ISSUE 171

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A SPECIAL REPORT

COVER ILLUSTRATION: THOMAS HEINZ

SPECIAL REPORT: OBESITY

FEATURES

Dr. Howard Pearson's legacy

Having trained in the Yale pediatrics residency at the end of Dr. Howard Pearson's tenure as chair, we enjoyed reading the history of Yale pediatrics in the recent issue of *Yale Medicine Magazine*.

However, the list of Dr. Pearson's landmark achievements is much longer than those listed in the article's brief summary of his chairmanship.

For a more detailed and personal description of Dr. Pearson's life and career, we refer readers to the oral history written by his grandson, Matthew Pearson, who was a 10th-grader at the time of the interviews. That oral history helped Matthew attain his Family Life merit badge, ultimately leading to his Eagle Scout certification. The history was published by the American Academy of Pediatrics: m.yale.edu/pearson-history/

There, you can read about Dr. Pearson's ground-breaking contributions to pediatric hematology, including the discovery of functional asplenia in people with sickle cell disease; the first description of the "born-again spleen"; his early work on standards of care for people with thalassemia; his description of one of the first mitochondrial diseases to be recognized, Pearson's marrow-pancreas syndrome; and his key role in the iron fortification of infant formula, which was adopted by the WIC program. This policy essentially abolished severe iron deficiency anemia in a high-risk population of infants in New Haven—findings that were replicated nationally.

And, as a bonus, you can learn about the bawdy song lyrics that Dr. Pearson penned as a student, get confirmation that Paul Newman did indeed have "very blue eyes," and find out why Dr. Pearson had a lifelong hatred of pea soup and creamed chipped beef.

Things we didn't learn as residents.

David J. Birnkrant, MD
Professor Emeritus of Pediatrics
Case Western Reserve University School of Medicine

Jane B. Black, MD
Clinical Assistant Professor of Pediatrics
Case Western Reserve University School of Medicine
Yale Pediatrics residents 1985-1988

Vital dyslexia research

I deeply appreciated the chance to learn more about the Yale Program for Learning Disability Research, and the possibility of early genetic screening for dyslexia risk, in the latest issue of the *Yale Medicine Magazine*. Dr. Jeffrey Gruen is absolutely right that early interventions for dyslexic students can be very successful, and yet far too few children receive them because of our wait-to-fail model in schools. As the parent of a dyslexic learner, I am familiar with both the power of interventions before third grade and the devastating impact of our current approach, where schools wait until a child has fallen significantly behind to provide services. A genetic test that accurately screens for dyslexia in preschool and kindergarten, such as the one Dr. Gruen and colleagues are piloting in a clinical trial, could be transformative for our educational system, and most importantly, for our students. Many bright kids with dyslexia don't leave school intact. Perhaps this research will change that.

Anna Nordberg, SY '01
Journalist, San Francisco, California

Join the conversation

We welcome hearing from our readers! Please send your thoughts and ideas to ymm@yale.edu or *Yale Medicine Magazine*, 50 Division Street, 2 Science Park, New Haven, CT 06511. Letters will be published, as space permits.

Issue 171

Executive Editor
Rebecca Shannonhouse

Contributors
Isabella Backman
Jenny Blair, MD
Jeanna Lucci-Canapari
Steve Hamm
Christopher Hoffman
Mary Ann Littell
Amanda Steffen
Ashley P. Taylor

Art Director
Chris Moore

Copy Editor
Rebecca Frey, PhD

Mailing List Inquiries
Davita Viale

Printing
The Lane Press

Correspondence
Editor, *Yale Medicine Magazine*
50 Division Street, 2 Science Park,
New Haven, CT 06511
Email: ymm@yale.edu

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Yale School of Medicine
Nancy J. Brown, MD
Jean and David W. Wallace Dean of Yale School of Medicine and C.N.H. Long Professor of Internal Medicine

Mary Hu
Associate Dean for Communications

Roopashree Narasimhaiah, PhD
Associate Vice President for Medical School Development

Nicole Wise
Senior Director, Content Strategy & Development and Chief Communications Officer

Abbreviations used in Yale Medicine Magazine include HS to denote the final year of residency for house staff, FW for the final year of a fellowship, and YNHH for Yale New Haven Hospital.

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A CONVERSATION WITH DEAN NANCY J. BROWN

Understanding the Origins of and Solutions to Obesity

IN 1998, THE NATIONAL INSTITUTES OF HEALTH proclaimed that obesity is a disease. The American Medical Association then followed suit. The World Health Organization made its own pronouncement, warning against "an escalating global epidemic of overweight and obesity"—and dubbed it "globesity."


Nancy J. Brown, MD

As the U.S. and global medical communities jointly sounded the alarm about obesity, the task of understanding and containing this ever-growing health threat has been immense.

To introduce our special report on obesity, *Yale Medicine Magazine* spoke to Nancy J. Brown, MD, the Jean and David W. Wallace Dean of Yale School of Medicine and C.N.H. Long Professor of Internal Medicine, about the public health danger posed by the condition and how YSM has responded.

Why has obesity remained such an intractable health threat? Human bodies are wired to survive in times of scant resources, and we live in an environment with abundant food access. However, it's not necessarily abundant *healthy* food access. In addition, most people are very sedentary. This combination of factors contributes to the epidemic of obesity.

As an internist who specializes in hypertension, how do you view the health risks of obesity? Obesity has been tied to almost every disease—not just hypertension, but also diabetes, cardiovascular disease, cancer, and many others. Many of the drugs that we use to treat obesity today also have positive effects on cardiovascular risk. And it's not clear whether those effects are related to weight loss or to a direct effect of the drug. I'm personally interested in that as a research question. But from a public health perspective, if we can reduce obesity, we can increase quality of life, as well as longevity. Recent studies have focused on pharmacological therapies. There is also a need to focus on the built environment and other approaches to reducing obesity.

How have you seen this issue evolve over the course of your career? Our understanding of the mechanisms of obesity has evolved considerably since the time when I was first training. I think we viewed obesity as a character flaw and as a sign of weakness; we have now come to understand the central mechanisms that control appetite, the other factors that affect metabolism, and conversely the effects of obesity on inflammation and other systems. So there have been tremendous advances in our understanding.

Do you believe that we've reached an inflection point in treating obesity? We have certainly reached an inflection point in that we have more—and safer—pharmacological tools available to us than we have ever had. We have a lot of considerations to weigh (no pun intended) around the utilization of these tools. For example, in whom should those therapies be used? How do we take into consideration things like pricing and affordability? How do we use those tools while still using multi-modality approaches to obesity that also include changes in lifestyle and habits?

How is Yale School of Medicine making a difference in combatting obesity? Our faculty and our volunteers are contributing extensively, from very basic science in understanding what causes obesity, how obesity affects insulin sensitivity, how it causes inflammation, how it causes specific organ damage—all the way to leading the clinical trials of the latest pharmacological agents to reduce weight.

YSM alum Mandy Cohen takes the helm at the CDC

By Jenny Blair, MD '04

IN JULY, MANDY KRAUTHAMER COHEN, MD '05, MPH, became the new director of the Centers for Disease Control and Prevention. Her appointment begins a new era for the embattled federal agency, which has lost public trust in recent years. Those who know Cohen well say she will be superb in the position—one that, in many ways, she's been preparing for long before medical school.

"I think she was an inspired choice," said Rahul Rajkumar, MD '06, JD '06, a classmate of Cohen's. "One of the things that makes her unique and distinctive is her ability to use science, but also navigate complex political situations. She'll do a great job restoring confidence in the organization and giving it a morale boost."

Howard Forman, MD, MBA, professor of radiology and biomedical imaging, had similar words of praise. "She's a very mission-driven person," said Forman, who was a faculty advisor of Cohen's. "It was her mission to practice medicine and primary care, to improve the health of populations, and work within governments and outside of governments. And she has done that par excellence."

A JOURNEY TOWARD HEALTH POLICY

Cohen grew up in Long Island, New York; her mother was a nurse practitioner whose patients often stopped and thanked her at stores and restaurants. Cohen attended Cornell University, majoring in policy analysis and management, and worked with Massachusetts Senator Ted Kennedy on health affairs while still an undergraduate.

By the time she arrived at Yale School of Medicine in 2000, she had firm plans.

"A health policy career was her stated goal from week one of medical school," said Jillian Catalanotti, MD '05, a longtime close friend of Cohen's who is an internist and professor of medicine and of health policy and management at George Washington University.

A Yale-sponsored opportunity may have strengthened Cohen's resolve. In 2001, Cohen joined other medical students on a summer trip to South Africa, where they met with HIV/AIDS patients and health leaders there.

When Cohen returned, she was "really energized," Catalanotti recalled. "I think that experience shaped her and made her feel continually excited about health policy."

During medical school, Cohen took a year at Harvard's T.H. Chan School of Public Health to earn a master's degree. She returned to Boston for her internal medicine residency at Massachusetts General Hospital.

Her first post-residency job was with the Department of Veterans Affairs in Washington, D.C., where she served as deputy director of comprehensive women's health services. Along with the current Surgeon General, Vivek Murthy, MD '03, MBA '03, and Rajkumar, Cohen was among the co-founders of Doctors for Obama, which would later become Doctors for America, to push for health care reform. In 2013, she joined the Centers for Medicare & Medicaid Services (CMS), rising to become the agency's chief operating officer and chief of staff.

WINNING CHEERS, TRUST

In 2017, Cohen was appointed secretary of North Carolina's Department of Health and Human Services. There, she was instrumental in building Republican support for Medicaid expansion and for addressing the social determinants of health, among other bipartisan successes.

When COVID hit, she managed to steer an effective state public health response, in part by elevating transparency, accountability, and public communication.

North Carolinians of many stripes grew to trust her, naming her Tar Heel of the Year for 2020. One musician even wrote and posted online a song in her honor.

"People really did love her," said Rajkumar, who was Blue Cross North Carolina's senior vice president and chief medical officer during the pandemic's early months. (Now based in Bethesda, Maryland, he is founder and chief executive officer of Accompany Health, an in-home medical services provider.) "They came to see her as the voice and face of reassurance during a really tough time. I think that was generally true across the political spectrum."

Catalanotti recalled joining Cohen in May 2021 at the Durham Bulls' first post-lockdown game. Wearing a mask, a Bulls T-shirt, and sneakers, Cohen threw the first pitch.

"Everyone cheered," Catalanotti said. "And, oh, my goodness, the number of people who actually stopped Mandy, both on the street in Durham and within that stadium to say, 'Dr. Cohen, I just wanted to say thank you so much for all that you're doing to keep us safe.'"

Virginia Grace Cohen, MD '04 (no relation), who is an associate clinical professor of pediatrics at George Washington University School of Medicine, began a close friendship with Cohen in medical school. Like Catalanotti, she lives and works in the Washington, D.C. area. During the pandemic, she was particularly impressed with how North Carolina handled school openings and closings. "From my perspective as a pediatrician, the state managed it in a very reasonable, rational, but not unsafe way," she said.

Mandy Cohen's accomplishments in North Carolina may be all the more impressive given that, with a Democratic governor and a Republican-dominated legislature, it's a purple state. But under her leadership, North Carolina navigated the pandemic effectively and without significant disunity on the topic of public health.

"North Carolina outperformed much of the country [in its COVID response] by almost any measure," Forman said.

In December 2021, Cohen left her state health job to become chief executive officer of Aledade Care Solutions, a company that seeks to help primary care practices improve patient outcomes in a cost-effective way. That private-sector position burnished a career in high-level leadership in the nonprofit sector and in state and federal government, giving Cohen the broad experiences, accomplishments, and contacts that caught President Joe Biden's eye.

Rajkumar, who also has a longstanding interest in public policy, said he learns from Cohen in every conversation they have. "She's just someone whose career and path I've admired," he said. "We're now many, many years out of medical school, and it's really something special to watch one of your classmates grow into an exceptional leader. Mandy's the best that there is."

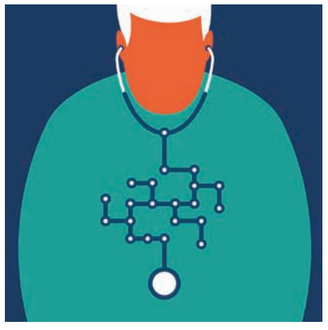
PHOTO: CDC/ LAUREN BISHOP

Mandy Cohen, MD, MPH

Getting it "right" with medical AI

By Christopher Hoffman

AS OPENAI'S CHATGPT, GOOGLE'S BARD, and other artificial intelligence (AI) platforms race to dominate the marketplace, industries from finance and banking to auto manufacturing and media are assessing the impact of what is arguably the most transformative development of the 21st century. When it comes to the field of medicine, the stakes are as high as they come.



Will medical AI usher in a utopia of more precise, life-saving treatments with fewer medical errors—or a dystopia of algorithm-driven medicine that sidelines doctors, undermines quality of care, and defies common sense?

To address such questions, Yale School of Medicine (YSM) experts attended a medical AI forum at Connecticut's Capitol this summer. Representatives from the U.S. Department of Health and Human Services, the Massachusetts Institute of Technology, and Harvard's T.H. Chan School of Public Health also participated in the event.

Speaking to *Yale Medicine Magazine* after the event, the YSM experts called for hard guardrails to ensure that AI medicine doesn't veer off into dangerous directions. These cautions might include strong regulatory controls; careful review and testing of models before they are widely used; and a thorough understanding of what algorithms can and can't do.

These experts, along with others at Yale who are on the cutting edge of medical AI, believe the promise of medical AI is enormous, but so are the potential pitfalls. These include leakage and misuse of sensitive medical data; bias inadvertently built into AI models; medical insurance discrimination; algorithms gone haywire; and black-box treatment models whose underlying reasoning no one fully understands.

"Innovation in technology is always a good thing for us to be experiencing," said Manisha Juthani, MD, who is on leave from her YSM professorship of medicine (infectious diseases) while serving as Connecticut's commissioner of public health. "Physicians could potentially benefit from this, and if we work together, we could potentially leverage it to be something useful. Where I have my radar up, and what I want to be aware of, is that it is used for good—and that it is shown to be better than what we do now."

Juthani's final thought is perhaps the biggest question mark hanging over the nascent AI revolution: Will it actually improve care?

For example, AI can already do a better job of predicting patient outcomes than most physicians, said YSM Associate Professor F. Perry Wilson, MD, MSCE, who has studied informatics and AI in medicine for nearly a decade. "Our ability to prognosticate is way better than it's ever been before," he said. "AI can already outprognosticate doctors like myself." But whether that information will actually lead to improved care is an open question. "Just because I know a patient is more likely to develop a certain type of cancer does not mean that I can prevent it," Wilson said.

That is one of many reasons why AI models should be subject to the same level of regulatory scrutiny and approval processes that we require for new drugs and medical devices, Wilson and other experts say.

THE REGULATION HURDLE

That's music to the ears of U.S. Sen. Richard Blumenthal, D-Conn., JD '73, who also participated in the forum and has made regulation of fast-emerging AI technology a signature issue. He agreed that medical AI models and treatments should undergo the same level of scrutiny as pharmaceuticals and medical devices. While some have suggested that the Food and Drug Administration could take on that additional role, Blumenthal leans toward creating a new agency entirely devoted to AI regulation.

"I think there ought to be some sort of entity, some governing body, a government agency perhaps modeled on the FDA," he said. "We need an entirely separate expertise."

Speaking from his perspective as an attorney, Blumenthal said that AI could produce a pretty good legal brief, but he'd want to read it carefully and make any needed corrections before submitting it to a court. Medical AI needs to be far better than that, he said, which is another reason why regulation and thorough testing are needed before AI models are put into widespread use, he said.

"In life-or-death situations, you don't want it right nine out of 10 times," he said. "You want it right 10 out of 10 times."

But getting it "right" in medical AI is not always as straightforward as it sounds, said Mark Gerstein, PhD, YSM's Albert L Williams Professor of Biomedical Informatics. That's because—in contrast to less risky uses of AI such as managing inventory or mining ad data—medical AI models are often "black boxes"; we don't fully understand how they reach their conclusions and make their recommendations, Gerstein said.

"If you have a medical issue, and it (the AI model) says, 'Cut your arm off,' you want to be able to understand how it came to its conclusion," he said.

Opening those black boxes and determining what's inside and how it works will be a vital job for regulators, he said. To address the problem, builders of medical AI also must incorporate scientific principles into their treatment and diagnosis models.

"One thing that comes up in medicine that makes it special compared to, for example, supply-chain mining, is that medicine is grounded in biochemistry, physiology, and natural laws," Gerstein said. "We want our models to be understanding underlying biomedical theory."

That also means that doctors cannot and should not be sidelined, experts say. While some specialties like radiology—Wilson says AI is already on the cusp of reading medical images better than any human—may soon be in less demand, physician training, observations, and judgment must remain at the center of medicine, they said. Instead of supplanting doctors, AI should assist them, becoming yet another tool in their toolbox.

"Your doctor has more information at their disposal than AI ever will," Wilson said. "It can't look at a patient sitting in a clinic room and pick up on the set of the eyes, or the dynamics of their facial expressions, or the cadence of their conversation. There's all this data at their fingertips that doctors are exquisitely tuned to. Doctors can use that along with AI."

AN EYE ON PRIVACY

Patient privacy is another major concern, said Wilson and others. The huge amount of data that is collected and fed into AI programs creates a myriad of opportunities for leakage and misuse, he noted. In addition to regulation, Wilson called on Congress to pass legislation prohibiting discrimination in insurance and other areas based on the predictions and conclusions of medical AI. An existing law banning discrimination based on a person's genome provides an excellent model, Wilson said.

"I personally think we should go beyond that and provide some protections to prevent the broad-scale harvesting of personal data without explicit consent," he said. "Consumers need to know what information an insurance company, government, or others who might seek to profit from the data are using and what their data sources are."

from the journals

a collection of recent scientific findings

DISPARITIES IN DEATH

Black Americans consistently died at higher rates than white Americans from 1999 through 2020, according to a study published in *JAMA*. The researchers, led by Harlan Krumholz, MD, SM, Harold H. Hines, Jr. Professor of Medicine (Cardiology) and director of the Center for Outcomes Research and Evaluation (CORE), also calculated how many deaths would have occurred in the Black population and how many more years Black Americans would have lived if the Black population had the lower mortality rates of the white population. According to this analysis, 1.63 million excess age-adjusted deaths occurred, and more than 80 million years of potential life were lost among Black Americans during the study period due to their higher mortality rates. The study should be a call to action for policy makers, the researchers say.

A GENETIC CLUE ABOUT MULTIPLE SCLEROSIS

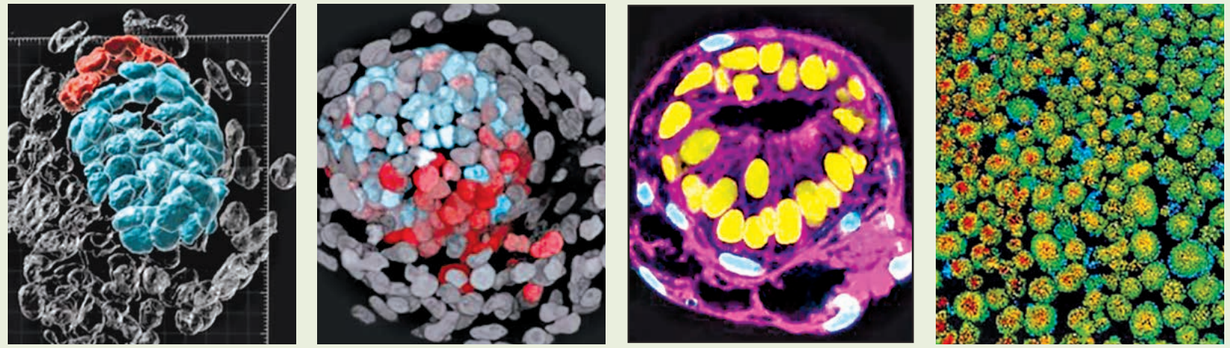
A genome-wide association study has identified a genetic variant that is linked to faster progression of multiple sclerosis (MS). In the study, published in *Nature*, David Hafler, MD, William S. and Lois Stiles Edgerly Professor of Neurology and Professor of Immunobiology, worked with international collaborators to look for associations between particular inherited genetic variants and more severe disease in more than 22,000 people with MS. This is the first known genetic variant that's associated with MS severity and the first that seems to be related to the neurological side of the disease, the researchers say. Hafler and colleagues hope that the variant could lead to the discovery of new drugs that could slow disease progression.

ROUTINE MAMMOGRAM RISKS FOR OLDER WOMEN

Women age 70 and older who receive regular mammograms are more likely to be diagnosed with breast cancers that would not have caused symptoms if they had gone undetected. This phenomenon, known as overdiagnosis, can lead patients to undergo cancer treatments that do not extend or improve their lives, says study author Ilana Richman, MD, MHS, assistant professor of medicine (general medicine). After analyzing data from 54,635 older women who chose either to continue or discontinue their mammography screenings, the rates of overdiagnosis among those who continued screenings and were diagnosed with breast cancer ranged from 31% for those aged 70 to 74 to 54% for those aged 85 and older. The study was published in *Annals of Internal Medicine*.

TARGETED TREATMENT IMPROVES LUNG CANCER SURVIVAL

Post-surgical (adjuvant) treatment with the targeted therapy osimertinib improved survival in people with early-stage non-small cell lung cancer (NSCLC), according to a clinical trial led by Roy Herbst, MD, PhD, Ensign Professor of Medicine (Medical Oncology), deputy director of Yale Cancer Center, and assistant dean for translational research at Yale School of Medicine. Study participants, whose cancer had epidermal growth factor receptor (EGFR) mutations, were assigned at random to take either oral osimertinib or a placebo pill daily for up to three years following surgery to remove their lung cancers. Five years later, the overall survival of those in the osimertinib group was 88%, compared to 78% in the placebo group. Based on results from this trial, published in *The New England Journal of Medicine*, the Food and Drug Administration approved adjuvant osimertinib for NSCLC patients with EGFR-mutated tumors—a group representing 10% to 15% of NSCLC patients in the United States.



MICROSCOPIC IMAGES OF EMBRYO MODEL
Photos by Monique Pedroza, Ipek Gassaloglu, Berna Sozen

A PEEK AT EARLY DEVELOPMENT

Thanks to human embryonic stem cells, researchers can model the earliest stages of human development in the lab. But most systems for cultivating stem cells do not allow researchers to study gastrulation, the process in which the embryo begins to differentiate into multiple cell types. Berna Sozen, PhD, assistant professor of genetics and of reproductive sciences, and colleagues have developed a novel way to grow stem cells so that they develop not just the embryonic tissues that give rise to our bodies, but also the extra embryonic tissues, such as the yolk sac and the placenta, that help the embryo on its way and play roles in gastrulation. This model of the human embryo will allow researchers to study gastrulation in the lab, according to the study, which was published in *Nature*.

Berna Sozen, PhD

Sorting frozen samples at the CURE Hospital in Uganda.

BACTERIUM ON THE BRAIN

Hydrocephalus, nicknamed "water on the brain," is an accumulation of cerebrospinal fluid (CSF) and pressure in the brain. It's the leading reason for pediatric neurosurgeries worldwide. In Uganda, an unusually high number of babies develop hydrocephalus and die following infections and sepsis. In a study to determine the cause of this hydrocephalus, published in *The Lancet Microbe* and in *Clinical Infectious Diseases*, Steven Schiff, MD, PhD, professor of neurosurgery and vice chair for global health, and colleagues found that the bacterium *Paenibacillus thiaminolyticus* was present in the CSF of 44% of babies with post-infectious hydrocephalus. Among infants with sepsis, 6% had *P. thiaminolyticus* infections, and of those, 14% developed hydrocephalus. The researchers found no evidence that the infections pass from mothers to babies; instead, the bacteria may come from the environment. Preventing those infections is the next step, Schiff says.

Body Weight

A LOVE/HATE RELATIONSHIP

By Steve Hamm

VIEWED FROM THE LONG LENS OF HUMAN HISTORY, our relationship with body weight has been capricious at best. From one era to the next, cultural attitudes about portliness have idled for long periods, then shifted into new beliefs. What seems clear is that throughout history, we have held contradictory attitudes about human heft.

On this page, the Venus of Willendorf, photo by artist Nathan Lewis. Opposite page, "The Death of Adonis," by Peter Paul Rubens, courtesy of The Israel Museum, Jerusalem.

As far back as the Stone Age, corpulent people were depicted in ornamental figures. Among them is the well-known endomorphic Venus of Willendorf artifact, dating back some 25,000 years. Were such figures objects of reverence signifying fertility or power? Or something else? We don't know for sure.

With food scarcity prevailing throughout much of our history, the energy conservation provided by extra body weight was long considered a helpful, much-needed survival tactic. Medieval Christians, however, countered this belief by condemning overindulgence in food and drink as one of the Seven Deadly Sins.

Fast-forward to the 17th century, and the famous Dutch painter Peter Paul Rubens glorified full-figured females in paintings that came to be known as "Rubenesque" masterpieces. Portliness also found its way into literature—remember Shakespeare's Sir John Falstaff in *The Merry Wives of Windsor* and Miguel de Cervantes' Sancho Panza in *Don Quixote*. By the 19th and early 20th century in the United States, portraits of prosperous industrialists also accentuated their girth as an emblem of wealth and power.

In the world of medicine, attitudes weren't quite so forgiving. Ancient Greece's Hippocrates, widely considered the father of Western medicine, warned of the dangers of excess body weight, writing that "it is very injurious to health to take in more food than the constitution will bear, when, at the same time one uses no exercise to carry off this excess."

Over the next several centuries, a few other physicians echoed similar concerns. One was the English physician Tobias Venner, who proposed regular baths to avoid what he then termed "obesity" in his treatise of 1660. "Wherefore let those that feare obesity…be careful to come often to our Baths: for by the use of them, according as the learned Physician shall direct, they may not only preserve their health, but also keep their bodies from being unseemly corpulent."

However, well into the 20th century, a good many physicians believed that carrying 20 or more pounds of excess fat was a healthy practice—a reserve of energy that could help ward off illness. It wasn't until the 1930s and beyond that physicians and the life insurance industry began to formally recognize excess weight as a contributor to diseases such as diabetes and heart disease—and to early mortality.

By the 1960s, the pendulum of public opinion swung even farther. Women wanted to look like Twiggy, the ultra-thin British model. Hence, the weight-loss industry was born even as fast foods became ubiquitous, and ad agencies promoted obesity-causing foods one day and weight-loss products the next. With such societal changes as a backdrop, physicians soon began to employ the body mass index (BMI) to monitor weight gain—but with limited effect. Not long thereafter, various medical organizations stepped forward with unequivocal warnings about the health threats posed by obesity.

This brief history brings us to the present. Excess weight has rightly become a concern for society and the medical profession alike; yet even today, ambivalence about bulk remains—think NFL linemen, for example, and proponents of the body-positive movement. How can we make our way through this labyrinthine issue?

When Naomi Rogers, PhD, professor of the history of medicine, lectures Yale medical students and undergraduates about nutrition and obesity, she strives to sensitize them to the complexity of the issues. "I want them not to see obesity as a poor personal choice for which people should be shamed," she says. "I want them to understand that there are no easy answers."

The Next Era

OF OBESITY MEDICINE

By Isabella Backman

THE WARNING SIGNALS OF AN IMPENDING OBESITY CRISIS have been flashing for decades. Now, amongst ever more dire statistics, there is reason to believe that the trajectory may soon begin to shift.

The predictions have been truly alarming. By 2030, researchers estimate that nearly half of Americans will have obesity, and by 2035, it will affect nearly a quarter of the world's population. The health consequences can be ruinous. Obesity is a driver of over 200 serious weight-related diseases, and some researchers believe it may be a contributor to our country's shrinking life expectancy—the disease can shave as many as 14 years off an individual's life.

But overcoming obesity is no longer a hopeless battle. Scientists are entering a new era of obesity research that recognizes the condition not as a choice, but as a chronic neurometabolic disease with a clear pathophysiology. And for the first time, patients with obesity have novel, highly effective therapeutics that, by targeting the underlying mechanisms of the disease, are transforming treatment.

"The field is moving forward rapidly," says Michelle Van Name, MD, assistant professor of pediatrics (endocrinology). "We are gaining more and more insights as well as treatment options for our patients."

A TRIPLING OF WORLDWIDE OBESITY

Obesity is a chronic and relapsing neurometabolic disease involving the overproduction of adipose, or fat, tissue that can create problems throughout the body. Clinicians have long defined obesity in adults as a body mass index (BMI) of 30 or above and class 3, or severe, obesity (formerly known as "morbid obesity") as a BMI of 40 or above. (See "BMI reconsidered" on page 17.) In a child or teen, clinicians consider those whose weight is in the 95th percentile or higher based on age, height, and sex as having obesity.

The list of health complications from obesity is long. It increases the risk of certain cancers, including breast cancer and kidney cancer—particularly a type called renal cell carcinoma. Obesity is also a risk factor for cirrhosis, a chronic disease of the liver that can lead to scarring or liver failure. Other potential risks include joint problems, cardiovascular disease, stroke, sleep

ILLUSTRATION: THOMAS HEINZ

JOHN MORTON, MD //

"There is no single culprit driving the rise of obesity, but rather, a 'perfect storm' of contributing factors."

apnea, asthma, worsened acid reflux, type 2 diabetes, poor circulation, high blood pressure, and high cholesterol. Beyond physical health, the condition can lead to depression, anxiety, and social phobias. "For almost any bodily system you can think of, being overweight or having obesity can increase the risk of disease in that system," says Janelle Duah, MD, assistant professor of medicine (general medicine).

The societal costs of diabetes alone can be enormous. In 2017, the American Diabetes Association found that diabetes led to $237 billion in direct medical costs and $90 billion in lost productivity. Addressing obesity is essential for mitigating both personal and social impacts. Fortunately, studies show that a reduction of even 5% to 10% in body weight is linked to improved liver function, blood pressure, cholesterol, diabetes, and more.

Unfortunately, the trend toward weight gain was recently exacerbated by the pandemic—48% of Americans involved in a 2022 study published in *Diabetes & Metabolic Syndrome* reported gaining weight as their daily routines were upended by COVID-19. Among those who considered themselves to be slightly overweight before the pandemic, the effects were even starker, with 58% reporting weight gain.

The problem is not limited to adults. Sonia Caprio, MD, professor of pediatrics (endocrinology), has been studying type 2 diabetes and childhood obesity for 30 years. In the early days of her career, the prevalence of childhood obesity was relatively low, and youth-onset type 2 diabetes was rare. But now, both of these diseases are on the rise. A 2019 global assessment of child malnutrition by UNICEF reported that, from 2000 to 2016, the proportion of overweight youth increased from 1 in 10 to nearly 1 in 5. Furthermore, a 2021 study in *JAMA* said that the number of youths in the United States with type 2 diabetes nearly doubled over a recent 16-year period.

If these trends continue, scientists warn that there will be dire consequences. In 2022, the Centers for Disease Control and Prevention reported that by 2060, researchers predict that the prevalence of type 2 diabetes in young people will increase by nearly 700%. "Historically, clinicians have ignored the complications facing these kids because they had thought they would get better and lose weight over time," says Caprio. "We now know this isn't true, because 80% of kids with obesity become adults with obesity. The problem is not going to melt away and get better."

THE PERFECT STORM OF AN OBESOGENIC ENVIRONMENT

There is no single culprit driving the rise of obesity, but rather a "perfect storm" of contributing factors, says John Morton, MD, professor of surgery (bariatric, minimally invasive). "One thing for certain is that we can't say it's all genetic, because our genes and our gene pool didn't change overnight," Morton explains. "So it's partly genetic, but clearly the environment has also changed."

There are several key elements in play, including physical, social, and cultural factors, that create an obesogenic environment. First, people tend to lead more sedentary lifestyles—a 2014 study led by Stanford University School of Medicine researchers found a significant relationship between a decrease in activity and obesity between 1988 and 2010. Furthermore, various medications can lead to weight gain, including insulin and many antidepressants. Sleep deprivation also plays a role. "If you don't sleep enough, your body is going to sense that it's stressed and won't give up calories because it views calories as necessary preserves," says Morton.

But the biggest change over time, says Morton, is the food supply and portions. "There have been studies showing that dinner plates have increased in size over time," he says. And now, people tend to include more ultra-processed foods in their diets, which are devoid of many intrinsic nutrients, especially fiber. This has negative consequences for our waistlines. Digesting food burns energy.

"That's partly why you feel sleepy after eating—because the blood supply is going to the stomach and your body is working hard," says Morton. "If you eat ultra-processed foods, your body doesn't have to work as hard to digest." These foods also tend to get converted very quickly into sugar, increasing blood sugar levels. When an individual's blood sugar rises, their insulin also rises to bring it back down. But insulin is also a growth agent and causes people to gain weight.

Finally, Morton adds, there are environmental factors leading to obesity that researchers are still trying to understand. "Clearly, there are some obesogens out there—including chemicals around us that make us gain weight," he says. For instance, Morton led a 2018 study that found individuals with higher levels of bisphenol-A (BPA)—a chemical widely used in many hard plastics, including many food containers and water bottles—lost less weight after bariatric surgery. "These chemicals tend to mimic estrogen, which is weight-promoting," says Morton.

A NEW UNDERSTANDING OF OBESITY PATHOPHYSIOLOGY

As a primary care physician with a passion for obesity medicine, Duah traces her interest, in part, to her own experience with the disease. "I struggled with obesity from when I was a kid, but when I went to doctors' appointments with my parents, we were always told to lose weight. But they never explained how to do this. Or we were told very vaguely to exercise more or eat less," she says. "A common thought about obesity then was that it was almost like a moral failing—that if you just ate less and exercised more, you wouldn't have the disease."

Ania Jastreboff, MD, PhD, associate professor of medicine (endocrinology) and of pediatrics (pediatric endocrinology), finds it "incredibly unjust" when patients face such stigma, bias, blame, and shame. "This often makes patients with obesity feel uncomfortable speaking with their provider about having the disease and pursuing obesity treatment," she adds.

To that end, emerging research is finally reshaping medicine's view of obesity. Obesity specialists now recognize that "calories in, calories out" is a gross oversimplification that fails to consider sleep, stress, medications, and other factors that research has shown contribute to the disease. "Two people could do the same exercise and not burn the same number of calories, even if they have the same weight and build," says Duah. "There are just so many levels to what affects a person's body weight other than them eating too much or exercising too little."

Furthermore, researchers now better understand the pathophysiology behind obesity. "Our body has designed a beautiful, sophisticated system whereby hormones signal to our brain about our energy state," says Jastreboff. "They tell the brain whether we're hungry, whether we're full, and specifically how much fuel we're carrying." This fuel is stored as fat mass. The body wants to carry enough fat mass so that if there isn't enough food available, it doesn't starve. At the same time, it doesn't want to carry so much fat that it interferes with the activities of daily life.

Scientists call that sweet spot the defended fat mass setpoint. Now, this setpoint has been pushed up on a population level due to our obesogenic environment. As a result, even if an individual is overweight or has obesity, their body's altered physiology makes it difficult to lose weight.

"Historically, losing weight has always been bad news for us—it indicated that bad things were happening, like famine," says Wajahat Mehal, MD, DPhil, professor of medicine (digestive diseases). So, when the body's internal sensors perceive that it has had less to eat, the body will deploy defense mechanisms even if the individual is still significantly overweight. "I like to

think of the physiology in terms of a business model. If a business all of a sudden starts going in the red every month, the CEO isn't going to say, 'That's fine, we have lots of money in the bank.' The CEO is going to try and figure out what happened."

A TRANSFORMATION IN OBESITY CARE

As part of the paradigm shift in obesity care, the medical community has begun to recognize the condition as a treatable chronic disease, rather than a consequence of insufficient willpower.

Patients with obesity now have a range of therapeutic options from lifestyle changes to minimally invasive surgery. The emerging field of culinary medicine empowers people to improve their nutrition in their own kitchens. They may also choose to work on behavioral changes under the guidance of a psychologist. When lifestyle interventions alone aren't helping, novel, highly effective and well-tolerated anti-obesity medications, such as semaglutide [brand name Wegovy® or Ozempic®], can work to target the underlying pathological mechanisms of the disease.

As the prevalence of obesity continues to skyrocket worldwide, these new therapeutics are urgently needed to safely and effectively treat the disease. "The concerning side is that a large percentage of the population is in need of these medications, and the health outcomes when not taking them continue to worsen," says Mehal, who has seen patients as young as 20 or 30 suffering heart attacks or cirrhosis. But even if young people feel relatively healthy, treating the disease still requires urgency, he adds, because significant health consequences as they enter their 40s and 50s are inevitable. "Not doing anything is a high-risk proposition."

Patients may also opt for endoscopic procedures like an intragastric balloon, which is a saline-filled, silicone device placed in the stomach, to help them feel fuller faster. Finally, a range of bariatric surgery procedures are available to alter the digestive process and promote long-term weight loss. "Bariatric surgery has never been more safe or effective," says Morton. "When I started 22 years ago, we did less than 10,000 cases a year in the United States. Now, we do about 250,000 cases a year."

When deciding which interventions are right for an individual, clinicians should consider both the patient's preference and the stage of disease, Morton says. "The treatment for stage one breast cancer is different from stage four breast cancer. And so we take the same approach in obesity treatment," he explains. "If your BMI is higher, it makes sense to try surgery first. If it's lower, it might make more sense to try medications." At Yale, Morton and his colleagues have been pioneering the use of combination therapy, in which they utilize medications to help patients lose weight before bariatric surgery as well as afterward to help safeguard results. "We have never had a better time for treating obesity," says Morton.

HOW YALE IS ADVANCING OBESITY MEDICINE

Yale School of Medicine (YSM) is home to some of endocrinology's leading experts who are producing groundbreaking research. Recently, for example, a team led by Mireille Serlie, MD, PhD, professor of medicine (endocrinology), discovered that patients with obesity have a reduced brain response to nutrients in the gut that persists even after weight loss. These findings may explain why patients with obesity struggle with dysregulated eating behavior and keeping off weight.

"In my clinic, when I see people with obesity, they often tell me, 'I ate dinner. I know I did. But it doesn't feel like it,'" Serlie told *YaleNews*. "And I think that's part of this defective nutrient-sensing. This may be why people overeat despite the fact that they've consumed enough calories."

Jastreboff's team is leading NIH studies investigating obesity pathophysiology by employing anti-obesity medications, such as semaglutide, and clinical trials of potential new anti-obesity medications, including a dual-hormone receptor agonist, tirzepatide, and a triple-hormone receptor agonist, retatrutide.

To expand on research in obesity medicine, YSM announced in March the launch of its new Yale Obesity Research Center (Y-Weight), led by Jastreboff. The mission of the center is to improve the lives of people with obesity by leading groundbreaking human, clinical-translational, and outcomes research to investigate novel pharmacological therapies—a focus at the onset of the center. "There is a great need for highly effective and safe obesity treatments," says Jastreboff. "Through studies conducted in our center, we aim to lead research that will help transform our patients' lives and health."

Y-Weight's mission involves three pillars of research, she says. First, human physiology studies, using anti-obesity medications to probe the pathophysiological mechanisms of the disease of obesity. Second, clinical trials that evaluate the efficacy and safety of potential new anti-obesity pharmacotherapeutics. Finally, outcomes research to investigate how anti-obesity medications are utilized and work in the real world, and how they impact long-term health outcomes.

In addition to shaping the growing field of obesity medicine through its research, Jastreboff says Y-Weight will also foster the development of physician-scientists and investigators in this specialty, and help educate the next generation of obesity medicine providers and leaders. Finally, the center will work to integrate clinical obesity research into the practice of obesity medicine.

"The disease of obesity is a huge problem that we need to look at from multiple different stances and across various specialties and departments," says Duah. "Our multidisciplinary approach will promote diverse ideas and ways of thinking that help advance research and, in turn, create better programs and protocols for our patients to help with their weight management."

Importantly, as obesity medicine at Yale continues to grow, the goal ultimately is about patient health, not a number on the scale. "My colleagues and I don't care about a patient's size or what their body shape is. We're not picking a random number out of thin air and saying, 'let's aim for X many pounds,'" says Mehal. "Our goal is not to achieve an arbitrary body weight, but to have a neutral discussion about what weight loss means to our patients and what holistic health benefits it will have for them."

BMI RECONSIDERED

By Ashley P. Taylor

For decades, the body mass index (BMI) has been the standard for determining whether a person is at a healthy weight, is overweight, or has obesity. Obesity screening has been used to help identify people who are at higher risk of obesity-related diseases, like heart disease and type 2 diabetes. But lately, medical experts have pointed out problems with BMI.

In June, the American Medical Association (AMA) adopted a policy that acknowledges the limitations of BMI and encourages clinicians to use the index in conjunction with other measures of risk when managing adults who are overweight or have obesity.

Although BMI is correlated with body fat levels at the population level, that relationship is less predictable on the individual level. BMI—weight (in kilograms) divided by height (in meters) squared—does not directly assess body fat. At the same BMI, women generally have more fat than men, athletes less fat but greater muscle mass than non-athletes, and older adults more fat than younger ones. Nor does BMI tell you where body fat is located, which matters. Belly fat, aka visceral fat, carries more disease risk than fat around the hips.

Metabolic disorders, including high blood sugar, are one of the well-established risks of obesity. But an estimated 15% of U.S. residents who have obesity, according to BMI, are metabolically healthy. On the other hand, some people with BMIs that are considered "normal" have metabolic disorders.

Finally, most data on BMI have been collected from non-Hispanic white people, so BMI categories based on those data may not be accurate when applied to people from other ethnic groups. At a given BMI, for example, Asian people tend to have higher fat levels than white people.

Insurance companies sometimes use BMI to determine whether certain treatments, such as bariatric surgery or inpatient treatment for anorexia, are medically necessary. In this way, the flaws of BMI can become barriers to health care.

Due to these and other limitations, the AMA suggests using BMI in conjunction with other measurements, such as:

Body adiposity index: It is an estimate of the percentage of body fat based on a formula that divides a person's hip circumference by their height.

Relative fat mass: It is an estimate of the percentage of body fat based on the ratio of a person's height to their waist circumference.

Waist circumference: It can be used to estimate visceral fat levels.

A CONVERSATION WITH ANIA JASTREBOFF, MD, PHD

New anti-obesity medications

By Isabella Backman

GREATER KNOWLEDGE OF THE PATHOPHYSIOLOGY of obesity has given rise to new and extremely effective therapeutics. "We are in a new era where these novel anti-obesity medications are transforming the way that we are able to treat our patients with obesity," says Ania Jastreboff, MD, PhD, associate professor of medicine (endocrinology) and of pediatrics (pediatric endocrinology).

Widely considered a groundbreaker in the development of anti-obesity medications, Jastreboff has led and collaborated on numerous clinical trials. *Yale Medicine Magazine* recently spoke with her to learn more about the medications' potential for managing the disease.

What are the underlying causes of obesity? Is obesity a choice?

Let's start by talking about obesity pathophysiology. Our bodies are really smart. They have this concerted interest in storing an appropriate amount of fuel, and they store that fuel as fat. Our bodies defend a certain amount of fat mass, and we call that the defended fat mass setpoint. How do our bodies do this? How do our brains regulate energy homeostasis? Many researchers are working on figuring this out. There are hormones in our body that communicate with our brain to inform us about energy homeostasis and about how much fat we are storing. Our bodies don't want to carry too much fat because then we can't do the activities necessary for daily life, and they don't want to carry too little fat—and, thus, too little energy—because then we would starve. Our bodies want to carry just the right amount.

So, if our bodies have devised this beautiful system

ILLUSTRATION: THOMAS HEINZ

to make sure we store just the right amount of fuel or fat, why is it that so many people have obesity? It turns out that our bodies are impacted by our obesogenic environment, which is one filled with highly processed foods, lack of sleep, lack of physical activity, and increased stress; this environment, in many people, results in an elevated defended fat mass setpoint. Thus, obesity treatment requires resetting the defended fat mass setpoint.

It's important to understand obesity pathophysiology so that treatments can be developed to target disease mechanisms. It's also important to talk about the biology of obesity with our patients so that they know and understand that having obesity is not their fault. Obesity is not a choice. It is a biologically driven chronic neurometabolic disease. And we need treatments that target disease pathophysiology and effectively treat obesity.

The prevalence of obesity has increased dramatically over the last decade. Why have nonpharmaceutical approaches like dieting and exercise been ineffective in curbing this rise?

Once the obesogenic environment exerts its impact and contributes to someone developing the disease of obesity, there's biology at play. So, any treatment that we utilize needs to target that biology. Lifestyle changes, whether it is a more nutritious diet or increasing physical activity, are critical for health. But to treat the disease of obesity, we need interventions that target disease pathophysiology.

How are the treatment options for obesity evolving?

Treatment options for patients with obesity have evolved over the years, and especially more recently with a class of medications called nutrient-stimulated hormone-based medications, which include semaglutide and tirzepatide. In terms of the pathophysiology of obesity, there are hormones in our body that signal to our brain about energy homeostasis—about how much energy or how much fat we are storing. They inform us about food intake, about what foods we crave, about how much food we want to eat, and they also potentially inform about energy expenditure, or how much energy we want to burn. The newer medications like semaglutide [brand names Wegovy® or Ozempic®] and tirzepatide are mimicking these nutrient-stimulated hormones and targeting receptors in the brain to impact mechanisms of energy homeostasis.

In 2022, you were the lead author in the SURMOUNT-1 trial investigating the drug tirzepatide as a treatment for obesity. What is this drug's mechanism of action?

Tirzepatide [brand name Mounjaro®] is a GIP/GLP-1 receptor agonist, which is a once-weekly injectable nutrient-stimulated hormone-based medication. It's currently FDA-approved for type 2 diabetes and is under FDA review for the treatment of obesity or chronic weight management. It targets [glucose-dependent insulinotropic polypeptide] GIP and [glucagon-like peptide-1] GLP-1 receptors of these nutrient-stimulated hormones. In the SURMOUNT-1 trial, we investigated tirzepatide for the treatment of obesity.

The response to this medication was quite striking, and not one that we had seen before in Phase 3 trials of a medication for the treatment of obesity. We found that after 72 weeks of treatment, the highest dose of the medication resulted in an average percent body weight reduction of 22.5%. And this translated to an average absolute weight reduction of about 52 pounds. Additionally, nearly 40% of participants lost at least a quarter of their body weight.

If the FDA approves tirzepatide as a treatment for obesity, is it intended to be used alone or with other obesity-fighting strategies?

It can be used in combination with other treatments or as monopharmacotherapy. It is important to consider that there are many different types of obesities with varying pathologies and phenotypes. Medications approved for the treatment of obesity can be used in combination to target different mechanisms. The medications can also be used in combination with bariatric surgery. So, someone can have surgery, and then later on, they can use anti-obesity medications to further treat their obesity. They can also use the medications before they undergo surgery. It is not about one

ANIA JASTREBOFF, MD, PHD //

> "The medication shortages underscore the fact that we need to really think as a society about how to treat our patients with obesity."

treatment, but rather what are the optimal treatments when we care for patients with obesity.

Additionally, with anti-obesity medications, we include healthy lifestyle changes in the care of our patients. With these medications, especially during the weight-reduction phase, patients will eat less if they are responding. So, we want to make sure that the food our patients are eating is as nutritious as possible; we want to prioritize lean protein and nutrient-dense foods such as vegetables. We also talk about ways to incorporate movement and physical activity into daily life—how do we add in resistance exercise and other forms of movement with the goals of minimizing muscle loss while maximizing fat loss? The important thing is that the focus is on optimizing health. Nutritious eating and increasing movement are things that maximize health as we treat obesity by targeting disease mechanisms with interventions such as medications.

What are the side effects of anti-obesity medications, and how do you counsel patients about them?

The most common side effects of medications such as semaglutide and tirzepatide are gastrointestinal. Most of the time, these side effects are mild to moderate, and most commonly occur during medication initiation and dose escalation. Not everyone has these gastrointestinal side effects, but if they occur, the most common ones include nausea, diarrhea, constipation, and, rarely, vomiting.

How can we mitigate these side effects? The most important way is by going up very slowly on the dose of the medications—always starting at the lowest dose and going up based on how the patient is doing. So, if a patient is experiencing nausea, we would not increase the dose because we don't want our patient to potentially experience vomiting. We would either go down on the dose; or if the nausea is mild, we would stay on the current dose and give our patient time to adjust to the medication. Once the nausea resolves, we can go up and continue escalating. Bottom line, start low and go slow.

There are also ways that the patient can help mitigate potential side effects. The first way is if they're experiencing these side effects, it is important to let their doctor know so that they can adjust the dose to diminish the side effects. The second thing is to know that if they're responding to these medications, they will feel full earlier, so it's important to not eat past the point of fullness. Patients should also know that they may want to eat more frequently—but consume smaller amounts at a given time rather than meal-size portions. The third thing patients can do is monitor what foods exacerbate their symptoms. For example, if they experience diarrhea and eating fatty foods, such as egg salad or pizza, worsen this side effect, then especially during dose escalation, they should eat less of that food. Once they get to a stable dose—or weight plateau—they may be able to tolerate more of these foods.

Do people who stop taking anti-obesity medications gain back the weight they have lost if they stop taking the medication?

Obesity is a chronic disease, which necessitates continued treatment as with any other chronic disease.

Let's consider an example of a patient with hypertension, or high blood pressure. If a patient has high blood pressure, and they are treated with an antihypertensive, their blood pressure improves. If we were to stop that antihypertensive medication, their blood pressure would go back up. So, in the same way, when we treat a patient with obesity with an anti-obesity medication, their defended fat mass setpoint is decreased. When we stop that anti-obesity medication, that defended fat mass setpoint goes back up, and the weight follows. So, in order to effectively treat a chronic disease, such as the chronic disease of obesity, we have to continue the treatment in order to continue to treat the disease.

Studies have now demonstrated that when anti-obesity medications are discontinued, on average, the weight is regained. The STEP 1 trial extension looked at discontinuing weekly semaglutide 2.4 mg after weight reduction. During the first year off the medication, on average participants gained back most of the weight. So, when these medications are discontinued, the weight is regained.

What is known about the long-term risks of taking anti-obesity medication?

GLP-1 receptor agonists have been FDA-approved for the treatment of type 2 diabetes for over 17 years, so there is data on this class of medications. But overall, while the disease of obesity is not new, the field of obesity medicine is relatively new. In terms of these highly effective treatments, we need to conduct research to investigate long-term outcomes. We need to look at how effective and tolerated these medications are in the clinical setting and in real life, as well as examine long-term health outcomes.

Anti-obesity medications have become very popular. Are you concerned about shortages of these drugs?

The medication shortages underscore the fact that we need to really think as a society about how to treat our patients with obesity, given that it affects such a large proportion of our population. I don't think we should shy away from this. If we think about diseases like type 2 diabetes, high blood pressure, and hyperlipidemia collectively, [there are] just as many people [who] have these diseases, and we did not shy away from treating these conditions. Furthermore, obesity is associated with over 200 obesity-related diseases. If we treat the disease of obesity, we're effectively treating the underlying cause or major contributor to over 200 other obesity-related diseases. We could transform our patients' lives and health and our population's health by effectively treating this one disease.

What do you foresee in terms of the cost barrier for anti-obesity medications?

Currently, in the United States, we are treating less than 5% of individuals with obesity with appropriate anti-obesity pharmacotherapy or bariatric surgery. Access and affordability are key issues that we need to address as a society, and we need to continue to work to figure out how to make these medications affordable and accessible to all patients with obesity who need them.

Do you expect these new drugs to change societal views on obesity?

These highly effective, novel therapeutics potentially open up the conversation between patients and providers about treatment options. Hopefully, they will also help destigmatize obesity and highlight that there's this underlying biology, and now we have tools to target and treat the underlying biology of this chronic disease.

How do you see obesity treatments evolving in the future?

We're at a pivotal point in our ability to effectively treat the disease of obesity with these novel anti-obesity medications. There are over a dozen nutrient-stimulated hormone-based medications in development in Phase 2 and moving into Phase 3, and there are even more in development in Phase 1. There are also additional anti-obesity medications in development that are targeting different mechanisms; for example, treatments that may preserve lean mass while effectively contributing to fat loss, thus improving the quality of the weight lost. Semaglutide and tirzepatide are the beginning of this incredible transformation where we will have many highly effective pharmacotherapeutics for the treatment of obesity. We also need to look beyond "just" weight reduction to treating obesity, to caring for our patients holistically, treating their disease while optimizing their overall health.

Ania Jastreboff, MD, PhD

You're also studying retatrutide for weight loss. What can you tell us about this drug, and when it might be reviewed by the FDA?

Retatrutide is a triple-hormone receptor agonist targeting three nutrient-stimulated hormone receptors—GIP [glucose-dependent insulinotropic polypeptide], GLP-1 [glucagon-like peptide 1], and glucagon (GCG). I led a Phase 2 trial of retatrutide evaluating the safety and efficacy of the molecule. And we found that with the highest dose of retatrutide, participants lost nearly one-quarter of their body weight over the 11 months of the trial. Ultimately, the results of the trial supported this molecule moving into Phase 3. [Phase 3 trials are the regulatory trials that are conducted so that the FDA has the information that it needs and requires in order to evaluate the safety and efficacy of a novel agent and can make a decision about whether a specific therapeutic will be FDA-approved.] The TRIUMPH Phase 3 trials evaluating retatrutide are starting this year [2023].

What would you like to say to people with obesity?

Having obesity is not a choice. Having obesity is not your fault. It is a chronic neurometabolic disease. And now we have highly effective treatment options that target the biology of obesity. We will care for you and guide you to treatment options for your obesity as we would if you had any other chronic disease—with kindness, compassion, and evidence-based treatments. I would advise patients to speak with their provider about options and what therapy may best fit their needs and treat their obesity.

Jastreboff serves on the scientific advisory boards for various companies that are developing novel anti-obesity medications, including Novo Nordisk (makers of semaglutide) and Eli Lilly & Company (makers of tirzepatide and retatrutide), which funded the trials.

ILLUSTRATION: THOMAS HEINZ

Diabetes

YALE'S TRADITION OF TRANSFORMING CARE

By Jenny Blair, MD

IN THE UNITED STATES, it's highly likely that there is at least one person with diabetes on every bus and in every restaurant and workplace. This complex disorder of blood sugar regulation affects over 11% of the population. Both type 1 and type 2 diabetes can saddle people with a lifetime of thinking about blood sugars, navigating complex treatment regimens, and coping with dire complications.

"Diabetes is not part-time. It's full-time," said Kevan Herold, MD, C.N.H. Long Professor of Immunobiology and of Medicine (Endocrinology) at Yale School of Medicine. "If you have diabetes, there is nothing you do without thinking about it. You don't go to sleep, you don't wake up, you don't eat anything, you don't do any activity, you don't go to school—diabetes is in every aspect of your life."

Herold and his fellow immunology and endocrinology researchers at Yale have worked for decades to ease that burden. Through pioneering studies of insulin pumps, the development of a preventive drug, or elucidation of insulin resistance and its relationship—or not!—to obesity, advances made here have repeatedly changed how doctors and patients grapple with diabetes. Since 1993, investigators from diverse disciplines have received ongoing support for research focusing on diabetes and related metabolic and endocrine disorders at the Yale Diabetes Research Center.

GETTING PUMPED

Insulin regulates blood sugar, and diabetes occurs when insulin is not doing its job. Either it's absent, as in type 1 diabetes, in which the beta cells of the pancreas stop producing the hormone; or cells in the rest of the body stop responding to it normally, as in type 2 diabetes.

While insulin injections are just one among numerous treatment options for type 2, for type 1, they are absolutely necessary for survival—sometimes many a day.

This is no small task. Insulin is finicky and expensive, and getting the dose right can be tricky. In hopes of making insulin replacement easier on patients with diabetes, William Tamborlane, MD, professor of pediatrics (endocrinology), and his mentor, the late Robert S. Sherwin, MD, C.N.H. Long Professor Emeritus of Internal Medicine (Endocrinology), undertook pioneering work on insulin pumps. Their partnership spanned 40 years.

"For most of us, we don't have to worry about how much insulin our body's making," Tamborlane said. Pumps can reduce that worry among people with

diabetes by delivering a tailored response to glucose fluctuations; this feature can result in better glucose control and fewer long-term complications.

Tamborlane and Sherwin began working together in 1976. At the time, researchers were debating the roles played by insulin and the hormones glucagon and somatostatin in type 1 diabetes.

To untangle these relationships, Tamborlane suggested studying a multi-day infusion of somatostatin in children with type 1 diabetes. The researchers used a pump they had seen pediatrics colleagues use to treat children with iron overload. It had a button to deliver extra doses—handy at mealtimes for those with diabetes.

To be sure, researchers had been working on insulin pumps as long ago as the 1960s, but early versions were bulky and cumbersome. By the late '70s, however, some, like the pediatricians who caught Tamborlane's attention, had hit upon the expedience of adapting a pump designed to deliver hormones to animals. Grasping the possibilities, Tamborlane and Sherwin set out to study its use in humans with type 1 diabetes.

In 1979, they showed that a portable pump could reduce fluctuations in and normalize levels of blood glucose, normalize hormone responses to exercise, and improve cholesterol and triglyceride levels. They also examined its use within days after a child's diabetes diagnosis and during pregnancy, among many other variables.

Lauded by Tamborlane in a eulogy as "one of the greatest of great diabetes investigators," Sherwin was a celebrated researcher. He set the intellectual tone among Yale diabetes scientists with a well-attended weekly meeting that nourished many careers and lines of inquiry. Tamborlane has called the last quarter of the 20th century "Yale's golden age of clinical diabetes research."

And thanks in part to Sherwin's legacy, that notable age continues. In recent years, Tamborlane and his colleagues have published prominent papers on pediatric diabetes drugs, treatment standards, and the holy grail of insulin pumps: automated closed-loop therapy, also known as the artificial pancreas.

"It's still a challenge," Tamborlane said of the disease, "but this pump makes it a little easier."

THE MYSTERIES OF INSULIN RESISTANCE

Diabetes has a complex relationship to obesity. Many people with high body weight also have insulin resistance, in which muscle tissue and the liver, normally sensitive to insulin, stop responding as usual. Beta cells buy time by producing more insulin but can't keep up. The result of these derangements can be (but is not always) type 2 diabetes.

Though there is no causal relationship with type 1 diabetes, obesity can also occur in people with the condition—and when it does, the extra weight is associated with increased health risks. In fact, people with high body weights and type 1 diabetes may have the worst of both worlds. Not only do their beta cells no longer produce insulin, but their bodies often develop insulin resistance, resulting in a hard-to-treat condition called "double diabetes."

But even type 2 diabetes is not inevitable among high body-weight people, and both insulin resistance and type 2 diabetes can occur in lean people, too.

A Yale husband-and-wife team have worked to illuminate the complex machinery that determines how insulin interacts with cells and how it can go wrong. What they've learned about insulin resistance challenges the notion that high body weight causes diabetes—and it opens the door to treatments that do more than reduce blood sugar.

"Insulin resistance is the strongest predictive factor for the development of type 2 diabetes, but it also promotes the development of heart disease, fatty liver disease, Alzheimer's disease, and probably all obesity-associated cancers," said Gerald I. Shulman, MD, PhD, George R. Cowgill Professor of Medicine (Endocrinology) and professor of cellular and molecular physiology, as well as co-director of the Yale Diabetes Research Center and Howard Hughes Medical Institute Investigator Emeritus.

"If you understand the molecular basis of insulin resistance, you can then go on to target the triggering factor and not only reverse type 2 diabetes, but then also slow down the progression of these other associated diseases," he said.

Together with his wife, Kitt Falk Petersen, MD, professor of medicine (endocrinology), and colleagues, Shulman showed that reduced muscle glycogen

KEVAN HEROLD, MD //

> "If you have diabetes, there is nothing you do without thinking about it."

synthesis, due to reduced insulin-stimulated transport of glucose across the cell membrane, is a key step in causing insulin resistance in skeletal muscle. What underlies this defect, the group then determined, is ectopic lipid—that is, fat stored in the wrong place (i.e., the liver and muscle).

In many people, the body stores fat not only in the usual subcutaneous depots, but also in muscle and the liver. "In our studies we have been able to dissociate obesity from insulin resistance and found that it is the ectopic lipid stored in the liver and muscle cells that causes the insulin resistance," Shulman said. "This explains why even young, lean offspring of parents with type 2 diabetes and individuals with lipodystrophy [a rare group of syndromes that affect how a person stores fat], who have very little subcutaneous and visceral body fat, can become insulin-resistant."

How does ectopic lipid do this? The Shulman lab has gone on to elucidate the molecular basis for the way in which ectopic lipid causes insulin resistance by identifying the intracellular fatty acid-derived lipid metabolite (sn-1,2-diacylglycerol) that causes insulin resistance in the liver, muscle, and adipose tissue. The metabolite does this by binding to a protein called protein kinase Ce, which in turn binds to and inhibits insulin receptor activity—a requirement to mediate insulin action.

This mechanism also provides a potential evolutionary basis for insulin resistance. During starvation, fat is mobilized from adipose tissue to deliver energy in the form of fatty acids to the liver and muscle tissue, as well as to other organs, and triggers insulin resistance in these organs through the same mechanism, Shulman explained.

"We have shown that the liver and muscle become insulin-resistant and therefore take up less glucose during starvation, thus preserving glucose in the bloodstream for the brain and other obligatory glucose utilizers, such as red blood cells and the renal medulla," Shulman said. "This has obvious beneficial effects for survival during starvation. Now, in our toxic environment of highly processed food and sugary drinks, this same lipid pathway is being triggered to cause metabolic syndrome, metabolic dysfunction-associated steatotic liver disease (MASLD) [formerly known as nonalcoholic fatty liver disease, or NAFLD], metabolic dysfunction-associated steatohepatitis (MASH) [formerly known as nonalcoholic steatohepatitis, or NASH], and type 2 diabetes."

These insights suggest a new way to address type 2 diabetes at its foundations.

"Virtually all agents we have to date to treat type 2 diabetes do not get at the root cause of insulin resistance, which is ectopic lipid in the liver and muscle," Shulman said. "What if we can rev up the mitochondria to burn the ectopic fat in the liver and muscle?"

To pursue this goal, his group has developed a series of liver-targeted mitochondrial uncoupling agents to promote increased fat oxidation by the liver mitochondria. Shulman's group has now shown safety and efficacy for this approach to reverse insulin resistance, MASLD/MASH, and diabetes in rodent and nonhuman primate models of metabolic syndrome and type 2 diabetes.

In collaboration with Gilead Pharmaceuticals, Shulman has developed a third-generation liver-targeted mitochondrial uncoupling agent that is now marching its way through Phase 1 clinical trials. "I think liver-targeted mitochondrial uncouplers will be a very safe and effective approach to reverse liver and muscle insulin resistance as well as hyperlipidemia, and offer a novel and effective approach to treat our patients with MASLD, MASH, and cardiometabolic disease."

FENDING OFF A DIAGNOSIS

Most people with type 1 diabetes—the majority of them children—are neither obese nor insulin-resistant. It is an autoimmune process of beta-cell destruction that begins years before clinical diagnosis.

But what if we could block that destruction in at-risk people and delay or even prevent type 1 diabetes? That goal has motivated Herold since medical school, around the time that researchers were first realizing diabetes is an autoimmune disease.

Trained in both endocrinology and immunology, Herold was fascinated early in his career by news that researchers had used an antibody to reverse type 1 diabetes in a mouse model. He and colleagues at the University of Chicago began to test a new antibody to the T-cell CD3 receptor.

"CD3 is the business end of a T cell. As we began to understand that type 1 diabetes is largely driven by T cells, this became a likely thing to target," Herold explained.

The drug doesn't kill T cells. Rather, it delivers a partial agonist signal—one that seems to inactivate or exhaust the cells and keep them from attacking beta cells in the pancreas.

In 2002 at Columbia, Herold's team showed that in people with newly diagnosed type 1 diabetes, a two-week course of the antibody, now called teplizumab, maintained or improved insulin production for least a year. That in turn improved chronic hyperglycemia and reduced the amount of insulin patients required.

By 2009, with Herold now at Yale, some of these patients had preserved insulin function for five years after the end of the two-year trial. The drug did not work as well for patients who had had diabetes for four to 12 months before treatment, suggesting that getting a jump start on the disease is important. That insight led to a key study.

Autoimmune destruction in type 1 diabetes begins long before symptoms. In stage 1, autoantibodies to pancreatic islets appear in the bloodstream, but blood sugars are normal. Already, though, the attack on insulin-producing beta cells has begun. In stage 2, abnormal blood sugars are found when the beta cells are challenged with glucose. At this time, the risk of being diagnosed with stage 3 or clinical diabetes, with classic signs like extreme thirst and urination or complications like diabetic ketoacidosis, is about 50% in two years. Although nearly all patients can still make insulin when they present with stage 3 diabetes, this ability is lost over time.

Herold and his team decided to see whether they could interrupt this process early. They conducted a placebo-controlled trial in 76 adults and children at high risk of developing type 1 diabetes; all of them also had a close relative with the disease. All of them were in asymptomatic stage 2 diabetes when they enrolled. The treatment group received a two-week teplizumab course; then all participants underwent periodic testing for outright stage 3 diabetes.

By 2019, the results were in. In the teplizumab group, full-blown diabetes arrived after a median of 48.4 months, while in the placebo group it took 24.4 months. One adolescent remained diabetes-free for 11 years. The drug had clearly delayed disease onset in high-risk participants. Combined with years of evidence showing that the drug preserved beta-cell function in every trial that had tested it, the study led to FDA approval in 2022.

"If you're 10 years old and you're not going to get diabetes until you're 20, that's a huge difference," Herold said.

In the future, Herold said, screening could detect high-risk people with early signs of autoimmunity; they could then be treated with teplizumab or a similar drug, perhaps allowing them to dodge the disease altogether.

More work with teplizumab remains to extend its duration of activity and improve the frequency of responses. Herold expects it to one day become part of a combination-therapy approach, even in combination with beta-cell replacement therapy for patients who have already been diagnosed with stage 3 type 1 diabetes. Even absent full prevention, this approach could defend enough beta cells to reduce diabetes severity and make it easier to manage. Every partial advance helps lighten patients' load.

"It's better not to have diabetes than it is to have diabetes," Herold said. "If we can identify someone who's going to develop an autoimmune disease and stop it, why don't we try to do just that?"

ROBERT S. SHERWIN, MD:

A CONSUMMATE PHYSICIAN AND SCIENTIST

Robert S. Sherwin, MD, C.N.H. Long Professor of Medicine, Emeritus, passed away March 31, 2023, at age 80. He was a prolific and influential endocrinology and diabetes researcher, and a beloved clinician and mentor.

"Bob was the consummate physician-scientist, linking what he observed in patient care to asking fundamental questions in research, and then learning from his research findings to help provide even better patient care," wrote Silvio Inzucchi, MD, professor of medicine (endocrinology), in a comment on Sherwin's obituary.

Added a patient, "He helped me with my diabetes. He was always there to listen to all my concerns. I truly miss…his caring, thoughtfulness, and understanding."

Sherwin's over 400 scientific papers have been cited roughly 35,000 times. His key contributions included foundational work in glucose metabolism; the treatment of type 1 and type 2 diabetes; autoimmunity and type 1 diabetes; and metabolic function in children with obesity.

He devised crucial research tools as well as patient-care innovations. Early in his career, he developed glucose clamps, which became indispensable techniques in studies of glucose metabolism and diabetes drug development. He also helped pioneer the insulin pump. Mid-career, he helped make Yale a global center of research into autoimmunity and diabetes.

"It is hard to imagine that anyone will have the credentials to fill Bob's shoes in the future," wrote William Tamborlane, MD, professor of pediatrics (endocrinology), in a 2021 career tribute in *Diabetes Journal*.

Robert S. Sherwin, MD

PHOTO: HAROLD SHAPIRO

Born in New York City in 1942, Sherwin graduated from Albert Einstein College of Medicine in 1967. In 1972, following residency at New York's Mount Sinai Hospital and the National Institutes of Health, he came to Yale, joining the faculty two years later.

By 1995, he was head of the Endocrinology & Metabolism section. A decade later, he became the inaugural leader of the Yale Center for Clinical Investigation, an early recipient of the NIH's Clinical and Translational Science Awards that nurtured human subject research at Yale.

Sherwin also directed the Endocrine Fellowship beginning in 1984 and Yale's federally funded Diabetes Center from 1993 until he retired in 2018.

Sherwin also played national roles, leading the American Diabetes Association (ADA) and serving on many journals' editorial boards. Among his many honors were three from the ADA alone: the Banting Medal for Service in 2001, the Banting Award for Lifetime Scientific Achievement in 2007, and the Albert Renold Award for Mentoring in Diabetes Research—an acknowledgment of his having mentored more than 200 trainees.

Said one of those mentees, Assistant Professor of Medicine Janice Hwang, MD, to the *Yale Daily News* upon Sherwin's retirement, "He never forgot the North Star, which was to help patients."

Stigma

ADDS FUEL TO THE OBESITY EPIDEMIC

By Steve Hamm

IN THE 2009 FILM PRECIOUS, the main character, Claireece "Precious" Jones, a Black teenager with obesity who lives with her abusive mother in New York's Harlem neighborhood, starts her day by primping in front of a mirror. Instead of seeing a reflection of herself, though, she envisions a thin, blonde white girl—society's stereotypical ideal of teen beauty. Hungry, Claireece asks her mother for money to buy food but gets turned down. So she goes to a nearby diner, orders a 10-piece bucket of fried chicken, flees without paying, devours the chicken as she runs through city streets, and vomits into a wastebasket after she arrives at her social worker's office.

This episode dramatically illustrates the harm that social stigma does to people with overweight conditions. Obesity experts at Yale School of Medicine say that until society and the medical profession figure out how to deal effectively with weight bias and stigma, it will be difficult to halt the growth of the obesity epidemic. "Stigma is pervasive and creates a vicious cycle," says Janet Lydecker, PhD, assistant professor of psychiatry. "It leads to stress, which leads to binge eating, to weight gain, to poor treatment from others, and to more stigma. It just keeps growing."

In addition, obesity and weight stigma are often associated with mental health issues—not just eating disorders such as binge eating and bulimia nervosa, but also anxiety and depression. According to one study, over half of the people who experienced weight stigma also had at least one psychiatric disorder.

At the core of weight stigma is the widely held yet false belief that people with overweight conditions have only themselves to blame: They are heavy because they lack the self-control to avoid becoming overweight and the willpower to lose weight. Some people with overweight conditions also blame themselves—a phenomenon called weight-bias internalization, which further diminishes their self-esteem and often leads to overeating.

Obesity is a frequently stigmatized chronic medical condition in part because the problem is immediately

ILLUSTRATION: THOMAS HEINZ

visible—which makes people who suffer from it particularly vulnerable to discrimination and derisive comments.

ERADICATING WORDS THAT HURT

When it comes to body weight, there's tremendous variety and savagery in the language of disparagement; many hurtful words likely come to mind. To make matters even worse, there's a strong impulse in society, even among well-meaning people, to pressure those with overweight conditions to do something about it—"tough love" that often involves harsh accusations. Even some physicians use language that further traumatizes the people they are trying to help.

That's why a movement is afoot to destigmatize the language we use when talking about body weight. A group of Yale researchers in 2016 conducted a survey of people with weight issues aimed at identifying harmful words and phrases as well as preferred terms. Harmful language included "excess fat," "large size," and "obesity"—which is the official medical term to describe the condition of being severely overweight. Preferred terms included "BMI" and "unhealthy body weight."

In their journal article, published in the *International Journal of Clinical Practice*, the authors urged health care professionals to avoid using stigmatizing language when talking to patients. The same guidance applies to everybody in society. "I think the safest thing is to not use 'obese' as an adjective. Say 'people with obesity' rather than 'obese people,'" advises Carlos Grilo, PhD, professor of psychiatry and of psychology.

The power of language should not be underestimated. The National Eating Disorders Association argues that the rise of national obesity prevention campaigns in the United States has actually contributed to the incidence of weight stigma, in part because of the language that weight-loss advocates use. The messaging from marketers of weight-loss products and services is also hurting rather than helping. Journalists are prone to using inconsiderate language, as well.

Weight experts had hoped that when the American Academy of Pediatrics published its first-ever clinical practice guidelines for evaluation and treatment of children and adolescents with obesity last January, it would help destigmatize the condition. Unfortunately, some parents reacted strongly against a new recommendation that pediatricians consider prescribing medications for adolescents 12 years and older. "People said, 'How can we put our children on medication?'" says Mary Savoye, RD, associate director, Yale Pediatric Obesity. "But if a child has asthma, they are prescribed an inhaler. Why is obesity treated differently? It's because of stigma. It's supposedly the person's fault."

Until recently, there were no truly effective medications for the treatment of obesity. Now, physicians can prescribe semaglutide (brand name Wegovy®) and liraglutide (brand name Saxenda®), which are FDA-approved for weight management in people with obesity or overweight. In addition, diabetes drugs, including Ozempic® (the brand name of semaglutide when it's prescribed for diabetes) and tirzepatide (brand name Mounjaro®), promote weight loss. The medications approved for chronic weight management should be combined with nutritional and physical activity counseling, and, ideally, with lifestyle behavioral counseling.

MONA SHARIFI, MD, MPH //

> "If we as a nation are going to address this, we have to do it at the health care level for those affected, and at the societal and policy level for prevention. "

ADOPTING A NEW CALCULUS

For Yale School of Medicine programs that combine clinical care with research, destigmatizing weight is part of the calculus that goes into the treatments and language that appears in medical journal articles and in conversations with patients and families.

Grilo directs the Program for Obesity, Weight and Eating Research (POWER) at Yale. Since he launched the program in the mid-1990s, it has focused on developing and testing approaches for helping people manage diverse eating and weight concerns, including eating disorders and obesity. Treatment decisions are highly personalized and target specific behavioral and psychological needs, including body-image concerns. "We view our patients and participants in our treatment studies as 'collaborators' in both the treatment process and in the research goals of helping advance knowledge to help others," says Grilo.

Faculty members in the program were among those laying the groundwork for the medical profession establishing binge-eating disorder (BED) as an officially recognized formal diagnosis in the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5) classification published in 2013.

One of the complexities that physicians who treat obesity face is the fact that most popular diets do not work long term for most people, which amplifies feelings of inadequacy and failure. The typical pattern is for people with excess weight to lose weight in the initial stages of a formal diet but then regain it over the long term. That's why Grilo and other Yale specialists work with patients to develop sustainable lifestyle eating plans involving healthier nutritional and eating behaviors, increasing physical activity, improving coping skills, and enhancing body image. Importantly, these effective approaches help patients stay away from restrictive and unhealthy weight control attempts.

For Grilo, addressing stigma is an essential piece of what he sees as a winning prescription for dealing with obesity on a national scale. His three key calls to action are strengthening regulations governing unhealthy foods (calorically dense, high-salt, overly processed foods with limited nutritional value); promoting compassion and respect; and switching the focus from dieting to achieving healthy lifestyles.

PROTECTING CHILDREN AND TEENS

Obesity is an even more confounding problem when it comes to dealing with children and teens. That's partly because there is so much intense bullying in the early years. Family and physician pressures also play a powerful role. Yet it is critically important to identify these issues before individuals establish cognitive and behavioral patterns that could stick with them for life.

Bullying has tremendously negative consequences, including self-harm and suicide, yet little research has been done on the impact of bullying on children and teens with obesity and eating disorders, according to Lydecker, who runs the teen program at POWER at Yale. One result is that few teens get treatment for weight bullying. That's why she and her colleagues launched a study and developed a new treatment approach, which includes weekly talk-therapy sessions focused on helping the young people process the trauma of being bullied.

"Cyberbullying is the worst," says Lydecker. "It retraumatizes a child every time somebody comments or shares a post. They feel they're being targeted by the whole world, and it doesn't stop. Sometimes, bullies even urge kids to kill themselves. It's horrible and unthinkable, but it's happening."

In their work with teens, Lydecker and her colleagues embrace a "body-neutrality" approach. They urge teens to focus less on their appearance and more on taking care of their bodies so they can do what they enjoy in life. She also publishes social media posts on Instagram and Facebook to share practical information about eating disorders and to spread positive body-neutrality messages.

Lydecker's most recently published research focuses on school problems caused by weight bullying. Through interviews with parents, she and colleagues found, for instance, that children who had experienced verbal weight bullying were more than two and a half times as likely to skip school as those who were not verbally bullied. They wrote that the research provides further evidence that weight bullying is detrimental to children's well-being, and they called on schools, communities, and clinicians to take it seriously and develop strategies to reduce it.

BODY NEUTRALITY FOR CHILDREN, TEENS

At Yale's Bright Bodies Healthy Lifestyle Program for children and their parents, the staff and volunteers are so focused on avoiding stigma that they don't require kids to stand on a scale at first. They don't even

call it a weight-reduction program. Mary Savoye, the dietitian who launched the program more than 25 years ago, advocates a "non-diet" approach. She and her colleagues talk through real-world situations with the kids and help them understand how to respond to urges, to avoid unhealthy foods, or to just eat less of them. "Diets don't work. We empower the children to make the best choices they can in any given situation—which helps build self-esteem. We do a lot with nutrition and exercise, but we're also heavy on behavior modification," she says.

The staff at Bright Bodies also factors stigma into the way they measure progress for their young patients. In addition to monitoring changes in BMI and body fat, they also use surveys that trace the impact of the program on a child's self-concept and quality of life.

The Bright Bodies program has been adopted elsewhere in the United States and around the world. Unfortunately, lifestyle programs like it are not supported by most health insurance policies. As a result, they're hard to launch and sustain. Savoye raises money for her program through grants and charitable contributions, and she recruits students and medical professionals to help on a volunteer basis.

Savoye and Mona Sharifi, MD, MPH, associate professor of pediatrics, received a $3.96 million grant from the National Institutes of Health (NIH) to study the implementation of Bright Bodies nationally, and the Centers for Disease Control and Prevention has recently funded applicants in all 50 states to implement family healthy-weight programs like it.

PROTECTING POPULATIONS MOST AT RISK

While obesity affects people of all races and ethnicities, it is more prevalent among people of color. For instance, 49.6% of non-Hispanic Black adults and 44.8% of Hispanic adults have obesity compared to 42.2% in non-Hispanic white adults, according to the NIH. Although these variations have many causes, researchers point to differences in social and economic status related to race or ethnicity.

In poor neighborhoods, people have limited access to nutritious food. Social and economic stresses can drive binge eating. Certain regional and cultural traditions also can promote unhealthy eating—think heavy pasta or rice dishes, fried chicken, and sweet tea. Another factor: food producers aggressively market unhealthy foods and beverages to poor people.

When you combine the factors of weight, poverty, and race, people in racially segregated communities face a triple-whammy of stigma. "Environments make it hard to have a healthy lifestyle and healthy weight," says Sharifi, whose research focuses on obesity prevention and treatment in community settings as well as psychosocial factors in the emergence of childhood obesity in communities affected by health inequities.

Sharifi calls for more screening for weight issues earlier in life and earlier interventions—especially for children in disadvantaged neighborhoods. But she cautions that health care providers must be thoughtful about how they ask about food and weight gain—to avoid further trauma and stigma.

Sharifi says she is alarmed by the obesity epidemic, but, as one of the authors of the new pediatric obesity guidelines, she is also optimistic that we can make progress against it. The guidelines promote non-stigmatizing and family-centered care, and new and effective treatment options, including medication. They also acknowledge the role of social issues, psychosocial factors, the environment, and genetics, which all collide to cause obesity.

"If we as a nation are going to address this, we have to do it at the health care level for those affected, and at the societal and policy level for prevention," she says.

For Gabourey Sidibe, the actress who played Precious in the movie, life since then has been a mixed bag—success as an actress, but continuing struggles with weight and stigma. She is open about her experiences with bulimia and depression. She has type 2 diabetes and underwent bariatric surgery to control her weight. She regularly sees a nutritionist and a therapist. "Being depressed is one thing. If you add an eating disorder to that, that's a whole other monster you have to fight," she said on Taraji P. Henson's Facebook Watch talk show, "Peace of Mind with Taraji."

Savoye of Yale seemingly speaks for Sidibe and all people who struggle with weight when she says: "A healthy lifestyle is a journey. Things don't happen overnight."

Carolyn M. Mazure, PhD

WHRY celebrates 25 years of advancing women's health

By Amanda Steffen

IT IS SEPTEMBER 4, 1991. Researchers from academic centers across the country are gathered at the Hunt Valley Conference Center in Maryland. To an observer, the event looks like any other professional conference. However, it is anything but ordinary. It is the start of a new frontier in health research.

The scientists hail from different fields of study, yet all are devoted to studying women's health. Invited by the newly established Office of Research on Women's Health within the National Institutes of Health (NIH), they are tasked with setting a research agenda to address the troubling gaps in scientific information on the health of women. It is a pivotal moment in the history of science and medicine.

Over the previous 40 years, the United States had made a dramatic investment in scientific research. The NIH had grown to become the world's greatest single funder of biomedical research and set the standard for the direction and design of future research. There was, however, a glaring omission: NIH policies did not require the inclusion of women in clinical studies.

At the time, researchers believed that women's hormone cycles could complicate study results. It was also thought that women needed to be protected from any possible risk involved in scientific inquiry—despite safeguards dictated by protocols. As a result, women were generally excluded as research participants, and that's why the Hunt Valley gathering was so important. These scientists were poised to change the standard of research, leading to federal legislation in 1993 that required women to be included in all future clinical research funded by the NIH.

BREAKING DOWN BARRIERS

That 1991 gathering was a galvanizing moment for Carolyn M. Mazure, PhD, Norma Weinberg Spungen and Joan Lebson Bildner Professor in Women's Health Research and professor of psychiatry and psychology. It reinforced her commitment to women's health research as a scientific field of inquiry.

For nearly a decade, Mazure collaborated with the NIH Office of Research on Women's Health to advance the message that women's health had to be studied at the national level. A turning point came in 1998, when Mazure secured a grant from The Patrick and Catherine

Carolyn M. Mazure, PhD, leads a meeting of the WHRY's Scientific Review Committee, which reviews Pilot Project grants.

Weldon Donaghue Medical Research Foundation and the support of Yale School of Medicine to create Women's Health Research at Yale (WHRY), one of the first research centers in the country devoted to studying a wide array of conditions that affected women. Now, as the center celebrates its 25th anniversary, that focus has expanded to include research on the influence of biological sex and the social construct of gender on health, as well as the evolving ways in which people identify their genders.

After years of excluding women from research, there was an enormous knowledge gap regarding disorders of high morbidity and mortality that affect women. Yet even after eventually acknowledging that women should be included, researchers were stuck. They could not obtain funds from granting institutions, including the NIH, without feasibility data to show how a proposed investigation might advance women's health. "Our WHRY Pilot Project Program was designed to generate these feasibility data and broaden the scope of conditions studied in women," said Mazure. "This research almost immediately reaped practical benefit for women's lives in both the short and long term."

BROADENING THE SCOPE OF RESEARCH

With research that focuses on conditions ranging from cardiovascular disease to various cancers, WHRY now supports laboratory and clinical investigations that bring interventions to medical settings and the wider community. Through WHRY Pilot Project grants, Yale faculty have made innovative discoveries and provided new health information to improve the lives of women and girls.

To highlight just a few of more than 100 WHRY pilot studies: investigators have developed better diagnostics for identifying heart attack in women; uncovered a lupus antibody that has been developed into a therapy and will soon be tested in clinical trials to fight breast and ovarian cancer; expanded the use of an effective therapy for autism spectrum disorder to benefit girls; and identified a culturally sensitive therapy that can be used remotely to treat insomnia in Black women. At the beginning of the COVID-19 pandemic, WHRY also fast-tracked studies investigating sex differences in the immune response to the novel virus and resilience in frontline health care providers that yielded meaningful data on both women and men.

While advancing human health, the WHRY Pilot Project Program has also fostered the careers of Yale researchers. Nearly three-quarters of the funded researchers have been junior or mid-level faculty who needed initial funding to launch their research, and 60% of funded researchers are women. All WHRY researchers are supported before, during, and after their grant periods.

WHRY also has served as a scientific home for NIH center grants focused on women's health and on sex and gender differences, while also forging interdisciplinary collaborations among scientists to help answer complex questions. One such partnership brought together scientists whose expertise in neuroscience and biostatistics allowed them to better understand the genetic risk associated with Alzheimer's disease in women. As a result of this novel team's work, its members secured new NIH funding. Collectively, WHRY's pilot studies have generated more than $115 million in subsequent grants to Yale faculty to further their investigations. Of this total, 86% are funded by the NIH, which is three times the success rate for new investigator-initiated NIH applications.

SPREADING THE WORD

Along with developing new research findings, the center began engaging the wider community from the very beginning. "Researchers were largely focusing their time and efforts on their programs of investigation, but thanks to the forward thinking of the Donaghue Foundation trustee Raymond Andrews, WHRY began sharing its findings with local and national audiences in a new way," said Mazure.

Today, the center's outreach includes a quarterly newsletter, an informative website, and a social media presence, as well as local, national, and international presentations, and webinars. These efforts, among others, are guided by a community council of advisors, strengthening the connection between WHRY's work and those who can benefit most. The center and its director are also active in the national conversation on women's health, advocating for greater understanding of the ways in which the experience of gender influences health. Along with that, WHRY's work strives to ensure that the past and current cultural norms that reduce women's health equity are addressed.

A VISION FOR THE FUTURE

Just as the creation of WHRY forged new paths into scientific inquiry, that guiding principle will continue in the future. The center came into being "before an understanding of how sex and gender relate to health and well-being became a significant focus of many major institutions," said Marc Potenza, MD, PhD, Albert E. Kent Professor of Psychiatry and the director of WHRY's Women and Addictive Disorders Core. "Dr. Carolyn Mazure recognized the need to research these topics and translate the data into practical benefit. Her visionary program has made substantial contributions to the health of women and girls across the globe."

Now, the needs—and opportunities—have expanded. In addition to its many areas of ongoing research, WHRY has also become a leader in the developing area of study that examines the influence of biological sex and the social construct of gender on health. Here, the center seeks to include data regarding these influences, along with other key findings on the health of women into the YSM curriculum to help inform the patient care and research of future physicians and physician-scientists. Recognizing the value of a scholarly home for learning, WHRY also offers research fellowships to Yale undergraduates to foster their interest in this field.

Carolyn M. Mazure, PhD //

> "This research almost immediately reaped practical benefit for women's lives in both the short term and the long term."

As knowledge increases, new directions of study will undoubtedly be uncovered, and the work of WHRY will continue—a fitting testament to those at the Hunt Valley conference who first sounded the alarm on the need for women's health research.

After founding WHRY 25 years ago, Mazure now plans to write and teach about the value of studying diverse populations of women; the effects of sex and gender on human health; and how human biology and social experience intersect to determine human health.

Medicine meets computer science

Lucila Ohno-Machado, MD, PhD, MBA

LUCILA OHNO-MACHADO, MD, PhD, MBA, is the Waldemar von Zedtwitz Professor of Medicine and Biomedical Informatics and Data Science, deputy dean for biomedical informatics, and chair of the new section of biomedical informatics and data science. Born in Brazil, she came to the United States to earn her PhD and stayed to build a career in academia. She recently joined YSM to create a new department aimed at supporting the use of biomedical informatics and data science through applied research, with the goal of improving human health and eliminating disparities. *Yale Medicine Magazine* spoke with her about her current initiatives and future plans.

How did you first become interested in computers and medicine?

My first encounter with a computer-like device was in high school, when we used programmable calculators in physics class. I was fascinated. After class, our professor taught us how to program them, and that was super-interesting. I thought, how can I use this in my career?

As a medical student at the University of São Paulo, I learned about the emerging field of medical informatics. The school had just established a medical informatics residency, so I became one of its first residents in this specialty. After that, I obtained an MBA, focused on health care administration and IT. Having exhausted my educational possibilities there, I applied to graduate schools in many countries and was lucky to get a spot at Stanford, where I earned a PhD in medical information science and computer science. At the time, HIV-related research was exploding. So that's how I got my start—in informatics applied to HIV.

Describe the work Yale recruited you to do.

At the University of California, San Diego, I built a biomedical informatics program from scratch. Creating something that didn't exist before was exciting—like being at a start-up. Now I get the chance to do it again at Yale! Building a department of biomedical informatics and data science includes three pillars: training, research, and a service component. It is a wonderful opportunity that will take some years to bring to fruition.

Right now, we are recruiting a multidisciplinary faculty in different subspecialty areas, with a goal of 40 to 50 new faculty. Informatics brings together people in basic science, clinical care, community engagement, health disparities, computers, engineering, and other areas. It is a huge collaboration focusing on essentially anything that involves data—which is everything.

Settling into our dedicated space, currently located on the 9th floor of 100 College, and moving to the 10th floor of 101 College when completed, we're setting up systems and processes, managing a large portfolio of research grants, and expanding the existing training program to educate biomedical informatics professionals. For our service component, we will collaborate with biomedical researchers and clinicians to take on the questions and challenges facing the health care system and biomedical research (basic, translational, and clinical).

How is the intersection of computer science and medicine transforming research and patient care?

In the past, and it's still true today, the experience of individual expert clinicians has been key to making a diagnosis, prescribing treatment, and understanding what treatments work and don't work—and in what subtypes of patients.

But we are moving past that point. Data now permits us to gain that expertise from what's called the "learning health care system." This is a concept that came about in the last decade or so. Essentially, it means utilizing all the data collected every day in electronic health records and other systems. For example, when patients have an adverse event from a medication, there is no mechanism in place for automatic surveillance or monitoring. But now, patients' physicians can record such incidents into electronic health records, where they become part of a larger record. By accessing the data from a larger collection of patients being treated, we establish patterns that tell us what we are doing right and what we can do better.

Of course, the question arises: With large amounts of computerized data, how do you use it for research while protecting the privacy of patients? In my informatics research, we've devised ways to distribute this data in a privacy-preserving manner by building models that allow accessibility, while keeping the data private within the institution.

What's the most misunderstood aspect of this field?

I would say it's the perceived danger or threat of artificial intelligence. Used correctly, AI should be viewed as a helpful tool, rather than a threat. It can be impactful because it processes much more information than one brain can. AI will not only uncover health disparities, but also propose ways to mitigate and possibly eliminate them.

Machine learning, a subset of AI, uses algorithms to automatically recognize patterns from data, and then apply that information to better decision-making. It requires a large amount of data. When machine learning processes millions of records, it can discover disparities and demonstrate when outcomes from a particular subgroup are worse than the larger group. Imagine yourself as a clinician seeing many patients. One patient in a particular subgroup does not respond well to a certain treatment. Because your experience is limited to your own patients, you wouldn't know that the same thing is happening to the clinician next door. By aggregating the data of a large group of patients, you'll know that this treatment, in this subgroup, is associated with poor outcomes.

What is the biggest challenge in biomedical informatics?

This field is relatively new, compared to other specialties in medicine. It takes time for a new field to gain status as an established science, attracting young scientists to the field. The fact that this field is interdisciplinary also creates challenges. Combining a mathematical/statistical area with a clinical/biomedical research area makes the training harder, because you must be trained in both disciplines.

What is unique about working within the Yale community?

With deep resources and an excellent faculty, Yale offers solid foundations we can build on. A primary reason why I came here is for the opportunity to create a new department in an outstanding institution. There are few such departments; perhaps only five or six universities have a large, impactful biomedical informatics department. To create one at a university like Yale can change the way other institutions view the field, igniting many new efforts.

Looking toward the future of biomedical informatics and data science, what excites you the most?

I'm excited because the field of biomedical informatics and data science has assumed its place of importance in academia. This field will have a substantial impact on human health and the health care system.

I'm also excited because here at Yale, every department wants to have their own point person in biomedical informatics and data science, and we will work together to ensure that everyone benefits. We're not just throwing our hats into the ring, saying, "We'll build a department," and then checking off that box. We are building THE department, and we want to make it succeed and have a major impact inside and outside the university.

PHOTO: ROBERT LISAK

To nominate a subject for Q&A, write to:
ymm@yale.edu or *Yale Medicine Magazine*, 50 Division Street, 2 Science Park, Floor 2, New Haven, CT 06511.

Skin in the game

A physician-scientist's passions

By Mary Ann Littell

MANY CREATURES are covered with scales, shells, fur, even quills protecting them from the external environment. Humans, on the other hand, have only their thin, pliable skin. The body's largest organ, it has a veritable army of immune cells. But what happens when disease sets in?

While some 84.5 million people in the United States—roughly one in four—are affected by skin diseases, the impact is often minimized. "A common misconception is that dermatological disorders are inconsequential—annoying, perhaps, but not serious," says Keith Choate, MD, PhD, Aaron B. and Marguerite Lerner Professor and chair of dermatology, professor of genetics and pathology, and associate dean for physician-scientist development. "Many people don't realize that we also treat patients with severe disorders that profoundly affect their lives."

Consider the nonstop itch of severe atopic dermatitis, the acute discomfort of having up to 90% of your body covered with the silvery scales of psoriasis, or the challenge of a yet-undiagnosed genetic skin disease. These are the patients Choate is drawn to help. Trained in dermatology, human genetics, and pathology, he treats rare and unusual skin conditions that most physicians have never even seen. He does this by understanding the genetics of the disease.

Keith Choate, MD, PhD

PHOTO: ANTHONY DECARLO

"I walked into dermatology with the idea of treating patients with severe systemic diseases, and I did it at a moment when biologic therapy was just coming into being," says Choate. "Patients had been treated for decades with less efficacious drugs, including those that damaged their DNA and caused a host of adverse side effects. But with new, precision molecular therapies, we can treat patients with far greater efficacy."

Choate is a pioneer of several groundbreaking discoveries and collaborator on many more. His work in the laboratory has led to the identification of genetic defects in more than 18 rare disorders. These range from inherited forms of ichthyosis (a disorder featuring scaly skin with or without systemic findings) to severe, sometimes lethal pediatric vascular malformations. This basic genetic work has allowed Choate and colleagues to glean fundamental biologic insights into disease and pave the way for effective therapies for conditions that were previously untreatable.

Equally focused on clinical care, he is known as a physician who takes on the most complicated cases and strives to find solutions. "This is possible because I am part of an institution and a department with tremendous resources and talented people," he says. "It's the quality of your colleagues that enables you to do special things."

A YOUNG MAN'S DREAM

Choate knew from an early age that he wanted to be a physician. Growing up in rural Connecticut, he admired two primary care doctors who were pillars of the community. "I wanted to be like that," he says. "I loved the idea of practicing medicine and having the opportunity to effect change in people's lives."

His education provided a window to a career path combining research and clinical care. At Stanford, where he received his undergraduate degree, he learned the advantages of being part of a research university. As the first individual in his family to consider a career in medicine, Choate sought career advice from a Stanford cardiologist. "I was told that if I wanted to get into medical school, I'd have to do research," he explains. "This was news to me! But if that's what it took, I'd do it."

Choate found a position in the lab of a world-renowned cell biologist. "But the rule was that you had to prepare solutions for two years before you could actually pick up a pipette and do an experiment," he notes. "Whenever I asked, they always said 'no.'"

Idly paging through a campus research directory one day, Choate noticed an interesting ad. Assistant Professor of Dermatology Paul Khavari, MD, PhD, was seeking a lab assistant. "I went to meet him and found this incredibly charismatic, enthusiastic investigator," says Choate. "During our chat, he described how to extract plasmid DNA from bacteria. While this is a routine part of laboratory practice, at the time I was fascinated."

Choate had the good fortune to meet Khavari at a moment when scientific knowledge of human genetics was exploding, and new genetic causes of disease were rapidly being discovered. This was the case for lamellar ichthyosis, a rare genetic skin condition characterized by severe scaling all over the body.

"A few of our Stanford colleagues had developed remarkable retroviral vectors that were being used to modify cells for gene therapy," says Choate. "So we came up with a wild idea: Why don't we try to use gene therapy for ichthyosis?"

Choate and Khavari made many trips to a major ichthyosis center at the University of California, San Francisco. "We took skin biopsies and grew out the cells in the lab," says Choate. "I became quite proficient at growing patient keratinocytes, the primary cells that comprise the skin. It was heady stuff for a 20-year-old. But what was amazing was that we were able to restore the defective gene causing this disease. I then learned how to make skin equivalents that we used to reconstitute corrected skin on mice, achieving the first effective *ex vivo* gene therapy for genetic skin disease." This experience fueled Choate's desire to become a physician-scientist—and kindled his strong interest in dermatology.

THE GIFT OF EXCEPTIONAL MENTORING

Attracted by its outstanding medical scientist program, Choate returned to Connecticut to attend Yale School of Medicine (YSM) in 1996. He found another brilliant mentor in geneticist Richard Lifton, MD, PhD, now president of The Rockefeller University. "He was really pushing the field forward in understanding the genetic basis of disease," says Choate.

He continued his work with Lifton through his residency, when the two made another notable discovery studying ichthyosis with confetti, a rare disorder characterized by abnormally thick, scaly skin. Dermatologist Leonard Milstone, MD, had a keen interest in ichthyosis and followed patients from all over the country. He brought Choate a fascinating question. "All the patients developed many white patches, which were, in fact, normal skin," says Choate. "Len asked, 'Do you think there's a way that we can figure out the genetic basis of this disease?'"

They brought the question to Lifton, who thought the white spots represented widespread revertant mosaicism, a naturally occurring phenomenon involving spontaneous correction of a cellular mutation. He suggested that these cells were actually losing the genetic mutation via a process called loss of heterozygosity, a common genetic event in cancer development. In essence, the cells were curing themselves.

"He proposed doing loss of

heterozygosity mapping to figure out this problem," says Choate. "It took five years, but we were able to identify the genetic basis of this disorder as mutations in the gene that encodes keratin-10. My laboratory continues to study mechanisms of genetic self-correction, among many other things."

increasingly difficult, and all early career scientific faculty face challenges," says Choate. "To address gaps and accelerate career development, we established funding mechanisms and developed resources, including a grant library, a mock study section, professional development courses, and cohort-building activities—all to support early investigators to launch their careers."

Another component of the program supports international physician-scientists who are ineligible for traditional sources of funding. "With investments from the dean's office and private donors, we're providing the means to retain them so they can continue their work in Yale labs," says Choate.

Named chair of dermatology in 2022, Choate continues to expand the department's research and clinical services. These efforts are unlocking the secrets of how skin diseases occur—and how to treat them.

His own lab continues a major focus on ichthyosis. Partnering with a patient group, the Foundation for Ichthyosis and Related Skin Types, has enabled his team to enroll patients in clinical trials and compile valuable patient data. "We attend patient support meetings and hold pop-up clinics around the country," he says. "These events are incredibly powerful, because often this is the first opportunity these patients have to meet a doctor who actually understands their disease."

In the course of studying mosaic-patterned disorders, Choate's lab has also identified the genetic basis of another rare disorder, linear porokeratosis. Patients in this study were found to have a mutation in a gene that is key in cholesterol biosynthesis. Armed with this information, the team created a simple topical therapy: a cholesterol-lovastatin combination.

"We then began using this combination therapy to treat patients with disseminated superficial actinic porokeratosis, or DSAP," adds Choate. "This disorder affects a much larger population. The results were profound. These patients had been treated with myriad therapies, with no success. But with this combination, we were actually curing them. It is now used in common clinical practice."

He adds: "These are the moments that are the most gratifying. Patients come through our doors because no one has been able to find solutions for them. We seek to find answers. Sometimes these come from a different approach to therapy, and in others, through research. Every day, the faculty of Yale Dermatology are finding ways to change patients' lives, and that's at the heart of what we do."

Keith Choate, MD, PhD //

> "A common misconception is that dermatological disorders are inconsequential—annoying, perhaps, but not serious."

GIVING BACK AS A PHYSICIAN-SCIENTIST

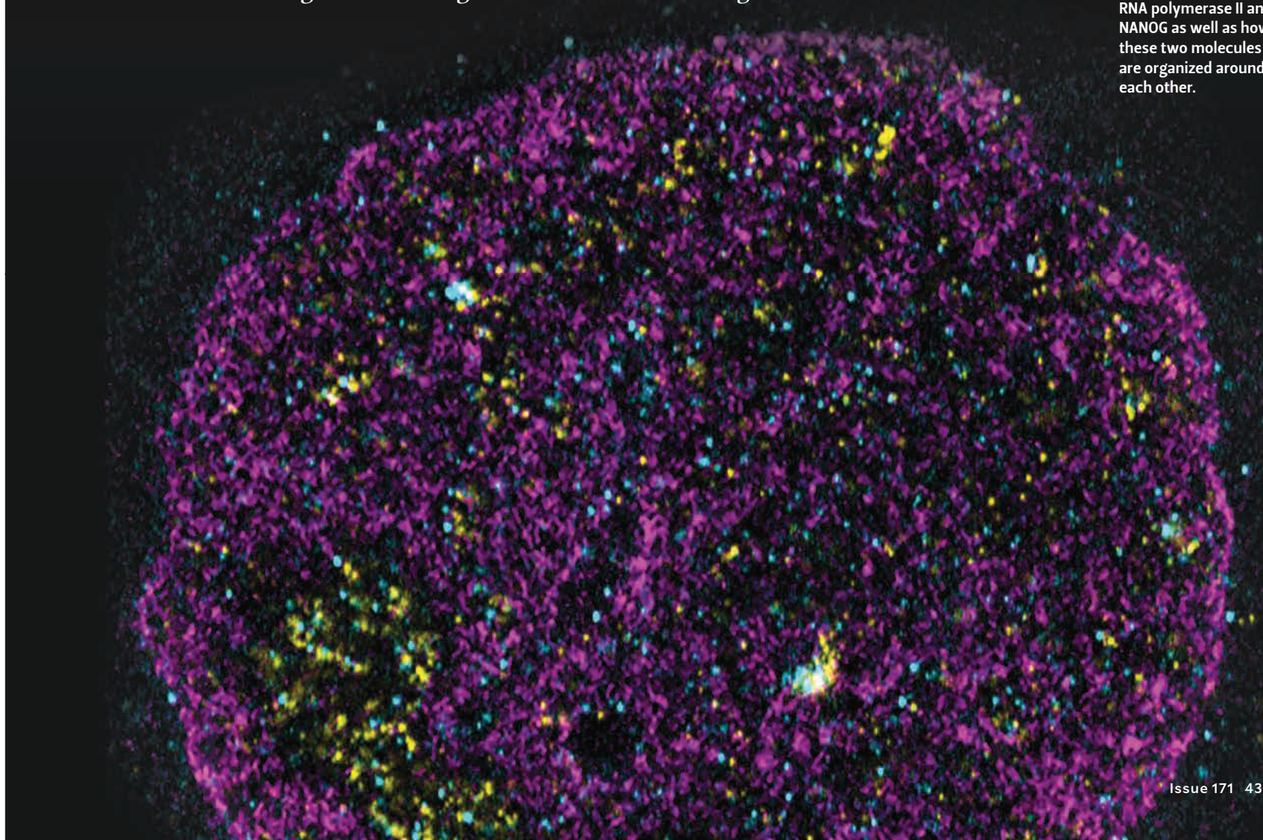
Following a postdoctoral fellowship in dermatology and genetics, Choate joined the Yale faculty. In 2015, he became associate director for diversity, equity, and inclusion in the medical-scientist training program, as well as co-director of the Department of Dermatology's physician-scientist training program. These positions gave him the opportunity to mentor others as he had been mentored.

In 2020, YSM Dean Nancy J. Brown, MD, who arrived at Yale with a long track record of developing mentoring programs, appointed Choate associate dean for physician-scientist development, and he founded the Office of Physician-Scientist and Scientist Development. "The development and retention of physician-scientists has become

Supersize the cell: Unlocking secrets of the genome through expansion microscopy

By Isabella Backman

THE ABILITY TO TURN GENES ON OR OFF IS FUNDAMENTAL to the diversity we see in cells, in individuals, and even in terms of health and disease. This process, known as gene transcription, involves converting the information stored in our DNA into a "carbon copy" called RNA. Until recently, scientists have relied on inexact illustrations and indirect experiments to understand this process, as it occurs on a molecular level and is not directly visible. However, a breakthrough microscopy technique now enables researchers to observe previously unseen molecular processes within genetic material, providing valuable insights into how genes are activated and regulated.



Nucleus imaged by ChromExM, showing the DNA (magenta), RNA polymerase II (yellow), and the transcription factor NANOG (cyan). ChromExM revealed the existence of distinct nanostructures for RNA polymerase II and NANOG as well as how these two molecules are organized around each other.

Antonio Giraldez, PhD //

"Our research allows us to see fundamental processes in the nucleus that are the basis for everything in life, from the making of an embryo to cancer. We can see processes that we could only imagine before."

Antonio Giraldez, PhD, Fergus F. Wallace Professor of Genetics at Yale School of Medicine, studies DNA codes in the genome and how cells interpret these codes to make an embryo. A crucial aspect of comprehending these processes involves our ability to visualize the genome. Unfortunately, traditional microscopy methods have limitations. To overcome these constraints, Giraldez and his colleagues, including the study's first author, PhD candidate Mark Pownall, collaborated with Joerg Bewersdorf, PhD, Harvey and Kate Cushing Professor of Cell Biology and a renowned expert in microscopy, to develop a new technique called chromatin expansion microscopy (ChromExM). In a paper published in *Science* on July 7, 2023, they demonstrated its success in increasing the physical volume of the nuclei of zebrafish embryonic cells 4,000-fold to drastically improve image resolution. The technique allowed researchers to see for the first time how individual molecules shape gene expression in cells during embryonic development and to come up with a new model of how genes are regulated.

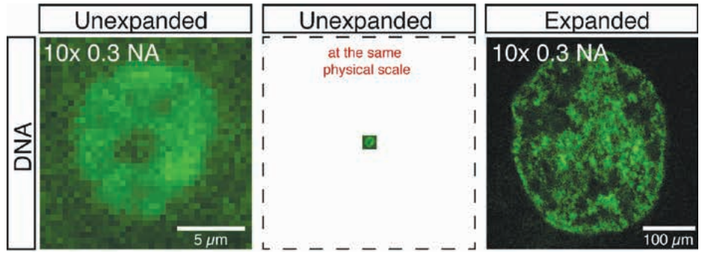
"Our research allows us to see fundamental processes in the nucleus that are the basis for everything in life, from the making of an embryo to cancer," says Giraldez. "It allows us to see the processes that we could only imagine before."

After sperm fertilizes an egg, the genome is initially "silent," says Giraldez. The fertilized egg must transform into a transient pluripotent stem cell, or a cell that can give rise to many different cell types, to develop a healthy embryo. Programming the ability of this cell to make other cells requires jump-starting the genome.

For years, Giraldez and his team have studied how the genome becomes activated. They have made significant strides, from identifying important players to learning which genes are turned on. "But we had never seen the genome activating for ourselves," says Giraldez. "There is a difference between describing how things might be happening and actually witnessing how things are happening."

MICROSCOPY HELPS VISUALIZE THE GENOME

In his previous work, Bewersdorf, who is co-senior author of the study, developed a technique called pan-ExM, which involved anchoring cells to an expandable gel to enable visualization of cellular features with unprecedented resolution. As the gel expanded, it pulled apart the cell and the proteins within them while maintaining their spatial organization until the cell was 64 times bigger in volume. Then, the team repeated the process with a second gel so that the volume of the cells grew 4,000-fold. For this new study, the Giraldez and Bewersdorf labs collaborated to create ChromExM and applied it to embryos to visualize how genes are regulated. Now, each individual cell was about the size of an embryo. "We used a very conventional tool, a confocal microscope, which allowed us to get this incredible resolution of the molecular machinery of the cell when combined with ChromExM," says Giraldez. "Even the most powerful microscopes could not visualize this."



BEFORE AND AFTER: Unexpanded and expanded nuclei with the DNA fluorescently labelled and imaged with a 10x objective shows how ChromExM dramatically improves resolution. The middle panel shows the unexpanded nucleus at the same physical scale as the expanded nucleus, demonstrating the ~15x physical expansion factor achieved by ChromExM.

The process, he explains, is like the toy eggs that expand into dinosaurs when placed in water. When the egg is first dropped into the glass, the dinosaur's features are not yet visible. But as the toy grows, it transforms from something amorphous into a creature with detailed features. "That dinosaur has probably grown two or three times in size," says Giraldez. "Now imagine that growth at a 4,000-fold scale."

Through ChromExM, the team was able to see for the first time the fundamental processes of the genome in action. This allowed them to develop a new model of how genes are regulated, which they named "kiss-and-kick" to describe the transience of how the regulatory regions in the DNA called enhancers interact with the beginning of the gene (promoters) to trigger expression of the gene, and how the burst of transcription then separates the regulatory regions of the gene (or kicks away the enhancer) to pause expression. "It's like going from the pixelated black-and-white cell phone screens of the '80s to the super high-definition, colorful big screens of today," says Giraldez. "Our technique allowed us to see detail that was not possible before."

With this new method, the team looks forward to testing hypotheses that until recently were untestable. For example, in addition to seeing fundamental molecular processes, they also hope to explore how different genes are switched on or off, how they are positioned with respect to other genes in the nucleus, and how mutations affect gene positions. Furthermore, while other microscopy techniques may be prohibitively expensive, ChromExM is accessible for most laboratories. "Our work will democratize a method to see how molecular processes happen within the nucleus, which will open up new areas of research," says Giraldez.

The team now hopes to improve the resolution of its technique even further. While researchers are now able to visualize molecules interacting with the genome, they still can't identify individual genes. "Imagine you are in space, and you take a picture of New York City. Before you could just see the island, but now you can see people in the city," Giraldez explains. "But we still don't know who these people are. If you think of those people as the genes we want to see, we next want a camera that will allow us to focus on individual people." This detail will allow scientists to understand the fundamental principles of how genes are turned on and off, broken, or repaired, and how mutations affect their function—all fundamental steps to understanding how our genes work in health and disease.

PHOTO: GIRALDEZ LAB

For a half-century, Yale's Physician Associate Program has evolved with the times

By Jeanna Lucci-Canapari

WHEN BURDEEN CAMP, PA-C '73, entered Yale School of Medicine's (YSM's) newly established Physician Associate (PA) Program in 1971, she knew she was embarking on a journey into unknown territory. "The fun part of starting a new profession is that what we were going to be was undefined," she recalls. "I just knew that I wanted to take care of patients." At the age of 22, she was the youngest student in the program—and the only woman.

Today, as Yale celebrates the 50th anniversary of its first graduating class of PAs in 1973, which included Camp, the role of the PA has evolved into an essential part of a patient-centered health care team. With a broad scope of practice, PAs deliver care across all settings, from primary care to medical and surgical specialties. Working on a team along with physicians, nurse practitioners, nurses, and other health care professionals, they have the capacity to order and interpret tests, diagnose conditions, formulate treatment plans, prescribe medications, counsel, and maintain the health of patients. In the past 50 years, Yale has graduated more than 1,400 physician associates—and, now, most of the graduates are women.

In Camp's time, that was not the case. "The profession grew out of the military in the mid-1960s," says Alexandria Garino, PhD, PA-C, associate dean for Physician Associate and Assistant Education at Yale School of Medicine. Vietnam veterans, mostly male and particularly those who served as medics, found themselves returning home without any professional outlet for their new clinical skills; at the same time, the country was suffering significant physician shortages.

At Yale during this time, Jack Cole, MD, Ensign Professor of Surgery and chair of the Department of Surgery, saw a need to address what he viewed as the troubled state of emergency medical care and nationwide issues in the field of trauma response. In 1969, Cole started Yale's first program to train physician assistants, which Yale named the Physician Associate Program. He recruited Paul Moson, PA, MBA, a graduate of Duke's second PA class, along with collaborator and co-founding director Alfred Sadler, MD. As one of the first PA programs in the United States, Yale's was the first to emphasize acute and emergency care, while maintaining a generalist focus. "The Yale Physician Associate Program is not only one of the oldest in the country, but it is also unique in its focus on critical thinking and leadership in teams," adds Nancy J. Brown, MD, the Jean and David W. Wallace Dean of the Yale School of Medicine and C.N.H. Long Professor of Internal Medicine.

Yale School of Medicine physician associate students (from left to right) William Laurent Aziz, James H. Brown, George F. Smith, Burdeen M. Camp, and Richard D. Hall from the first graduating class (January 1973).

CREATING A PROFESSION'S SCOPE OF PRACTICE

Students in Yale's first class, like Camp, had a role in shaping what the role of the PA would look like going forward, and in determining how a health care professional, who was neither a doctor nor a nurse but a knowledgeable medical provider, was going to be integrated into patient care. "We had never seen what we thought we were going to be in action, in a clinical sense," says Camp. "The first challenge was to prove to the established medical community that we were thinking medical professionals, capable of formulating a differential diagnosis and ordering the appropriate tests to diagnose a problem."

Camp, like many Yale PA graduates in the past 50 years, rose to the challenge. She became a leader in the field who, in turn, trained other PAs as the role gradually became established, and the number of PAs and PA programs grew throughout the country. In addition to Camp's clinical practice as an oncology PA, she joined the faculty at Yale and advocated for the profession on a state and national level, serving as speaker of the American Academy of Physician Assistants House of Delegates from 1983 to 1984. She was also a founding member of the Connecticut Academy of PAs and the Connecticut Physician Assistant Foundation. Today, she is retired from the PA profession and coordinates a large team of medical volunteers for the Special Olympics of Connecticut.

"Our program's most important contribution to health care and to the profession is our alumni," says Garino. "Our alumni are outstanding clinicians and leaders in their communities and nationally, working to improve the health of patients and populations. Early alumni were

PHOTO: HAROLD SHAPIRO

Students in the class of 2025 of the PA Program received their white coats this August—50 years after the first class of PA students graduated from the program.

pioneers who created the profession's first scope of practice regulations as they cared for patients. They had to break down many barriers and demonstrate the value of the profession."

That forward-thinking effort continues today. The program counts among its alumni many PA educators, leaders of health centers, heads of professional organizations, researchers (including a MacArthur Fellow), and many who work to improve the health of patients and influence health policy.

LEVERAGING THE POWER OF INTERPROFESSIONAL COLLABORATION

Though the Yale PA Program's education of PAs has evolved in the past years in step with changes in medical knowledge and health care delivery, the early tenets of the program remain largely in place. As it did from the program's early days, Yale maintains its focus on training medical generalists. "Even though many PAs work in specialized areas of medicine, PAs apply a broad understanding of medicine to every patient encounter," says Garino. "We continue to educate PAs with a focus on critical thinking and team-based care, graduating competent clinicians in 28 months because we focus on the fundamental skills needed to provide evidence-based, holistic care to patients."

The curriculum offers a solid foundation in various aspects of medical knowledge, explains David Brissette, MMSc, PA-C, assistant professor in the Physician Associate Program and the program's interim director. "We provide an integrated curriculum that combines basic science, clinical medicine, and professional skills development to help students understand the interconnectedness of medical knowledge," says Brissette.

Meanwhile, the program also has implemented innovative changes that set it apart and helps further develop the role of the PA as an integral team member in patient care. For example, interprofessional education allows PAs to train side-by-side with physician and nursing trainees at Yale. The Interprofessional Longitudinal Clinical Experience (ILCE) course, developed as a collaboration between the Yale School of Medicine and the Yale School of Nursing, began as a pilot course in 2014 and became part of the first-year curriculum in 2017.

In the ILCE course, PA, medical, and nursing students learn alongside each other in a variety of settings, including clinical experiences, small groups, history taking, physical exams, oral presentation skills, and early clinical reasoning. "We aim to build bridges early in the training in the hope that they are better able to work collaboratively, in order to prepare them for the real world in which collaboration and teamwork are essential," says Brissette.

Will Cushing, PA-C, MMSc '02, graduated from the program before the inclusion of ILCE, but in his professional capacities exemplifies the role PAs play coordinating care across professions. While in clinical practice as a PA hospitalist at Yale New Haven Hospital (YNHH), he also serves as YNHH's executive director of Hospital Medicine, leading a variety of medical professionals, including PAs and nurse practitioners. He also acts as a clinical instructor in ILCE. "The Yale PA program's history of promoting interprofessional collaboration has been instrumental in allowing me to be effective in my clinical, educational, and administrative responsibilities," says Cushing.

MEETING CHANGING NEEDS IN THE COMMUNITY

Going forward, PA education at Yale continues to evolve and adapt to the changing medical landscape, with an emphasis on compassionate, culturally sensitive care. PA education at Yale, says Garino, will maintain its focus on creating an inclusive learning community that values diversity. "We recognize that patients have better outcomes when clinicians understand the nuances of a patient's experience," says Garino. "So we are working to refine the systems and structures needed to diversify the Yale PA community and educate our students on the importance of health justice and equity." As health care becomes increasingly team-led, and as the PA profession takes root internationally, the program also will continue to provide robust clinical learning experiences that provide students with a global understanding of health care and its challenges.

There is no doubt PAs have come a long way in 50 years. Burdeen Camp recalls that when she decided to enter the Yale program in 1971, she saw an "unfortunate" article in *Life* magazine examining the new PA profession, titled "Less than a Doctor, More than a Nurse."

"That magazine doesn't even exist anymore," scoffs Camp, yet the PA soldiers on.

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