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New Clues to Women Veiled in Black

By SUSAN GILBERT

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For centuries, doctors have recognized women's vulnerability to depression and proposed a variety of explanations. The female of the species, with her "excitable nervous system," was thought to wilt under the strain of menstruation and childbirth, or later, the pressures of work and family.

But researchers are now constructing more scientific theories to explain why women are nearly twice as likely as men to become depressed. Social bias and women's higher rates of physical and sexual abuse and poverty, experts say, clearly play a role. But scientists are also studying genes that may predispose girls and women to the disorder.

They are examining the likely role of estrogen and even linking the development of clinical depression to negative thinking, which is more common in women than in men.

There is no question that women bear the brunt of the illness that Winston Churchill referred to as his "black dog." The National Comorbidity Study, a large survey of adults in the United States released last year, found that 1.7 women for every man had experienced at least one episode of depression. Roughly the same ratio has been found in recent studies in nine other countries, including Canada, Brazil, Germany and Japan, said Dr. Marta Meana, an associate professor of psychology at the University of Nevada at Las Vegas.

"This is a global phenomenon," said Dr. Meana, who will address the issue at a meeting of the International Association for Women's Mental Health in Washington this week.

It is unlikely that any single gene, hormone level or type of experience explains the higher incidence of depression in women, experts say.

Instead, several genes probably work in concert with the ebb and flow of reproductive hormones to change brain chemistry in ways that might set the stage for depression, especially after an emotional ordeal.

Another risk factor appears to be something that researchers call overthinking, a tendency to dwell on petty slights, to mentally replay testy encounters and to wallow in sad feelings. Studies show that this type of negative thinking is far more common in women than in men, and that it can be a harbinger of clinical depression.

"The gender difference in overthinking is strongly tied to the gender difference in depression," said Dr. Susan Nolen-Hoeksema, a professor at the University of Michigan and a leading researcher on women and depression.

About half the risk of depression is thought to be genetic. The single gene, 5-HTT, that has been definitively linked to depression is no more common in women than in men. But preliminary research suggests that there are other depression-related genes that mainly affect women.

For example, after scanning the genomes of people with major depression in 81 families, Dr. George Zubenko, a professor of psychiatry at the University of Pittsburgh School of Medicine, identified 19 regions of chromosomes that were especially common and, therefore, likely to contain genes that promote depression. Four of these regions showed up only in the women and one only in the men, Dr. Zubenko and his colleagues reported last July in *The American Journal of Medical Genetics*, an online publication.

Such findings suggest that more genes may help to set off depression in women than in men, Dr. Zubenko said, explaining in part why more women become depressed. One may be CREB1, a gene that Dr. Zubenko's group has identified as a strong candidate. Especially intriguing, Dr. Zubenko said, is that CREB1 interacts with estrogen receptors.

Though the details of the relationship between CREB1 and estrogen are unknown, researchers have long thought that levels of sex hormones play some role in depression. For one thing, the sex difference in depression is most pronounced in women during their reproductive years, when sex hormone levels are highest. Before puberty, boys and girls have roughly equal rates of depression. The incidence of depression climbs in both sexes during puberty, but the climb is steepest for girls.

In a national telephone survey of 4,028 adolescents ages 12 to 17, about 14 percent of girls and 7 percent of boys met the criteria for major depression. The survey was published in August in *The Journal of Consulting and Clinical Psychology*.

In their reproductive years, women are also especially prone to bouts of depression when their sex hormones are in flux — just before menstruation and just after childbirth. Two subtypes of depression that affect only women — premenstrual dysphoric disorder and postpartum depression — occur then.

A leading theory is that sex hormones help induce depression in some women by affecting messenger chemicals in the brain that influence mood. Dr. Meir Steiner, director of the Women's Health Concerns Clinic at St. Joseph's Healthcare in Hamilton, Ontario, who studies the relationship between hormones and mood, thinks that the sensitivity of these neurotransmitters may increase when hormone levels are high or in a state of flux and decrease when they are low and stable.

But to blame women's higher rate of depression on hormones is too simplistic, experts say. Not all women become depressed when their hormone levels seesaw. A study sponsored by the National Institute of Mental Health showed that manipulating women's levels of estrogen and progesterone affected the moods of some women but not others.

Specifically, women who usually suffered from premenstrual syndrome, a condition characterized by moodiness in the week or so before menstruation that is less severe than premenstrual dysphoric disorder, found that their moods lifted when they were given a drug that kept their hormone levels low.

When their hormone levels went back to normal, these women felt blue. But women who did not suffer from premenstrual syndrome did not experience ups and downs in mood during the study.

Such findings indicate that it is not hormone levels per se that make some women feel moody or depressed at times of hormonal flux, but an underlying vulnerability, said Dr. Mary Blehar, formerly of the National Institute of Mental Health and now director of cancer prevention, control, behavior and science at the National Cancer Institute.

"What that vulnerability is is the big question," she said.

Genes may tell much of this story. Dr. Zubenko, for example, suggests that some genes that raise women's risk of depression may exert their effect in the presence of high levels of estrogen, their influence then decreasing when estrogen falls after menopause. But biology cannot entirely explain the sex difference.

"It's not just genetics," Dr. Steiner said.

Women, Dr. Nolen-Hoeksema says, are at least twice as likely as men to be abused, and abuse often leads to depression. Another important factor, she said, is the greater tendency of girls and women to ruminate over the common curveballs of life, like criticism at work or school or rejection by a friend.

In studies over the last decade, Dr. Nolen-Hoeksema has consistently found that women react more strongly than men to such experiences, mulling them over and over without being able to come to a resolution or to simply move on. Dwelling on problems causes the initial sadness to snowball, she said.

By contrast, men are more likely than women to distract themselves from a problem, often by going off and doing something active, a healthy reaction, Dr. Nolen-Hoeksema said, because it blunts the emotional sting of everyday disappointments and setbacks.

Dr. Nolen-Hoeksema's studies have found that people who habitually ruminate but are not depressed are more likely than non-ruminators to develop depression later.

There may be biological reasons behind women's tendency to brood, but no genetic predisposition or difference in the brain has been found.

Still, Dr. Nolen-Hoeksema said, "There are cultural and personality contributors to rumination."

Women tend to forge intense emotional connections and to care deeply about relationships, she said.

"Our investment in relationships can be a source of great richness in our lives," but taken too far, it can also become destructive, Dr. Nolen-Hoeksema said.

In her research, Dr. Nolen-Hoeksema has found that the sex difference in negative thinking is apparent in children as young as 9, several years earlier than the sex difference in depression emerges.

In a book published last year, "Women Who Think Too Much" Dr. Nolen-Hoeksema recommends a variety of strategies to help teenage and adult women cut down on overthinking.

Staying active can help. For teenage girls, playing a sport or engaging in other extracurricular activities can keep them from brooding about bad grades or broken romances.

"If you have your self-esteem hinged on one thing, like a single relationship, you don't have a fallback if something goes wrong," Dr. Nolen-Hoesksema said. Another strategy is to cultivate a circle of friends.

"When women ruminate, we blow things up," she says. "It helps to have friends who can help you reflect on a problem and find a solution." Just make sure, she adds, that the friends are not too prone to rumination themselves.