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RETHINKING ANOREXIA

Challenging long-standing theories about the eating disorder, new research suggests biology is a powerful driver

By Jennifer Couzin-Frankel

In college in the 1990s, Alix Timko wondered why she and her friends didn't have eating disorders. "We were all in our late teens, early 20s, all vaguely dissatisfied with how we looked," says Timko, now a psychologist at Children's Hospital of Philadelphia. Her crowd of friends matched the profile she had seen in TV dramas—overachievers who exercised regularly and whose eating was erratic, hours of fasting followed by "a huge pizza."

"My friends and I should have had eating disorders," she says. "And we didn't."

It was an early clue that her understanding of eating disorders was off the mark, especially for the direst diagnosis of all: anorexia nervosa. Anorexia is estimated to affect just under 1% of the U.S. population, with many more who may go undiagnosed. The illness manifests as self-starvation and weight loss so extreme that it can send the body into a state resembling hibernation. Although the disorder also affects boys and men, those who have it are most often female, and about 10% of those affected die. That's the highest mortality rate of any psychiatric condition after substance abuse, on par with that of childhood leukemia. With current treatments, about half of adolescents recover, and another 20% to 30% are helped.

As a young adult, Timko shared the prevailing view of the disease: that it develops when girls, motivated by a culture that worships thinness, exert extreme willpower to stop themselves from eating. Often, the idea went, the behavior arises in reaction to parents who are unloving, controlling, or worse. But when Timko began to treat teens with anorexia and their families, that narrative crumbled—and so did her certainties about who is at risk. Many of those young people "don't have body dissatisfaction, they weren't on a diet, it's not about control," she found. "Their mom and dad are fabulous and would move heaven and Earth to get them better."

Timko wasn't alone. Other researchers were also questioning psychological theories of anorexia that had reigned for generations. "Hunger is a basic drive," says Cynthia Bulik, a clinical psychologist who runs eating disorder centers at the University of North Carolina, Chapel Hill, and at the Karolinska Institute. The idea that patients use willpower to override hunger "never rang true," she says. "My patients have said for years that ... when they starve, they feel better." She began to consider another possibility: What if their biology is driving them to eschew food?

Bulik and Timko are now part of a small band of researchers working to untangle

the biology of anorexia. The more they look, the more they find to suggest the disease's biological roots run deep. For instance, genetic studies indicate it's about as heritable as obesity or depression. The circuitry of the brain's reward system behaves differently in unaffected volunteers than in people with anorexia and those who have recovered. And new treatments drawing on biology are being tested, including deep-brain stimulation and psychedelic drugs. Those experiments aim not only to improve the outlook for patients, but also to explore how closely the disease aligns with others across psychiatry, including obsessive-compulsive disorder (OCD) and addiction.

Scientists pursuing those new ideas face a challenge, in part because of money: For

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Cynthia Bulik,

University of North Carolina, Chapel Hill

fiscal year 2019, anorexia got \$11 million in funding from the National Institutes of Health (NIH), a figure that hasn't changed notably in many years and that researchers decry as shockingly low given the disease's burdens. By contrast, schizophrenia—which has a similar prevalence and also surges during adolescence—garnered \$263 million. The dearth of funder interest, many say, springs from the view that anorexia's roots are cultural, along with shame and stigma still clouding the disease. But evidence is mounting that biology is at its core.

LORI ZELTSER PIVOTED to anorexia from studying obesity. A developmental neuroscientist at Columbia University, she studied the brains of developing mice, trying to identify feeding circuits that increase susceptibility to obesity in adulthood. Then about 10 years ago, Zeltser saw a notice for funding from the Klarman Family Foundation, formed by hedge fund manager Seth Klarman and his wife, Beth, now the foundation's president. The foundation wanted to stimulate basic research into eating disorders, and because of Zeltser's research on appetite, she submitted a proposal.

To get up to speed on anorexia, Zeltser turned to the literature. Researchers in Sweden and Minnesota had compared anorexia rates in identical and fraternal twins, a common approach to tease out heritability of complex traits and diseases. Those reports showed that 50% to 60% of the risk of developing anorexia was due to genes,

implying DNA is a powerful driver. By contrast, family studies suggest the heritability of breast cancer is about 30%, and that of depression is roughly 40%. "I was shocked," Zeltser says.

Layered on the genetics work was a data point that caught Zeltser's attention. An anti-psychotic drug, olanzapine, which causes profound weight gain as a side effect, had little to no effect on weight when tested in people with anorexia. Something in people's biology prevented olanzapine from causing weight gain, Zeltser believes. "That is not just [mental] control."

But a deep schism remains, with many practitioners concerned that biology is getting more attention than it deserves. "If I had to choose nature versus nurture in the development of anorexia and other eating disorders, I would choose nurture," says Margo Maine, a psychologist who has treated eating disorders for years. Eating disorders are primarily female, she says, in part because "gender is a cultural experience."

Psychotherapist Carolyn Costin, who recovered from anorexia in the late 1970s and established a network of private treatment centers around the United States, says biology plays a role but that cultural messages and psychological stressors are also important factors. She worries especially that the way biology research is described could discourage patients about their prospects for recovery. About 8 years ago, she says, "Clients started coming in, saying, 'It's genetic, why bother?'" trying to get well?

Such comments agitate researchers like Bulik. The patients she treats, she says, are reassured, not distressed, to learn that the disorder is rooted in biology and that biology doesn't translate into destiny. Although she, Zeltser, and others agree that anorexia has environmental drivers, as most chronic conditions do, they object to the idea that environment leads the way. "Exposure to this ideal [of thinness] is ubiquitous, but everybody doesn't get anorexia nervosa," Bulik says. "None of the sociocultural literature has ever been able to explain why." She adds, "A lot of patients will say, 'It was never about being thin for me, ever.'"

"If you look at psychiatric syndromes over 200 years, anorexia hasn't changed at all," whereas our culture has, says James Lock, a child psychiatrist who heads the child and adolescent eating disorders program at Stanford University School of Medicine.

To begin digging into the biology of anorexia, Zeltser used a 2010 grant from the Klarman foundation to build a mouse model of the disease. Because feeding is easy to measure, she reasoned that anorexia's restrained feeding behavior is well-suited for animal modeling. Her goal was to study the

eating and starvation patterns of the mice and explore how genetics and the environment interact to trigger the disorder.

In a 2016 issue of *Translational Psychiatry*, Zeltser described mice with a variant in a gene that in people is linked to anorexia. On its own, the variant didn't noticeably affect mouse feeding behavior. To mimic the pullback from eating that often precedes a diagnosis, the researchers restricted the animals' caloric intake by 20% to 30%. Then they induced stress, another factor linked to anorexia, by housing the normally social animals alone. The result: "The mice stop eating," Zeltser says.

Zeltser is talking with clinical colleagues about comparing her rodents' behavior with videos of patients in a "feeding lab," where researchers observe how much people eat, which nutrients they choose, and which they avoid. If the behaviors seem parallel, the mice could help point the way to new treatments or even different environments that could better support eating.

But publishing her animal work has proved difficult. Zeltser is often asked, "How do you know if what you're finding is relevant to humans?" That's a common question of anyone doing mouse work, but Zeltser says the challenge here runs deeper. "This is not taken seriously as a disease" that has a biological basis, she says. Instead, it's dismissed as "extreme girl behavior and 'oh my God, they're crazy,'" pushback she finds immensely frustrating.

Accumulating genetic data could change that by making anorexia's biological roots harder to ignore. Some of the strongest evidence emerged last summer, when Bulik and others published in *Nature Genetics* the largest genetics study on the disease, with roughly \$9 million in funding from the Klarman foundation and additional funds from NIH. By analyzing the genomes of nearly 17,000 people with anorexia and more than 55,000 people without, the researchers identified eight statistically significant genomic regions, along with other patterns of genetic associations that yielded important clues. Some of those associations tracked with results of studies of other psychiatric illnesses, including OCD and depression, which didn't surprise Bulik. What did were overlapping associations with DNA controlling body mass index (BMI), lipids, and other metabolic traits.

"We said, 'This doesn't look like any other psychiatric disorder,'" Bulik says. "It might be the inverse of obesity—these people might be genetically predisposed to

low BMI." In the February 2019 issue of the *Journal of the American Academy of Child & Adolescent Psychiatry*, she and her team sifted through BMI records for young people later diagnosed with anorexia and other eating disorders. The BMIs of 243 people diagnosed with anorexia began to diverge from those of a control group before they started kindergarten.

Bulik is now launching the Eating Disorders Genetics Initiative, with more than \$7 million from NIH, additional funding from Sweden and the United Kingdom, and potential infusions from other countries and individual donors. The initiative aims to include 100,000 people with anorexia nervosa, bulimia nervosa, and binge eating disorder. Although genetics is unlikely to of-



Lori Zeltser, a developmental neuroscientist at Columbia University, has developed a mouse model of anorexia nervosa.

fer quick solutions, Bulik hopes it can "shine the light in the direction you need to go" for effective therapies, including medications.

THE GENETIC FINDINGS might one day intersect with another line of research: studies of brain structures and signaling that are revealing tantalizing differences between people with and without anorexia. At Columbia, psychiatrist Joanna Steinglass wanted to understand how the brains of people with anorexia guide their food choices. In two studies, she and her colleagues recruited inpatients with eating disorders along with a control group. In people with anorexia, both during and after hospitalization, MRI scans showed the region of the brain associated with selecting foods was the dorsal striatum, which is key to forming habits. In people without an eating disorder, a different brain region guides choices. The work

first appeared in 2015 in *Nature Neuroscience*, and the team presented more findings at a conference last year.

"They're using different circuits when they make decisions," Steinglass says. This jibes with her idea that as people repeatedly restrict eating, the behavior moves to a different brain region and becomes less amenable to change. That could help explain why many recovered patients relapse.

Another clue to how the brain might throw eating off track was reported last month in *The American Journal of Psychiatry*. Walter Kaye, a psychiatrist who directs the eating disorders program at the University of California (UC), San Diego, led a study looking at how the brains of people with anorexia behave when their bodies are hungry. Kaye, whose program treats about 70 patients per day, ran a study that included 48 women, 26 of whom had anorexia. Each was studied twice with brain imaging, once immediately after a meal and, on a separate visit, after fasting for 16 hours.

Kaye knew hunger activates brain circuits that in turn motivate eating, making food desirable. That relationship was clear during brain imaging of the control group volunteers: When they were offered sugar water after 16 hours of fasting, their reward and motivation circuits lit up. But in people with anorexia, those circuits were much less active after fasting. "They could identify being hungry," Kaye says, but their brains couldn't convert that into a desire to eat. The patients also experienced heightened anxiety and inhibition, along with diminished reward signaling in their brains. That effect may further im-

pair their drive to eat. Kaye suggests people with anorexia "miscode food as risky rather than rewarding."

Psychiatrist Rebecca Park at the University of Oxford also suspects the disease hijacks the brain's reward system. Some of her patients experience "this sense of aberrant reward," almost a high from starvation, she says. Park's neuroscience research indicates aberrant brain responses to reward cues.

Are those brain differences a cause or a result of starvation? Studying people in remission eliminates the effects of malnutrition on the brain but can't definitively answer the question. It's likely that "starvation in adolescence is going to damage your brain," Park says. One way to begin to disentangle whether the brain differences predate the disease is to study people very early in its course. Steinglass is in the third year of a brain scanning study of reward

circuitry, which now includes 55 recently diagnosed teenagers and a control group of 25 others. The coronavirus pandemic has halted enrollment for now, but Steinglass hopes to have results in 2 to 3 years. Other researchers are working to understand how, and to what degree, the brain recovers once eating resumes.

THERE'S AN "OVERALL SENSE that we're joining the rest of the world" by finally applying scientific methods to anorexia nervosa, Steinglass says. The ultimate goal is new treatments, which are sorely needed.

The most studied and most effective strategy to date is called family-based treatment (FBT), which originated at the Maudsley Hospital in London. It was later refined by

in anorexia's onset, or they may feel that adolescents must want to get better before starting FBT—a view she disputes.

Laura Collins Lyster-Mensh experienced the regimen up close after her daughter Olympia, then 14, stopped eating one day in 2002. Lyster-Mensh says a succession of therapists urged her and her husband to stand back and let Olympia eat when she was ready. Meanwhile, her weight continued to spiral downward. "We had been told she wouldn't recover, families were really at fault, to back off and let her do this on her own," Lyster-Mensh says. Then she learned about FBT from a newspaper article and raced to try it.

The first agonizing meals took hours, while Olympia mashed her food into a

gate different situations, a psychological trait called flexibility.

Researchers are exploring ways to build on and improve FBT—or find new strategies to help patients in whom it has failed. Some clinical trials are testing whether certain talk therapies, such as cognitive behavioral therapy to help patients reframe their thinking, can help—for example, by reducing anxiety or other impediments to eating.

New biological models of anorexia hint at other kinds of interventions. An 18-person study at Johns Hopkins University is offering the psychedelic drug psilocybin to patients. Early data suggest it holds promise in helping smokers quit and combating alcoholism—and many researchers believe that in certain ways, anorexia shares some features with addiction. Park is leading a seven-person study of deep-brain stimulation in people with severe enduring anorexia, some of whom also have OCD.

"There's a certain neural network that's well characterized" in OCD, she says, and disrupting the signaling in that network with deep-brain stimulation can help those patients. Because OCD and anorexia have shared features and some genetic links, she's interested in whether disrupting the same neural network might also help people with the eating disorder.

Still, studies remain sparse, Lock says. With limited funding, there's little chance of attracting new scientists to a small field. "As researchers, you don't want to go to the pot that's empty," he says. "Why aren't we investing more?" It's especially frustrating because, Lock points out, many patients with anorexia successfully heal and enjoy a bright future. "What [other] illness in psychiatry can you say you cure?" he asks.

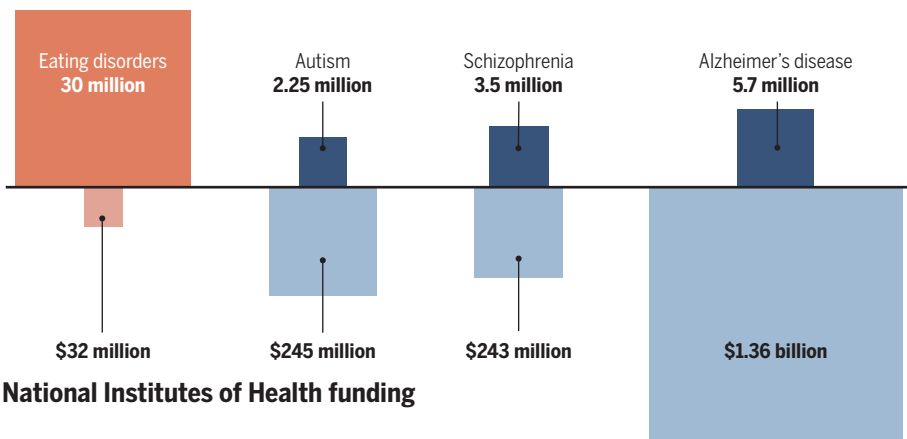
For families, regardless of whether a patient recovers, the shame can persist—and with it hesitation to speak up and lobby for funding. Lyster-Mensh is an exception. After her family's experience, she began to voice support for evidence-based treatment—first in a memoir, *Eating with Your Anorexic*, which she wrote under the name Laura Collins, and then through FEAST, a message board turned advocacy group.

"It's still a pretty small group," Lyster-Mensh says, of those willing to speak openly. "Most families are so burned out, crushed, guilty, that they don't want to come forward," she says. "There are still these myths out there—that these are chosen illnesses and parents somehow failed to prevent, or caused, or exacerbated the problem." Still, she hopes that as researchers doggedly track the disease's biological roots in genes and the brain, those enduring myths will fade. ■

Money woes

Many researchers lament that eating disorders, including anorexia nervosa, are underfunded given their prevalence. These numbers are drawn from 2017 data for the United States; the number of individuals affected is an estimate.

Individuals affected



National Institutes of Health funding

Lock and psychologist Daniel Le Grange, of UC San Francisco, who trained at Maudsley.

FBT asks parents to set aside many of their family's day-to-day activities—scaling back school, work, hobbies—to sit with their children, requiring them to eat. Faced with food as a form of medicine, and with their world having contracted, many young people do start to eat again despite the fear and anxiety it causes them. Researchers are working to understand how FBT is intertwined with the biology of the illness, but for about half who try FBT in adolescence—and perhaps 70% who try it early in the disease—the treatment is effective.

But many families aren't told about that therapeutic strategy, even though decades have passed since it first showed success in a randomized trial, in 1987. Practitioners may not be familiar with FBT, Timko says, they may believe the family played a role

pulp or cried and raged at her parents. "I know families whose kids have jumped out of moving cars to avoid a sandwich," says Lyster-Mensh, echoing comments of many clinicians who describe patients' crushing fear of food. Olympia ultimately recovered, although not without challenges that included a relapse during college.

The young patients treated with FBT who do start to eat again do well on the one measure that predicts longer-term prognosis: early weight gain. In 2019, a study in the *European Eating Disorders Review* led by Le Grange confirmed earlier research showing that gaining about 2.3 kilograms in the first month of treatment is a predictor of health 1 year later. Girls with anorexia who boosted their calorie intake and gained weight experienced increases in estrogen levels (which plummet in starvation), reduced stress, and improved ability to navi-

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