. The pineal gland, a small structure that resides deep in the mammalian brain, begins to secrete melatonin in the evening, as daylight wanes. Melatonin levels drop in the morning, when light hits the retinas of the eyes. Because nights are longer in winter than in summer, animals living in the wild secrete melatonin for longer periods each day during winter. Among animals that breed in summer, the onset of this extended daily melatonin secretion signals the presence of winter and shuts down the secretion of gonadal steroids that facilitate reproduction.

SAD researchers have long wondered whether a wintertime increase in the duration of melatonin secretion might also trigger depressive symptoms in susceptible individuals. In a series of ongoing studies designed to address this question, Wehr and his colleagues first asked whether humans, like animals, undergo seasonal changes in melatonin secretion. It is an important question, given that artificial light provides humans with an "endless summer" of sorts compared with animals in the wild. To find out, Wehr measured melatonin secretion in 15 humans when they were exposed to 14 hours of darkness and later to only eight hours of darkness each night. The results of this experiment, conducted mostly among men, were positive: people experiencing longer periods of darkness secreted melatonin for longer periods during the night, as wild animals do.

Next, the researchers asked whether this natural sensitivity to the seasonal day-length change persisted when people were allowed to follow their usual schedules, turning on artificial lights at night as they normally would. Here the researchers were surprised to find a gender difference. Under normal living conditions, women were more likely than men to retain a sensitivity to seasonal changes in day length. In other words, for women the duration of nocturnal melatonin secretion was longer in winter than summer; in men, however, there was no seasonal difference.

These results suggest that women are more sensitive to natural light than men—and that in a society where artificial light is everywhere, women somehow still detect seasonal changes in natural day length. Whether this gender difference puts women at increased risk for SAD is unclear; paradoxically, there is evidence that women with SAD symptoms may be less likely than unaffected women to have an increased duration of melatonin secretion in winter.

To complicate the story further, the relation between these findings and those regarding cortisol and estrogen are also unclear, because we don't know whether the duration of melatonin secretion affects reproductive function in women, as it surely does in animals. Researchers are now working to unravel the complicated relations between these hormonal systems and to determine whether, and how, they may influence individuals' risk for depression.

Social Rank and Serotonin

If women's bodies are in fact particularly sensitive to environmental changes, the explanation may lie within the system that controls serotonin, one of many so-called neurotransmitters that nerve cells use to communicate with one another. Serotonin modulates both cortisol and melatonin secretion. (The similarity in

PHOTOGRAPHS BY NAJLAH FEANNY *SABA*

Treatment alternatives such as light therapy (top) *and electroconvulsive therapy (ECT)* (bottom) *are used in special cases. Light therapy seems particularly effective in patients with the form of depression called seasonal affective disorder (SAD). ECT is most often used as a last resort, when all other treatment options have failed.*

names between serotonin and melatonin is no accident: the latter is synthesized directly from the former, and the two have very similar chemical structures.) And a great deal of evidence indicates that dysfunction in the serotonergic, or serotonin-secreting, system contributes to depression and anxiety disorders, which are also more common in women than men. Recently research in animals and humans has provided preliminary, but key, insights into this system.

First, it appears that the serotonergic system serves as a link between an animal's nervous system and its physical and social environment. That is, not only do stress and daylight act via the serotonergic system but an animal's social rank also appears to affect its serotonin level. A number of studies show that blood and brain serotonin levels change as an animal moves up or down dominance hierarchies. For instance, dominant male monkeys often have higher blood serotonin levels than subordinate ones do. In addition, a recent study by Shih-Rung Yeh and his colleagues at Georgia State University shows that the sensitivity of an animal's neurons to serotonin varies according to that animal's status. Specifically, Yeh found that neurons taken from crayfish that had recently won a fight responded to serotonergic stimulation more strongly than neurons taken from losing crayfish.

There also appear to be significant gender differences in the serotonergic systems of both animals and humans. Mirko Diksic, Sadahiko Nishizawa and their colleagues at McGill University recently provided the most dramatic example: to measure serotonin synthesis in the human brain, they devised a new technique using PET neuroimaging and found that the average synthesis rate was 52 percent higher in men than in women. The investigators note that with the exception of estrogen binding sites, this gender difference in the brain is one of the largest ever reported. The lower rate of serotonin synthesis in women might increase their overall risk for depression—especially if serotonin stores are depleted during stress or winter darkness.

A Gender Difference

Meir Steiner and his co-workers at McMaster University suggest that if serotonin mediates between an organism and its environment and if the neurotransmitter is regulated differently in men and women, it might explain gender patterns not only in depression but also in a range of psychiatric illnesses. Specifically, whereas depression and anxiety are more common among women, alcoholism and severe aggression are more common among men. And just as low serotonin levels have been implicated in depression and anxiety disorders in women, they have also been found in the brains of men with severe forms of alcoholism and aggression.

Such gender differences in the serotonergic system might ensure that females respond to stress with psychiatric disturbances that involve behavioral inhibition, whereas men respond to stress with a loss of behavioral control. Steiner suggests that such gender differences in the serotonergic system evolved because child rearing is more successful (in the narrow sense of more children surviving to adulthood) in species in which aggressive impulses are curtailed in females.

A researcher espousing either the sociological or psychological explanation of depression's gender bias might counter Steiner's theory by arguing that men are socialized to respond to stress with "act-

ing out" behaviors, such as alcoholism or aggression. In contrast, society teaches women to respond to stress with "acting in" behaviors, such as depression. To support this idea, they might point to epidemiological studies done in Amish and Jewish populations. In these communities, alcoholism is less common than in the population at large, and, interestingly, the rates of depression are as high in men as in women.

These contradictory data leave no doubt that the explanations behind depression and other psychiatric diseases are not straightforward. Biological and social influences not only coexist but also probably reinforce one another. After all, we would expect gender socialization patterns to evolve so that they complement biological differences between the sexes. In other words, we would expect "nurture" to reinforce rather than oppose "nature." And because nurture involves learning—and learning occurs when certain neural connections in the brain are strengthened—it is clear that both nurture and nature involve biological processes.

Scientists have made tremendous strides in treating depression. With the advent of such antidepressants as Prozac (which acts on the serotonergic system), more than 80 percent of depressed patients now respond to medication or psychotherapy, or a combination of the two. But much more work remains to be done. Because depression is so common, its cost to society is high. The National Institute of Mental Health estimates that depression claims $30.4 billion in treatment and in lost productivity from the U.S. economy every year.

And these costs are on the rise: depression is becoming more common in successive generations (the so-called cohort effect). No one knows what is causing the cohort effect—but it is moving much too quickly to have a genetic basis. Theories about what is causing the cohort effect range from increased drug abuse and familial disarray to the suggestion that perhaps older people are simply more likely to forget past depressive episodes when asked. The cohort effect and depression in general remain very much a mystery. And for the men and women who suffer from it, it is a mystery that cannot be solved soon enough. SA

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Treating PMS with Antidepressants

From time to time, almost all women experience what is known as premenstrual syndrome (PMS): mild cramping, bloating, irritability and fatigue. For some, the symptoms preceding menstrual periods are debilitating. An estimated 3 to 5 percent of all women suffer from marked distress, anger, tension and mood swings every month. For these women a range of remedies—including progesterone, estrogen, diuretics, vitamins, herbs and mineral preparations—have proved useless.

The bad news is that no one has figured out exactly what causes the condition—which psychiatrists now call premenstrual dysmorphic disorder (PDD). But scientists have found that a class of antidepressants, called selective serotonin reuptake inhibitors (SSRIs), can alleviate PDD in some patients. These medications represent a big improvement over the only previous solution—surgically removing the ovaries. And the fact that these drugs help also underscores the point that PDD has a biochemical basis. It is not—as many women have been told by their physicians—something they imagine.

Most evidence suggests that women with PDD have deficiencies in the neurotransmitter serotonin. SSRIs, such as Prozac, Zoloft and Paxil, act in the brain to raise serotonin levels. Studies show that tryptophan, an amino acid the body uses to make serotonin, can relieve symptoms of PDD, and laboratory tests reveal that women with PDD have abnormal blood levels of serotonin. In addition, the disorder often causes women to crave carbohydrates, a symptom that is also associated with a dearth of serotonin.

Since SSRIs were introduced in the late 1980s, roughly a dozen studies have demonstrated their efficacy in treating PDD; last year a large investigation—involving more than 200 women and 12 medical centers—corroborated the finding. Kimberly Yonkers of the University of Texas Southwestern Medical Center at Dallas and her colleagues published in the *Journal of the American Medical Association* that 62 percent of women treated with the SSRI sertraline (Zoloft) improved, compared with only 34 percent of women who received a placebo. It is unclear whether SSRIs can alleviate less severe forms of PMS, but further research should lead to answers. *—Kristin Leutwyler, staff writer*

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SSRIs such as Zoloft (top), *Paxil* (middle) *and Prozac* (bottom) *help some women with severe PMS.*