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ANOREXIA MAY REPRESENT A PROFOUND PSYCHIATRIC DISORDER
THAT SPAWNS AN ADDICTION TO DEPRIVATION **BY TRISHA GURA**

ADDICTED TO **STARVATION**

A recent tabloid captured the common wisdom about anorexia nervosa. In an interview, actor Christina Ricci blamed the pressures of success for her prior struggle with the disease. The headline flashed, “Ricci: Hollywood made me anorexic.”



But did it? True, anorexia is characterized by compulsive dieting or exercise to get thin. And the pursuit of thinness in contemporary culture—particularly in Hollywood—has become a seemingly contagious obsession. Yet there is thin, and then there is emaciated. Crossing over that line means a loss of a basic survival instinct—to eat in response to hunger—that culture should not be able to touch.

What is more, cultural cues cannot easily explain why the afflicted, who are shockingly skinny, misperceive themselves as fat. Anorexics also say they feel more energetic and alert when starving:

starvation boosts their metabolic rate, which is in stark contrast to the slowing of metabolism that occurs in most people during a fast.

Such mysteries cry out for a biological explanation. To find one, researchers are probing the brains of anorexics; their work is painting a new picture of anorexia as a multifaceted mental illness whose effects extend far beyond appetite. The illness is accompanied by disturbances in the brain's reward circuitry that may lead to a general inability to feel delight from life's pleasures, be they food, sex or winning the lottery. As such, the ailment shares characteristics with drug addiction—the drug in this case being deprivation

itself. The study of anorexia, therefore, may yield insights into brain mechanisms for producing pleasure and how something as seemingly unpalatable as starvation or extreme asceticism might, oddly, give rise to a sense of hedonism.

An estimated 0.5 to 3.7 percent of girls and women in the U.S. suffer from anorexia, according to the National Institute of Mental Health. (One tenth as many males experience the illness.) At least two thirds of anorexics do not fully recover even after years of the current treatment, which consists largely of psychotherapy. As a result, anorexia still holds the record for the highest mortality rate (up to 20 percent) for any mental illness in young females. Cutting that death rate will require a new approach, experts say. "People have long been blaming families and media," says psychiatrist Walter Kaye of the University of California, San Diego. "But eating disorders are biological illnesses, and better treatments will come from more biologically-based approaches."

Diet as a Drug

Most people abhor dieting. But when a person with anorexia diets, he or she actually feels *better*—more alert and energetic—when starving. Anorexics do feel hunger pangs; they simply find ways to override them. Dieting becomes the ultimate accomplishment, a fix that a certain kind of dieter learns to crave.

The lack of food may function like an addictive drug for anorexics, says biologist Valerie Compan of CNRS in Montpellier, France. Almost every drug of abuse acts on the brain's natural reward circuitry—and in particular on a pleasure hub called the nucleus accumbens—to boost the levels of a signaling chemical, or neurotransmitter, called dopamine. The release of dopamine prompts good feelings and also produces the "high" in the case of many abused drugs. Some such drugs, including the highly addictive club

FAST FACTS

Deprived of Delight

- 1>> Researchers are painting a new picture of anorexia as a multifaceted mental illness whose effects extend far beyond appetite.
- 2>> Anorexia is accompanied by disturbances in the brain's reward circuitry that may render patients unable to feel delight from life's pleasures, be they food, sex or winning the lottery. Some scientists compare anorexia to drug addiction.
- 3>> Anorexia's biological risk factors appear to exert much of their insidious power at puberty, underscoring the importance of timing in prevention. Eating too little to keep up with growth or activity levels may tip the balance in favor of anorexia in teenagers who are predisposed toward developing the disorder.

drug ecstasy, also suppress appetite—a clue that a refusal to eat might somehow arise from abnormal activity in the brain's reward system.

In October 2007 Compan and her colleagues found some evidence for that idea. When the researchers injected ecstasy into the nucleus accumbens of mice, the rodents acted like anorexics. When they were offered food, the animals did not eat much, and when food was withheld, they did not work to get it. Ecstasy suppressed the rodents' appetites, the researchers determined, by stimulating a receptor for the neurotransmitter serotonin. Activating that receptor on neurons in the nucleus accumbens led to the production of a neurotransmitter associated with addiction called CART (for cocaine- and amphetamine-regulated transcript) that ultimately depressed the desire to eat.

This mechanism connects activation of the brain's reward circuitry to a lack of appetite. And if the two effects happen simultaneously, an individual may come to associate a lack of food with reward. In this way, the person could become addicted to hunger itself. "Anorexia can be an addiction," Compan says, "and it appears to share the same mechanism as a drug of abuse."

Lights Out

Other data, too, point to perturbations in the brain's reward circuitry as a key problem in anorexia. Some research hints that an addiction to

RECENT DATA POINT TO PERTURBATIONS IN THE BRAIN'S REWARD CIRCUITRY AS A KEY PROBLEM UNDERLYING ANOREXIA NERVOSA.

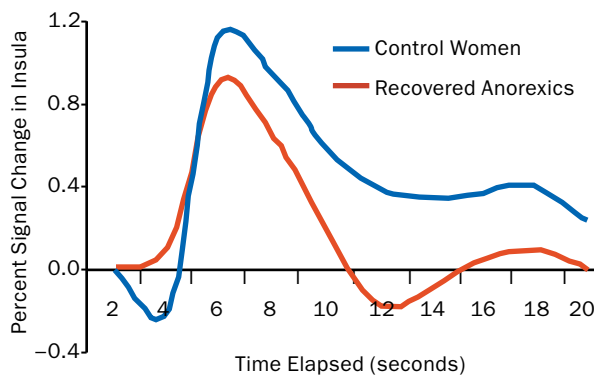
starvation renders anorexics, like drug addicts, incapable of feeling pleasure from food and possibly other amusements as well. Kaye, along with University of Pittsburgh psychiatrist Angela Wagner and others, scanned the brains of 16 recovered anorexics and 16 women who had always eaten normally while the subjects sampled water or sugar water and reported whether they were enjoying the drink.

In May 2007 the researchers reported that all the women in the control group enjoyed the taste of the sugar water more

than that of the plain water, and the pleasing sweet sensation lit up the insula, a brain structure important for recognizing taste. In contrast, in the women with a history of anorexia the insula responded much more weakly to the sweet taste, and its activation level bore no relation to how much the women enjoyed the sugar water, suggesting that these women lacked an ability to appreciate good tastes fully.

Anorexics' indifference to rewards is not limited to good-tasting food. In a study published in December 2007, Kaye's team had two groups of 13 women similar to those in the taste test play a decision-making game while lying in a functional magnetic resonance imaging scanner. Subjects had to guess if a hidden number was greater or less than five; they would win \$2 for every correct guess and lose \$1 for each incorrect answer.

The women in the control group responded appropriately to their wins and losses with commen-



In a control group of women who have always eaten normally, the taste of sugar water produced activity in a brain area called the insula (shown in red), which is important for processing taste. Drinking sugar water produced significantly less activation of the insula, on average, in the brains of recovered female anorexics (red line on graph) than in those of the controls (blue line), suggesting that anorexics cannot fully appreciate pleasant-tasting food.

taries akin to “Yeah, I won!” or “Bummer, I lost.” Those reactions were reflected in the participants’ brains: the wins lit up a central brain region called the anterior ventral striatum, which contributes to the processing of immediate rewards, whereas the losses did not. In contrast, the women who had once had anorexia did not express joy when they won or disappointment when they lost, and their brains were similarly indiscriminating; the anterior ventral striatum of these women looked the same irrespective of the outcome of each game trial, indicating that their emotional unresponsiveness to rewards was rooted in their reward circuitry.

Their brains did, however, display heightened activity in the caudate, part of the dorsal striatum, in response to a win as compared with a loss during the game. This brain region is part of a circuit that contributes to planning and evaluating long-term consequences. It may connect asceticism to reward in an anorexic’s brain. The finding is consistent with anorexics’ tendency to live in the future, planning for all contingencies, and to largely disregard the present. “People with anorexia have difficulty living in the here and now,” Kaye explains.

Testosterone produced by a twin brother in the womb may protect his sibling against eating disorders. In contrast, exposure to prenatal estrogen from a female twin may precipitate disordered eating.

PUBERTY IS AN ANOREXIA TRIGGER: AT LEAST 40 PERCENT OF NEW CASES OCCUR IN GIRLS 15 TO 19 YEARS OLD.

Wired for “Perfection”

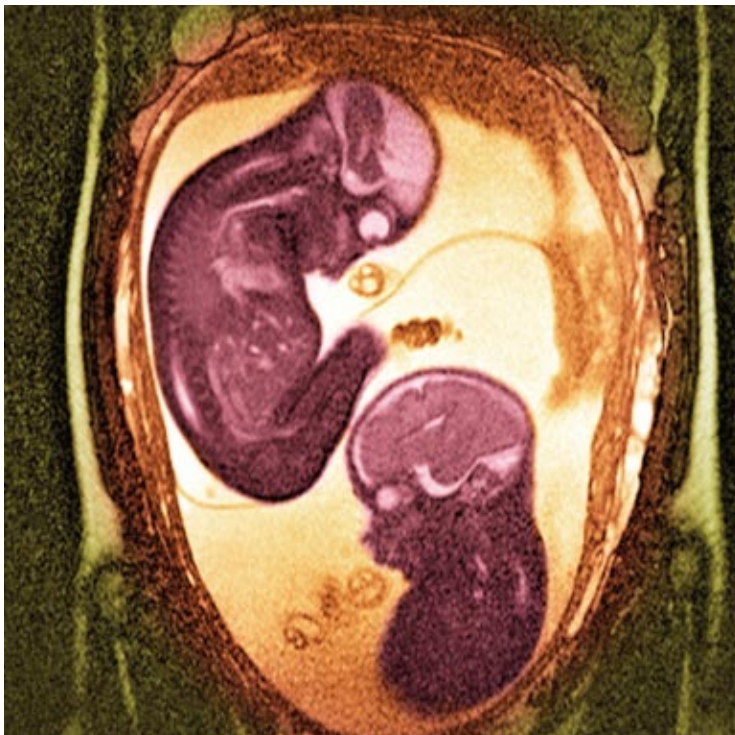
That difficulty coincides with other personality traits many anorexics share, including chronic anxiety—80 to 90 percent of anorexics report anxiety problems before the onset of disease—perfectionism, marked by a need to avoid mistakes and negative consequences (such as weight gain), and a focus on the attainment of goals. These traits define a person who worries intensely about living up to society’s ultraskinny standards and perfects the art of weight loss.

Such a personality and lifestyle do not constitute a recipe for contentment. Rather an anorexic’s existence revolves around rituals designed to attain an abnormal form of reward that is more about avoiding negative emotions—such as intense anxiety or the pain of perceived criticism—than about feeling good. From this standpoint, anorexia is not really about dieting but about coping with intolerable emotional distress. “Life is not rewarding for these individuals,” Kaye points out.

The root of such distress may lie in altered forms of genes. Thus far the strongest candidates are those with myriad effects on the brain, consistent with the idea that anorexia stems from a multifaceted mental illness rather than from a specific anomaly in appetite regulation. They include genes for a serotonin receptor, a dopamine receptor and a protein called brain-derived neurotrophic factor that plays a general role in the growth of new nerve cells and maintenance of existing ones.

To further explore the connection between the personality of individuals with anorexia and their unique genetic makeup, Kaye, along with an international team of researchers, including psychologist Cynthia M. Bulik of the University of North Carolina at Chapel Hill, is now trying to pinpoint variations in genes that correlate with anxiety and a form of perfectionism they call “obsessionality.” First reported in 2002 and still ongoing, preliminary analysis of the DNA from 1,167 individuals with anorexia has narrowed down the source to a stretch of chromosome 1 that contains at least 546 different genes.

But genes cannot be the whole story of anorexia. DNA analyses of identical twins (who share almost all of the same DNA) versus fraternal twins (who have many genetic differences) indicate that genetic variation accounts for only



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How Lean Can You Go?

Many people would prefer to boast very little body fat—but what does that mean? Your body-fat percentage is the weight of your fat tissue as a proportion of your overall body weight. A high percentage of body fat means you are relatively flabby, and a low percentage means you are relatively lean. Some body fat is essential for life and reproduction [see “Essential Fat” in chart], and that bare minimum is significantly greater for women than for men because of hormonal differences related to reproduction, according to exercise physiologist Cedric Bryant of the American Council on Exercise.

Even serious athletes usually pack on more fat than this rock-bottom number. The consistent gym-goer in the “Fitness” category has slightly more body fat than the athletes, followed by individuals in the “Acceptable” range who are healthy but might wish to look leaner. Meanwhile the obese carry enough body fat to compromise their health.

Basic Body-Fat Percentages

Classification	Women (fat percentage)	Men (fat percentage)
Essential Fat	10–13	2–5
Athletes	14–20	6–13
Fitness	21–24	14–17
Acceptable	25–31	18–24
Obese	32 and higher	25 and higher

Most American adults fall into the high end of “Acceptable” or the low end of “Obese,” Bryant says, whereas anorexics who exercise strenuously may sometimes dip into the “Essential Fat” range. In many cases, however, a person with anorexia does not have a very low body-fat percentage because she or he has lost so much lean body tissue that fat tissue makes up more of the body’s overall mass, Bryant explains.

—Ingrid Wickelgren, staff editor

50 percent of an individual’s susceptibility to anorexia, according to Bulik and clinical psychologist Kelly L. Klump of Michigan State University. In addition to genes, the environment also has enormous influence over the brain.

Hormone Havoc

To anorexia researchers, environment includes puberty, a complex maturation stage that is known to be one of the most potent triggers of anorexia nervosa. According to the National Eating Disorders Association, at least 40 percent of newly identified cases of anorexia occur in girls 15 to 19 years old.

Furthermore, in a 2007 study of 772 twin girls, ages 11 to 18, Klump and her colleagues noted that disordered eating rarely showed up in any twin before the beginning of menstruation. Her observation is consistent with results published by Bulik in 2002 and with her own previous studies showing that the genetic component of disordered eating exerts its effects mainly *after* the start of puberty.

No one knows for sure what accounts for puberty’s effects on gene activation, but one theory is that the surge of ovarian hormones, estrogen in particular, plays a significant role. Klump speculates that hormones trigger the expression of anorexia susceptibility genes and that the effect is most pronounced in girls with gene variants that cause anxiety, perfectionism and obsessiveness.

Hormones might play a role in anorexia long before puberty, too. In a March 2008 study in the *Archives of General Psychiatry*, Klump and her colleagues assessed the frequency of troubling eating habits such as fad dieting, bingeing and purging among 582 18- to 29-year-old twins. The young women with twin brothers ate more healthily than those who had twin sisters, the investigators found, but, more generally, disordered eating in *both* the females and males was lower in those who had a male twin. That is, females with twin sisters had the worst eating habits, followed by females with male twins and, after them, males with female twins. The best eaters were males with male twins.

What is going on? Klump believes testosterone is part of the answer. “We know that testosterone prenatally organizes the brain, making it more ‘masculine,’” she says. “Thus, testosterone produced by a twin brother in the womb may actually protect his female twin against eating disorders.”

(The Author)

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Exposure to prenatal estrogen may precipitate disordered eating; after all, the males in these studies had far better eating habits if their twin was male rather than female. Some researchers point out that female fetuses secrete sex hormones that might trigger the expression of anorexia susceptibility genes, such as the one for the serotonin receptor or those for related molecules. “We know that estrogen has effects on genes in the brain, and we know that estrogen is a pretty potent regulator of serotonin receptors,” Klump says. Such a latent fashioning of the brain’s architecture and functioning may explain, in part, the striking gender differences in anorexia. The possible influence of sex hormones also suggests that relatively large-scale distortions in brain physiology may underlie anorexia.

Hunger Strikes

Environmental influences outside the human body might also pull genetic triggers for anorexia. One of these is likely to be undernutrition itself. That is, a lack of sufficient calories might be an-

WARNING TO YOUNG ATHLETES: NOT EATING ENOUGH CAN LEAD TO POOR PERFORMANCE AND A DANGEROUS ADDICTION TO UNDEREATING.

other “on switch” for anorexia susceptibility genes in addition to the surges of estrogen at puberty.

Therapist Shan Guisinger, who is affiliated with the University of Montana, pointed out that the growth spurts of puberty and, in many cases, intense participation in athletics can boost the caloric requirements of teens far beyond what they are getting in their diet. A 1999 study of 1,445 Division 1 NCAA athletes supports the idea that young female athletes might be at particular risk. Craig Johnson, director of the eating disorders program at the Laureate Psychiatric Clinic in Tulsa, Okla., and his colleagues found that

more than one third of the females they surveyed reported attitudes and behaviors that put them at risk for anorexia, including dieting, using diet pills and wanting to have an abnormally low body-fat content. In fact, these female athletes reported a mean body-fat content of 15.4 percent, a figure that is often below that required for normal menses.

But does starvation really propel a person toward anorexia, or might the anorexia-prone simply be the ones who choose to exercise and eat too little? Supporting the former hypothesis is a renowned study conducted in 1944 by Ancel Keys and his colleagues at the University of Minnesota. To observe how to best refeed prisoners of war, Keys recruited 36 young men and cut their caloric intake almost in half for 24 weeks. During that semistarvation period the subjects obsessed, fantasized and dreamed about food. When they were allowed to eat normally again, the men gorged and regained weight. Yet some started engaging in anorexiclike behaviors, including dieting and complaining about too much fat around their bellies, thighs and buttocks. The study showed that deprivation, even in normal men, could prompt the onset of anorexia in a small number who are predisposed to the condition.

In case semistarvation can spark the disorder, eating disorders experts now educate coaches and gym teachers to be on the lookout for young athletes at risk. They tell coaches to counsel their charges that not eating enough can lead to poorer performance and, worse, to a dangerous addiction to undereating.

Meanwhile psychiatrist Christopher Fairburn of the University of Oxford is tailoring a

Young female athletes might be at particular risk for anorexia. Some data suggest that dieting practices common among these athletes might turn on anorexia susceptibility genes.



AGE FOTOSTOCK

Survival of the Thinnest

Why would a predisposition to anorexia survive in the gene pool, especially when one defining feature of anorexia is that a female stops menstruating for at least three consecutive cycles? Therapist Shan Guisinger, who is affiliated with the University of Montana, speculates that the answer may lie in the benefits of anorexia for helping early humans cope with famine.

A female whose genes made her more energetic when she was starving might well have helped her clan survive times of scarcity: she could scout and forage for food when no one else could. Traits of perfectionism and overachievement, moreover, could have helped her on difficult foraging journeys. Famine might even have activated her anorexic condition. And, Guisinger's theory goes, when food became plentiful again, the tribe would feed her enough for her to reproduce.

Although such a theory is impossible to prove, espousing it can be therapeutic. Telling a woman who suffers from a disease marked by misery and low self-esteem that she is genetically programmed to be Joan of Arc (who may have suffered from anorexia, according to Guisinger) may help her see herself as a hero rather than as a failure. She may then under-



In one theory of the origins of anorexia, the afflicted are likened to French heroine Joan of Arc (above).

stand that anorexia might have once been an asset in emergencies but is an illness in a culture that emphasizes thinness at all times.

"The explanation makes sense of their experience," says Guisinger, who has used the concept in her therapy. "It explains why they feel virtuous resisting hunger, see fat on their emaciated bodies, and feel driven to exercise. Patients tell me, 'It helped me to recover.'" —T.G.

type of cognitive-behavior therapy (CBT) to anorexia. Originally developed to treat depression, CBT is designed to help an anorexic patient change both his or her destructive eating habits and the mental state that led to them. Kaye's group and others are exploring psychotherapy strategies that either help anorexics feel pleasure or use incentives for adopting eating behavior that is geared toward immediate rewards rather than long-term results.

Another experimental frontier involves the use of the hormone leptin, produced by fat cells, to help women with a history of anorexia resume menstruation and possibly also develop healthier attitudes about food and life. In addition, Compan and her colleagues are testing a compound in mice that blocks the activity of one type of serotonin receptor in hopes of reducing its inhibitory effects on appetite in the nucleus accumbens.

As these and other treatment ideas move forward, their origins trace back to the neurobio-

logical, psychological and endocrine roots of disease that may have formed as early as embryonic development. "Until we better understand the biology of these conditions," Kaye says, "we can't devise better treatments." **M**

(Further Reading)

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- ◆ **The Genetics of Anorexia Nervosa.** C. M. Bulik, M. C. Sif-Op't Landt, E. F. van Furth and P. F. Sullivan in *Annual Review of Nutrition*, Vol. 27, pages 263-275; April 2007.
- ◆ **Anorexia Induced by Activation of Serotonin 5-HT₄ Receptors Is Mediated by Increases in CART in the Nucleus Accumbens.** Alexandra Jean et al. in *Proceedings of the National Academy of Sciences USA*, Vol. 104, No. 41, pages 16335-16340; October 9, 2007.
- ◆ **Altered Reward Processing in Women Recovered from Anorexia Nervosa.** Angela Wagner et al. in *American Journal of Psychiatry*, Vol. 164, No. 12, pages 1-8; December 2007.
- ◆ **Intrauterine Hormonal Environment and Risk of Developing Anorexia Nervosa.** Marco Procopio and Paul Marriott in *Archives of General Psychiatry*, Vol. 64, No. 12, pages 1402-1408; December 2007.