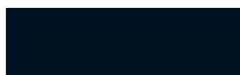


Why
We
Are

Fat

**A MED
BIOCHEMIST
SAYS THE
OBESITY
EPIDEMIC IS NOT
JUST ABOUT
CALORIES. IT
COULD BE THE
CHEMICALS.
BY BARBARA
MORAN**





We all know why Americans are fat, right? We gobble chips and chug 16-ounce sodas and then park our butts in front of the TV. Seems pretty straightforward. But what if that's not the whole story? Biochemist **Barbara Corkey** has an idea that turns this conventional wisdom on its head.

What if, asks Corkey, obesity isn't simply about eating too much and exercising too little? What if there's something more subtle at work? Maybe it isn't extra calories that make us fat, she says, but food additives like saccharin and emulsifiers.

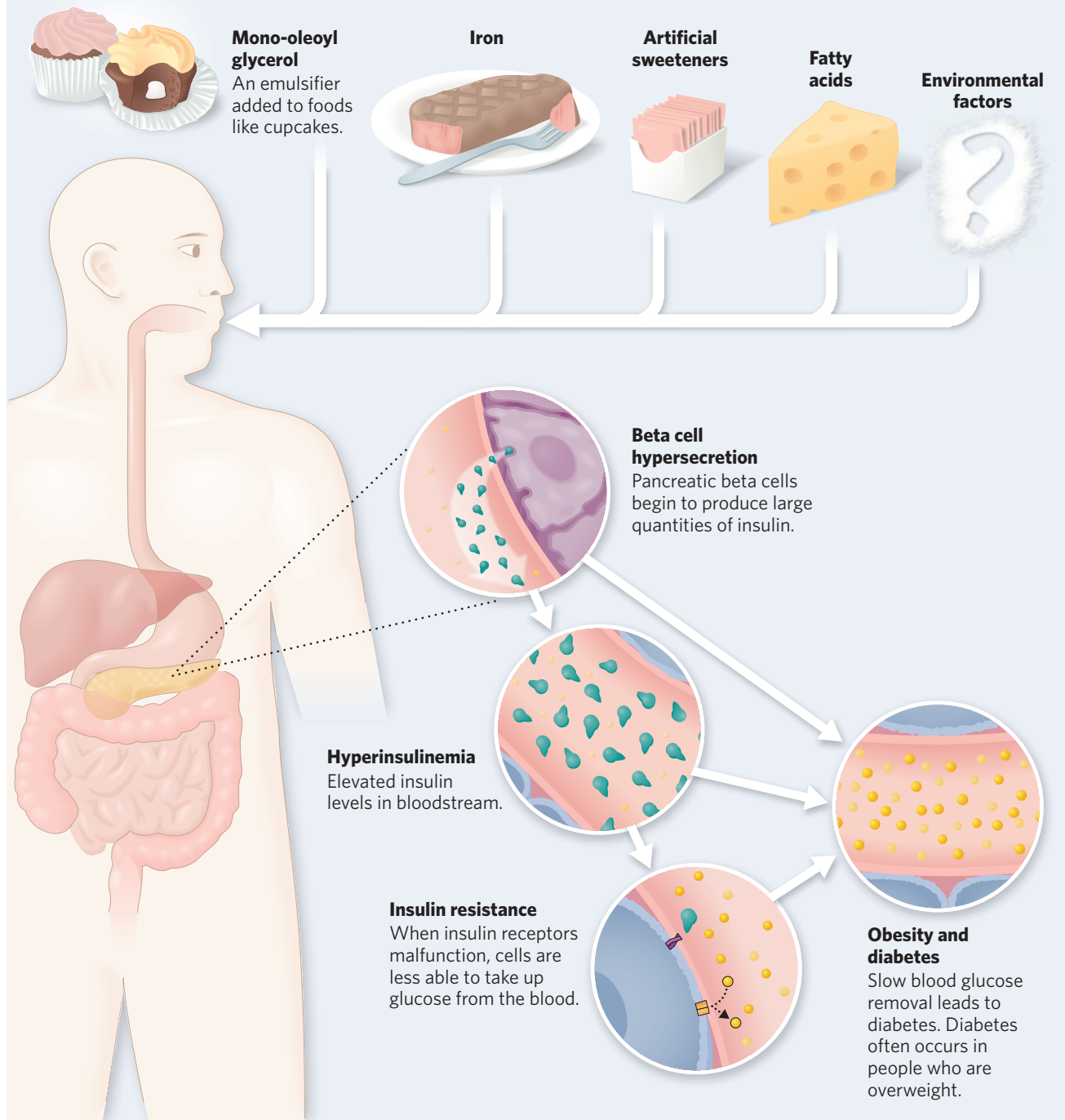
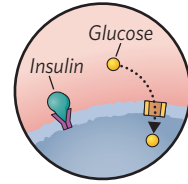
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ANOTHER LOOK AT DIABETES

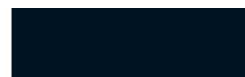
Biochemist Barbara Corkey suspects that food additives and other environmental factors play a role in the biochemical changes that lead to diabetes. Her research suggests that monoglycerides and saccharin stimulate beta cells to produce insulin at inappropriate times, which makes it hard for some cells to take up glucose and may cause the disease.

How insulin works

Insulin signals cells to absorb glucose from the bloodstream, converting it to energy.



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scientist with five decades of metabolism research under her belt. She's the vice chair of research at the School of Medicine department of medicine, and in November was appointed MED's Zoltan Kohn Professor in Medicine. She's the former director of the Obesity Research Center at Boston Medical Center and recent past editor of the medical journal *Obesity*, and last year she was awarded the Banting Medal for Scientific Achievement Award, the American Diabetes Association's highest scientific honor and one of the world's top science awards.

"Barbara is out of the box—completely," says collaborator Orian Shirihai, a MED associate professor of medicine. "She doesn't even know what's in the box. What she does is turn the box upside down and put it onto other scientists' heads."

Corkey's area of expertise is metabolism: she studies how cells, specifically cells involved in diabetes and obesity, communicate. "Metabolic disease has always interested me," she says. "It's a system where pathways all interconnect and talk to each other. And so if you push on one button over here, it has consequences everywhere else."

A key player in her research is the pancreatic beta cell, which produces insulin, a hormone that converts food into energy and stores it as either fat or glucose. In diabetics, the beta cells usually produce too much, too little, or no insulin. The reasons for beta cell breakdown are complicated, and that's what attracts Corkey.

"Barbara is one of the few people who really understand and integrate metabolism into diabetes research," says Ronald Kahn, past president of the Joslin Diabetes Center and a professor of medicine at Harvard Medical School. "Metabolism is coming back now, but for the last 30 years it has been a lost science." Kahn, who calls Corkey "the queen of metabolism," says that "she helped keep the field alive."

Fortuitously, it turns out. Diabetes now threatens to become a worldwide epidemic. According to the U.S. Centers for Disease Control and Prevention (CDC), 25.8 million children and adults in the United States—8.3 percent of the population—have the disease, which is the leading cause of kidney failure and blindness among adults. If current trends continue, a third of U.S. adults could have diabetes by 2050. Outside the United States, the numbers are equally grim. According to the World Health Organization (WHO), 346 million people worldwide—5 percent of all humans—have

"I don't believe that over-eating causes obesity," says Corkey flatly. "During my lifetime I have seen tremendous differences in food preparation and food packaging. When that novelty is associated with an increase in obesity and diabetes, is it rocket science to ask whether these things are related?"

Corkey's suspected connection may seem like a stretch, but she is not one to oversimplify science. She is a respected

diabetes, and diabetes deaths will likely double by 2030.

Decades ago, when the disease was not well understood, scientists knew that two types of diabetes existed—type 1 and type 2—but they didn't have a clear picture of the underlying causes. People with type 1 diabetes, which is usually diagnosed in children, cannot produce insulin and must inject it to survive. Scientists thought that type 2 diabetics, who are usually adults and often obese, had a less dramatic deficit: some insulin but not enough. But when scientists came up with a way to measure insulin levels, they found that people with type 2 diabetes actually had *too much* insulin.

If they had plenty of insulin, what caused the diabetes? The researchers theorized that insulin receptors in the muscle and fat tissue, bombarded by an excess of the hormone, became desensitized and didn't work as they should. This "insulin resistance" causes the beta cell to crank out more insulin, and sometimes to stop working altogether. By the 1980s, the idea that insulin resistance alone causes type 2 diabetes had solidified into scientific dogma.

There was only one catch: nobody knew which came first, the broken beta cells or the insulin resistance. Corkey was determined to find out. "I think perversely," she says. "Why is the beta cell secreting more insulin? The glucose isn't elevated. How can we explain this?" She suspected that the beta cells were partly responsible for triggering diabetes. And she spent the next two decades trying to prove it.

The role of outsider suits her. "I like to be in a comfortable place where we don't have to compete and rush, and we can do our science in a thoughtful and leisurely manner," she says. By all accounts Corkey also enjoys the role of scientific gadfly.

"She likes to be provocative," says Sarah Krawczyk (MED'11), one of Corkey's postdoctoral students. "Lots of her theories challenge dogma, though they're always backed up by sound science." For two decades, while insulin resistance dominated diabetes research in the United States, Corkey stuck stubbornly with the beta cell theory. "I just thought the whole United States was wrong," she says.

She was right. Scientists now widely accept that a person can't get type 2 diabetes without malfunctioning beta cells, a paradigm shift largely precipitated by Corkey.

"She just really changed that field and put metabolism into it, and she's basically regarded as *the* expert," says Susan K. Fried, a MED professor of endocrinology, diabetes, and nutrition. The beta cell research, along with similar work on fat cell metabolism, helped Corkey win the Banting Medal. "She was such a perfect choice," says Kahn. "She is an excellent scientist with a huge body of work, and she has been such an important catalyst in diabetes research."

GIVING WING TO HER INTELLECT

Corkey remembers the moment she decided to become a scientist. She was a teenager at New York University, majoring in fine arts while simultaneously pursuing an accelerated path to medical school. She loved painting, but considered it a "hedonistic pleasure" rather than a career and had set her sights on medicine.

Walking to class one day, she glanced into a tiny lab and saw a fascinating sight: a small beating heart, dangling on a string over a dish. She stopped in her tracks. Intrigued, Corkey asked the professor why the disembodied heart was still thumping away. "It's calcium," he told her. As she watched, he changed the calcium levels in the solution. The heart stopped beating, then started again. "That's when I knew that medical school was not for me," she says. She was so smitten by biochemistry that she dropped out of NYU without finishing a bachelor's degree and joined a laboratory. That job, in 1957, marked her first foray into diabetes metabolism.

From there her career followed an extraordinary path. Corkey married a Hungarian refugee at age 19 and had her first child, a son, at age 20. Her father, disapproving of the marriage and of foreigners in general, stopped speaking to his daughter. The young family moved to the University of Pennsylvania, where Corkey got a full-time job as a lab technician. After her second child was born, her husband

walked out, leaving her with two small children and a mountain of debt.

"It was almost impossible to live on my income," says Corkey. "I couldn't afford babysitters. I couldn't afford anything." Her daughter Valerie remembers her mother struggling to provide for the family, shuttling her around on the back of a bicycle because they didn't own a car. "But I don't remember wanting for anything," she says.

On the contrary, Valerie and her sister, Pamela, share happy

memories of playing in their mother's lab, spinning magnets on the centrifuge and snapping tiny plastic vials together into necklaces. "I wouldn't trade her for any other parent," says Valerie.

While Corkey remembers those years as lonely and stressful, they shaped the woman she is today. "I realized that I am in charge of me, and I'm responsible for my life," she says. "No one's going to take care of me except me. And no one's going to take care of my kids except me. So get over it."

Corkey dug her way out with characteristic optimism and energy. Her second husband, a medical student, encouraged her to get a PhD, and she persuaded the University of Pennsylvania to admit her without a bachelor's degree. She was awarded a doctorate in 1981, the same year her son graduated from college. She was 43 years old—ancient in scientist years.

"It's almost unprecedented to start a scientific career so late and achieve so much," says Richard Bergman, director of the Cedars-Sinai Diabetes and Obesity Research Institute in Los Angeles. "Barbara is one of the greatest role models for women in science—and for scientists in general—that I know."

Pamela frames her mother's accomplishments another way. "Having a bunch of kids and giving them home-cooked pot roast seven nights a week is one way to make a contribution to the world," she says. "But when your brain is capable of understanding and breaking down metabolic regulation, that's what you should be doing. I can't imagine how miserable she would have been if she hadn't given wing to her intellect."

LAST REMAINING BIGOTRY

Corkey is now 73, and with her cropped white hair and funky earrings she looks more Greenwich Village grandma than top-tier biochemist. She radiates an aura of competence, kindness, and joie de vivre that endears her to both students and colleagues.

At BU, she is known as a generous collaborator and a beloved but tough mentor. "The best mentors give you a hammer on the head and then a hug," says Shirihai. "With Barbara, you never know which it's going to be." As the department of medicine vice chair of research since 2007, Corkey helped build major research "cores" that allow scientists to use expensive equipment they can't afford in their own labs, such as cell imaging and high-throughput screening machines. She helped write a strategic plan for the department that included specific language to protect postdocs and junior faculty from exploitation. A gourmet cook and wine connoisseur, she encourages fraternization through food, from pairing wine and cheese for faculty gatherings to organizing an annual dim sum lunch, which draws hundreds of faculty and staff and their families.

Corkey is a modest woman who avoids the limelight and disdains what she calls the "billy goats" who often dominate science. She enjoys spending time alone, cherishing the quiet Friday afternoons when she can paint in her studio.

Krawczyk, who earned a PhD under Corkey, was unaware of her boss' status in the scientific world until they started attending conferences together and she saw other scientists treat Corkey like a superstar.

As the winner of the Banting Medal, Corkey had to give an hour-long talk to a crowd of 6,000 last June, and she did not relish the prospect. Shirihai, on the other hand, looked forward to it. "I wanted to see how she would use it to hammer 6,000 people simultaneously," he says. He was not disappointed. Instead of simply recapping her career, Corkey spent an hour discussing a controversial new direction for her research: whether the 4,000 additives in the U.S. food supply might be contributing to diabetes and obesity. "For those people who never got out of the box," Shirihai says with a laugh, "it was like having a high-volume enema."

Obesity statistics are troubling. One-third of American adults are obese, and the numbers are growing, according to the CDC, which describes the cost to the American health care system as "staggering"—an estimated \$147 billion in 2008 dollars. And the rest of the world is catching up. According to the WHO, worldwide obesity has more than doubled since 1980.

Corkey believes that extra calories alone can't possibly be causing this epidemic. "This gets to the last remaining

WEB EXTRA Through March, MED's Barbara Corkey will answer your questions about diet and obesity at bu.edu/bostonia.



In her downtime, Corkey enjoys painting the Boston skyline. Her abstract works are influenced by what she sees in the laboratory and under the microscope.

of course, doesn't give researchers much to do."

Such criticism only galvanizes Corkey, who began her newest line of research by screening about 500 food additives for effects on liver, fat, or beta cell tissues. Two hits proved especially interesting: a class of widely used emulsifiers called monoglycerides, often found in processed baked goods, and the artificial sweetener saccharin. Both additives made beta cells secrete insulin, but not in the normal way. Usually, says Corkey, calcium is involved in stimulating beta cells to produce insulin, and when stimulated they increase their oxygen consumption. But when monoglycerides and saccharin were put to the test, neither of

bigotry in the world, which is against obesity," she says. "If you're a good person and you do all the right things, you're going to be lean. And if you're a bad person and you eat like a pig and you don't do any exercise, you're going to be fat. It is the only body function that we look at this way."

This bigotry "has slowed the field down incredibly," she says. "We don't spend enough money on research. This is the main disease that is growing the health care budget in our society, and we don't even really consider it a disease. We don't study it. We don't understand it. We have no effective treatments, because if you say, 'Control yourself,' and think that's an effective treatment, then you're sticking your head in the sand."

Corkey is not alone in her suspicion that environmental factors may contribute to diabetes and obesity. Earlier this year, the National Toxicology Program, part of the U.S. Department of Health and Human Services, reported that certain environmental triggers, like arsenic poisoning and some pesticides, are associated with type 1 diabetes. It also found that children of mothers who smoked during pregnancy were more likely to be obese.

"There are many factors in the environment that are probably provoking this epidemic," says Harvard's Kahn. "Most researchers have focused on the obvious things: you eat at McDonald's, you sit at your computer, you get fat. I think it's much more complicated than that."

Many scientists and public health experts are skeptical. Nutrition expert Marion Nestle, Paulette Goddard Professor of Nutrition, Food Studies, and Public Health at New York University and coauthor of the forthcoming book *Why Calories Count: From Science to Politics*, says people are getting fatter simply because they eat too much.

As for possible environmental factors, Nestle says, "it's an Occam's razor situation—the simplest explanation is often the one that works. I still vote for calories, but that,

these things happened. Instead, the beta cells underwent some unexpected chemical changes and released molecules called reactive oxygen species, which have been implicated in cell damage, inflammation, and obesity.

What do these intriguing—but preliminary—findings mean? At this stage, Corkey says, it's impossible to know. But she suspects that background levels of certain food additives could cause subtle but critical changes in our metabolic tissues, possibly contributing to diabetes and obesity. Many caveats remain: perhaps the additives never reach levels in the food supply that could hurt an actual human, or perhaps the cellular changes that Corkey observed are beneficial.

"I have a model of how things might be happening," she says. "It's a hypothesis that needs testing. And it needs to be carefully tested."

While it's extremely unlikely that a single food additive could be the villain that causes obesity and diabetes, Corkey hopes to identify a handful of problem additives that could be removed from the food supply. She also knows that in the end, the additives themselves might not be the key. Rather, her research might lead to a new understanding of a metabolic pathway that could be modified to treat obesity and diabetes or to a better understanding of how individual people respond to certain chemicals.

"What I want is to find the cure, but what I don't want to do is get people all fired up in a direction that will be misleading," she says. "Important work needs to be done to prove or disprove what's right and what's wrong."

Corkey's colleagues describe her as a classic biochemist. She comes up with a hypothesis, tests it, and evaluates the data. "She has a vision, she's going about it systematically, and the science will take her where it takes her," says MED's Fried. "In her mind, it's as simple as that. If we don't do the experiment and find out, we will never know." ■