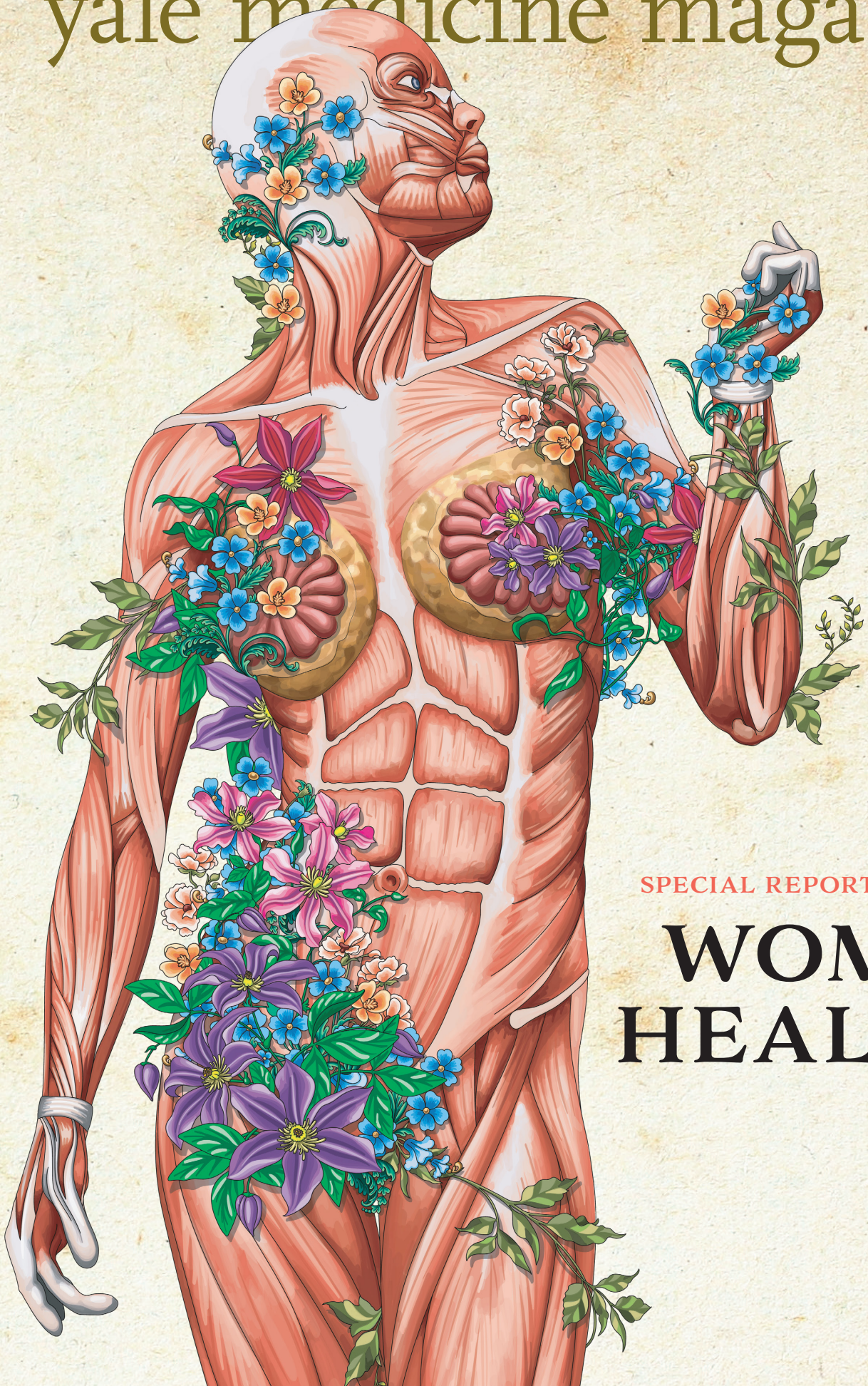
yale medicine magazine



ISSUE
172

ALSO

SPECIAL REPORT

WOMEN'S HEALTH

SPECIAL REPORT
WOMEN'S HEALTH

DEPARTMENTS

THIS PAGE AND COVER: CODEX ANATOMICUS ILLUSTRATIONS

letters

A lasting impact

I would like to express my gratitude for the opportunity to get acquainted with *Yale Medicine Magazine* on a regular basis. Although more than 30 years have passed since my postgraduate studies in orthopedic surgery at Yale, I still consider it one of the most significant turning points in my professional career. This happened thanks to the university and the late Kristaps Keggi, MD, professor emeritus and senior research scientist of orthopedics and rehabilitation, who died in July 2023.

Your magazine allows me to keep my connection with Yale alive, to delve into the activities of the medical school, and to become familiar with the developments in the life of the many clinics and scientific institutes.

Professor Jānis Vētra, Dr. habil. med. (doctor habilitatus medicinae)
Rīga Stradiņš University
Riga, Latvia

Notes from an alum

In addition to my practice as an ophthalmologist, I collect historical documents as a hobby. I've donated more than a dozen collections to research libraries, including seven to Yale University libraries.

I recently made an in-kind gift to the Harvey Cushing/John Hay Whitney Medical Library. The collection includes bound volumes of a renowned Yale medical student's hand-illustrated notes and diagrams from the early 1920s.

George T. Pack, MD, has an extraordinary affiliation with Yale School of Medicine (YSM). He was a graduate student at Ohio State University who was invited in 1918 by Milton Winternitz, MD, (later dean of YSM, 1920–1935) to lecture at the medical school. When Winternitz discovered that Pack was not a medical doctor, he invited him to enroll at YSM. Pack completed his MD degree in 1922.

Pack became a surgical oncologist to world leaders in the mid-20th century. He traveled twice (in secret) to operate on Eva Perón, the first lady of Argentina. As a physician to "very, very important persons," Pack also shared stories with colleagues and residents.

In one of Pack's 1960s lectures at Memorial Sloan Kettering Cancer Center, he told colleagues that a Boston-based friend, Frank Lahey, MD, had secretly diagnosed Franklin D. Roosevelt with "advanced cancer" and advised the president he might not survive a fourth term. The diagnosis was never confirmed, and FDR's death in 1945 was attributed to a stroke.

Visit m.yale.edu/pack-collection to view the collection online.

Ravi D. Goel, MD
Cherry Hill, New Jersey
Yale College '93

We'd like to hear from you...

As a reader of *Yale Medicine Magazine*, your opinions matter. Whether you're a Yale School of Medicine (YSM) alumnus or alumna, faculty member, student, prospective donor, or part of the larger medical, educational, and scientific community, this magazine is produced for you.

As we share articles that describe YSM's continuing tradition of excellence in biomedical research, advanced clinical care, and medical education, our goal is to not only inform but also create an engaging and thought-provoking reading experience. To help us achieve this objective, we'd like to hear what you want to see more of—or less of—in future issues of *Yale Medicine Magazine*. We'd also appreciate knowing whether you enjoy receiving a print copy of the magazine or would prefer a digital version.

With gratitude for your readership,
Rebecca Shannonhouse, Executive Editor

Email us at ymm@yale.edu or write to Yale Medicine Magazine, 50 Division Street, 2 Science Park, New Haven, CT 06511.

Issue 172

Executive Editor
Rebecca Shannonhouse

Contributors
Isabella Backman
Jenny Blair, MD
John Curtis
Cristina Deptula
David Freeman
Steve Hamm
Mary Ann Litell
Ashley P. Taylor
Rachel Tompa, PhD

Art Director
Jennifer Stockwell

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

Yale Medicine Magazine is distributed to alumni, faculty, students, and friends of Yale School of Medicine.

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

Zsuzsanna Somogyi
Acting Associate Vice President for Yale School of Medicine Development

Mary Hu
Associate Dean for Communications

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.

Yale SCHOOL OF MEDICINE

twitter.com/YaleMed
facebook.com/YaleSchoolofMedicine
instagram.com/YaleSchoolofMed

A CONVERSATION WITH DEAN NANCY J. BROWN

Women's health: challenges and opportunities

DESPITE SIGNIFICANT ADVANCES that have been made in women's health care over the past few decades, important challenges remain. In the United States, heart disease is still the leading cause of death for women, followed closely by cancer. Among women of reproductive age, over 10% are affected by the painful inflammatory disease of endometriosis, while miscarriage and stillbirth are also common occurrences, ending more than 1 million confirmed pregnancies in the United States each year.

For insights into women's health—the focus of this issue's special report—*Yale Medicine Magazine* spoke with 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 challenges and opportunities before us.

Where do you see the greatest opportunities for future advancements in women's health in the United States? There are many. We have opportunities in our understanding of the basic biology of sex differences. We've moved on from thinking that women are simply men with higher levels of estradiol, or men without testosterone. And that is helping us understand different presentations of disease in men and women.

What are the most pressing challenges that remain in women's health? Access is a pressing challenge—making sure that those of [a] lower socioeconomic class who are underserved can both be diagnosed earlier and receive treatment. We have terrific therapies today for breast cancer, for example. Yet women of color are likely to be diagnosed at later stages, have less access to care, and have poorer outcomes. That's true across many diseases.

We have opportunities and challenges in understanding aging in women. So many diseases of aging disproportionately affect women because we live longer. That includes neurodegenerative diseases, and diseases of the bone and joints that can lead to significant impact on quality of life. There's also a need for greater understanding of the differences in presentation of common diseases in women, such as heart disease and stroke.

How is Yale School of Medicine improving women's health? Yale School of Medicine is doing a lot in the arena of women's health. We are engaged in the search for a new director of our Women's Health Research at Yale, which is a 25-year-old center aimed at providing resources for investigators who are looking at the biological basis of sex differences in diseases.

We have one of the strongest departments of obstetrics and gynecology, ranked fourth in the country. That has an impact on health related to women's reproduction. Our cancer center is committed to making the diagnosis and treatment of cancer that is common in women, such as breast cancer, more accessible across our community. Our cardiologists are defining how women present differently with heart disease and how mechanisms of heart disease may differ in men and women.

Serendipity in action

BY STEVE HAMM

A dermatologist's 'buddy' leads him toward a revolutionary treatment for cancer, infections, and transplants.

MOUNTED ON A CEDAR STREET OFFICE WALL of Richard L. Edelson, MD, Anthony N. Brady Professor of Dermatology at Yale School of Medicine (YSM), is a framed artwork that serves him as a daily inspiration. Under the title "The Three Princes of Serendip" is a group of four desert scenes that includes a pregnant woman riding a camel; camel footprints in the sand; human hand- and footprints in the sand; and a path cutting between cultivated fields.

The four scenes are derived from a Persian fairy tale whose heroes discover the precise identity of a lost camel through a combination of close observation of trailside clues and previously gained knowledge. In the early 18th century, the British writer Horace Walpole read the tale in French and coined the English word serendipity. "Serendipity refers to the chance, unexpected occurrence landing on the prepared mind," says Edelson. "I owe my career from start to the present to my buddy serendipity."

Last year, Edelson embarked on the latest in a career-long series of ambitious inquiries into the nature and treatment of disease. He is a co-principal investigator on a $24.8 million grant—the first to be awarded in President Biden's Cancer Moonshot program.

The project is called "Curing the Uncurable via RNA-Encoded Immunogene Tuning," or CUREIT. The CUREIT research team, comprising scientists at Yale School of Medicine, Emory University, and the University of Georgia, is harnessing the human immune system to strive to develop personalized therapeutic vaccines to fight cancer, lupus, and emerging infections.

One of the key technologies the scientists are using is messenger RNA (mRNA), which entered the public consciousness in the early days of the COVID-19 pandemic when it was first used to quickly create vaccines that prevented or reduced the severity of SARS-CoV-2 infection. Edelson thought mRNA could also be used in combination with technology he has developed to manipulate the human immune system in powerful new ways: serendipity met science.

A record of Aha! moments

At age 78, a point in life when many professionals have wound down their careers, Edelson is charging into yet another endeavor with major potential consequences for medical science. This project may be the capstone on a career that includes a series of pioneering breakthroughs in immuno-oncology as well as stints at the helm of YSM's Department of Dermatology and the Yale Cancer Center.

"This is another major step on the pathway of his incredible journey," says Michael Girardi, MD, Evans Professor of Dermatology, who has known Edelson for 35 years. "Throughout his career, he has been able to see clearly what is possible. He sees through the murkiness and ends up being right about what is going on."

Edelson has dermatology in his DNA. When he was growing up in suburban New Jersey, his father ran a local dermatology

practice, and young Rick expected that he would someday follow in his dad's footsteps. But the war in Vietnam set his life on a different path. At the time he earned his MD from Yale School of Medicine in 1970, male graduates were required to serve in the deployed military, or if competitively selected, perform research at the National Institutes of Health. Along with 19 fellow YSM classmates, Edelson was selected by the NIH and began combining highly specialized clinical care with advanced scientific research.

Almost immediately, he made a major discovery. In 1972, he was working at the NIH in Bethesda, Maryland, and was put in charge of a ward of lymphoma patients whose illness presented as rashes and bumps on their skin. Scientists had recently identified two distinct classes of white blood cells known as lymphocytes—B and T cells—as key elements of the adaptive immune system.

Edelson found that in patients with lymphoma of the skin, the cancer most often had arisen from their T cells, which normally help the body's immune system ward off pathogens. In these patients, however, the T cells developed mutations that caused the cancerous cells to accumulate in the skin before spreading to other tissues. Edelson named the disease cutaneous T-cell lymphoma (CTCL) and began looking for biologically based treatments for it. He was just 27 years old.

When Richard Edelson started his career, cancer research and immunology were still in their relative infancies, and the two domains were not seen as being closely related.

After Edelson completed his NIH fellowship, Columbia University College of Physicians and Surgeons hired him as an assistant professor in 1975, and he advanced to full professor by 1980. In 1982, as leader of the Columbia University Cancer Center Immunology Program, he invented the breakthrough treatment for CTCL: photopheresis, a form of cellular immunotherapy.

Edelson devised a process for drawing blood from cancer patients using an IV; running it through a machine in which light "turned on" a drug called 8-MOP (methoxsalen) to kill cancer cells in the blood; and then returning the blood to patients' bodies. He had hoped that many of his patients' cancer cells could be killed, thus stalling the malignancy's progression.

But then Edelson's buddy serendipity entered the picture: he was stunned to find that after just three such treatments, two of five patients became cancer-free. "We had treated only 5% of the malignant cells, but they were cured," Edelson explains, surmising that activation of anticancer immunity had done the rest. "We had accidentally immunized those two successfully treated patients even though available immunologic knowledge at the time could not explain how that happened," he says.

To better understand the biological mechanisms, Edelson performed experiments using rodents. In 1973, researchers Ralph Steinman and Zanvil Cohn at The Rockefeller University had identified dendritic cells as specialized white blood cells that can selectively activate the immune system to attack microbial invaders or cancerous cells.

An international clinical study, led by Edelson and

ANTHONY DECARLO PHOTO

published in *The New England Journal of Medicine*, extended the original success to a larger group of CTCL patients. Edelson's laboratory teams, first at Columbia and later at Yale, then set out on a 40-year odyssey to elucidate the scientific mechanism enabling the treatment's successes, with the hope that ultimately it could be therapeutically applied to a larger range of cancers and immunologically caused diseases.

This journey, while tortuous, finally unraveled the mystery. Along with his closest laboratory colleagues, he ultimately discovered how the body signals monocytes—another type of white blood cell in the blood—to become dendritic cells; these are now recognized as the master switches of the immune system. "Serendipity works," he says. "We never could have made that discovery purely on purpose."

Paul Schneiderman, MD, a dermatologist in Long Island, New York, who worked alongside Edelson at the NIH and later joined the Yale faculty, marvels at his ingenuity: "Doctors had known about skin lymphomas for more than 40 years, but we didn't really know what it was until Rick came along," he says.

The first FDA-approved immunotherapy

Edelson then focused on developing a process for mass-producing dendritic cells from regular white blood cells so that he could amplify the effect of photopheresis. He invented what he called a "Rube Goldberg machine" made up of tubes, plastic plates, and mechanical hardware. This innovative treatment, delivered by a refined medical device, became the first FDA-approved immunotherapy for any cancer in 1988; and driven by Edelson's subsequent research, it has been miniaturized and can now be scaled for experiments in rodents or treatment of humans.

In essence, Edelson had conceived of the idea of immunizing patients against their own cancers, or alternatively applying it to reverse rejection of transplanted organs or benefit patients with autoimmune disorders. The treatment is now regularly administered in nearly all medical centers in the United States and Europe.

In 1986, Yale recruited him to be the head of the Department of Dermatology. "Yale was so strong in immunobiology, I felt I really had to be there to mature this field," he says.

Working with colleagues at Yale and elsewhere, Edelson further developed photopheresis techniques and added a major new step to the process—removing cells from the machine and modifying them to enhance their specificity for cancer cells. This innovation, now called transimmunization, may be adaptable to a broader range of cancers and immunologically mediated diseases, based on his team's experimental results.

A passion for mentorship, team building, and fun

During those years, Edelson wasn't just a clinician and a researcher; he was also a leader. Former students and colleagues describe him as being inspirational, supportive, good-humored, and adept in building a positive and creative institutional culture both at the Yale Cancer Center and within the Department of Dermatology. It was on his watch, as director of the Yale Cancer Center, that Smilow Cancer Hospital was conceived and built.

As department head, Edelson created a family-like atmosphere. He hosted faculty and staff parties at his own home for years and took colleagues to interesting out-of-the-way places for retreats. One exemplary retreat took place in Saratoga Springs, New York, where the attendees participated in a group bike ride, attended a concert, and went to the horse races. It was a team-building triumph.

Associates say that Edelson is passionate about mentorship of younger colleagues and students. He focused on recruiting people into the Department of Dermatology's residency and fellowship programs and helping them succeed, taking a succession of young research scientists under his wing. Since then, 13 trainees he mentored have become heads of dermatology departments at prominent universities, and many more have developed academic prominence.

As a mentor, Edelson not only gives sound advice but also supports his people when they encounter problems. Jonathan Leventhal, MD, associate professor, director of the Dermatology Residency Program, and director of the Onco-Dermatology Program at Smilow Cancer Hospital, remembers a time early in his Yale career when he observed rashes on the skin of clinical trial participants who received an experimental cancer treatment—apparently a side effect.

After Leventhal published his observations, the pharmaceutical company whose therapy was being tested "wasn't happy" with him. Worried that he might have made a mistake, he sought Edelson's advice. "Rick said, 'Jon, what you did was in the best interests of your patients and medicine. I have your back,'" Leventhal recalls.

To further the impact of medical science research, Edelson is an energetic and helpful research partner, say his scientist colleagues. Jennifer Schneiderman, MD, MS, professor of pediatrics at Feinberg School of Medicine, Northwestern University, says that Edelson has shared insights from his expanding knowledge of immuno-oncology to refine her techniques for using the same biological mechanisms to improve treatment of children after bone marrow transplantation by suppressing immune system reactions. Her group is now working on modifying the process to enhance the patients' tolerance to transplanted organs. Of Edelson, she says: "He figured out the pivot point of our immune system—how it enhances attacks on certain things and settles down other things."

Shooting for the moon

Edelson's efforts are now focused on the Biden Cancer Moonshot and the CUREIT project, along with projects funded by the Gates Foundation to control emerging microbial infections. As part of this work, he and his laboratory mates are deeply engaged with Philip Santangelo, PhD, at Emory University, an internationally respected expert in designing mRNA to fight cancer and pandemic-causing viruses.

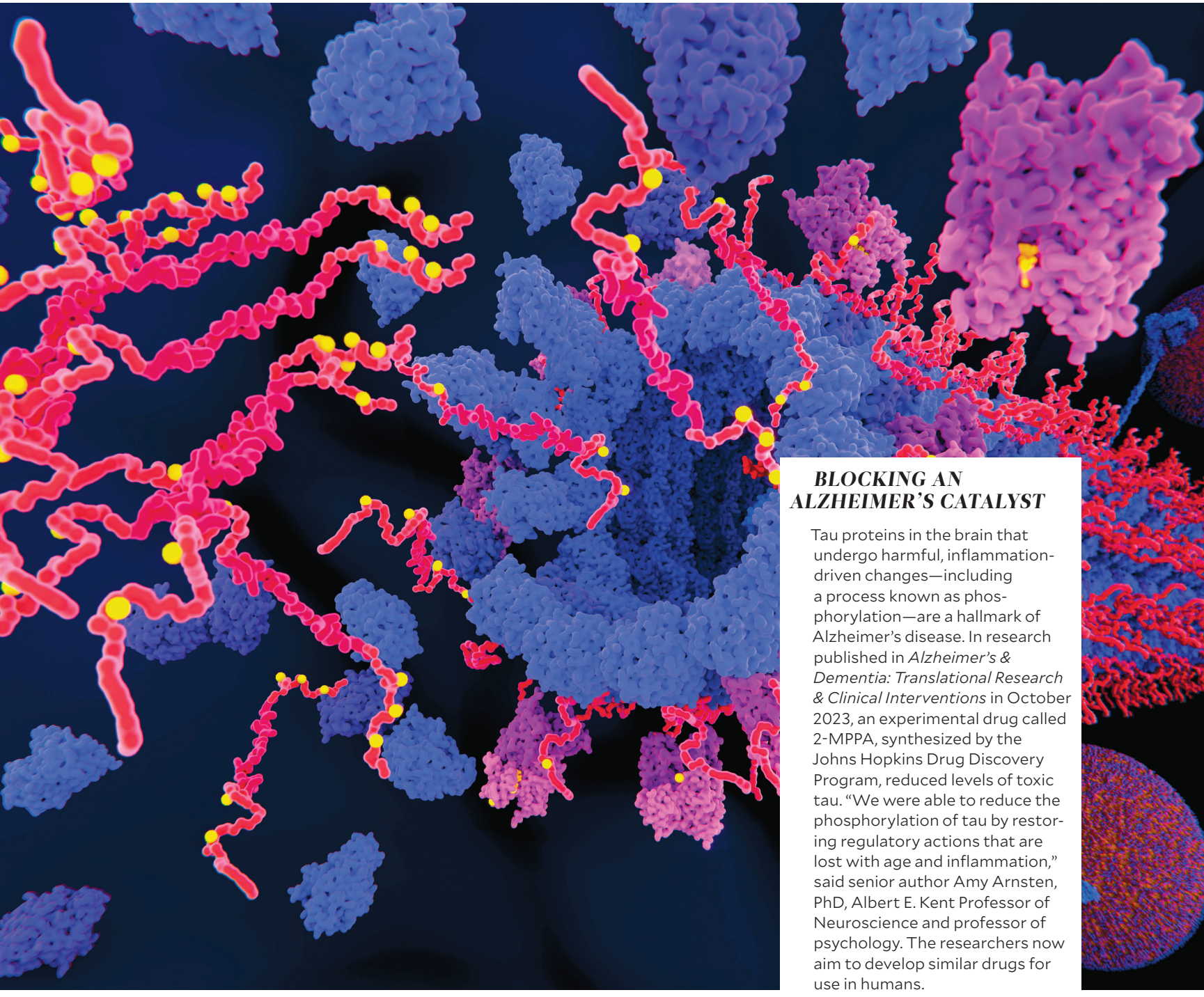
Within his own lab on Cedar Street, Edelson has assembled an A-Team of scientists—each with a deep reservoir of domain knowledge. The researchers have refined the core processes of creating and manipulating dendritic cells to the point where equipment that once filled a room has been reduced to a device the size of a microscope slide. Now, using mRNA, "we're developing the ability to create immune reactions that attack specific types of diseased cells," says Edelson.

The beauty of this approach is its simplicity—the scientists are essentially combining two well-understood technologies to do something new. "People assume that technology has to get more complicated to work better," says Aaron Vassall, MD, an associate research scientist and molecular biologist at YSM, who as a medical student was mentored by Edelson and is now a key faculty member on the CUREIT team. "We may show there's an alternative path that's not complicated or expensive."

Francine Foss, MD, professor of medicine (hematology) and of dermatology at YSM, says the CUREIT project has the potential to accelerate the development of new treatments for a wide variety of diseases, including cancers, autoimmune diseases, and preventive and therapeutic vaccinations against viruses. "This CUREIT project has the potential to shave years off the process of bringing new treatments to the clinic," she says.

When Edelson started out, cancer research and immunology were still in their relative infancies, and the two domains were not seen as being closely related. Edelson became one of the first cancer immunologists and has made a career of building bridges between the two disciplines. And he's not done yet. "I'll keep riding this motorcycle until the wheels fall off," he jokes.

In actuality, he hopes that within the three-year life of the Biden Cancer Moonshot grant, the research team will be on the way to developing a new generation of treatments. Says Edelson: "Our efforts are being driven by a team of talented and committed close colleagues. I would like us to make enough progress in this new field so that they don't need me anymore."



BLOCKING AN ALZHEIMER'S CATALYST

Tau proteins in the brain that undergo harmful, inflammation-driven changes—including a process known as phosphorylation—are a hallmark of Alzheimer's disease. In research published in *Alzheimer's & Dementia: Translational Research & Clinical Interventions* in October 2023, an experimental drug called 2-MPPA, synthesized by the Johns Hopkins Drug Discovery Program, reduced levels of toxic tau. "We were able to reduce the phosphorylation of tau by restoring regulatory actions that are lost with age and inflammation," said senior author Amy Arnsten, PhD, Albert E. Kent Professor of Neuroscience and professor of psychology. The researchers now aim to develop similar drugs for use in humans.

from the journals

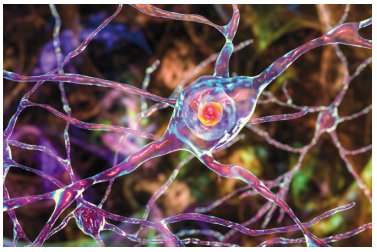
a collection of recent scientific findings

TYPE 1 DIABETES DRUG PRESERVES BETA CELL FUNCTION

In research led by Kevan Herold, MD, C.N.H. Long Professor of Immunology and of Medicine (Endocrinology), the drug teplizumab, a monoclonal antibody, was shown to preserve the function of beta cells in children and adolescents recently diagnosed with type 1 diabetes. This finding, published in *The New England Journal of Medicine* in December 2023, followed the FDA's 2022 approval of teplizumab (Tzield®). The approval was based on the results of an earlier Herold-led trial, which showed that the drug delays the onset of stage 3 type 1 diabetes. Teplizumab is the first treatment to alter the course of this autoimmune disease since the discovery of insulin in 1922.

GENETIC BASIS OF CANNABIS USE DISORDER

In a study published in *Nature Genetics* in December 2023, researchers analyzed the genomes of more than 1 million people to investigate the genetic basis of cannabis use disorder, as well as links to psychiatric disorders and other traits related to substance use. The research, led by Daniel Levey, PhD, assistant professor of psychiatry, and Joel Gelernter, MD, Foundations Fund Professor of Psychiatry and professor of genetics and of neuroscience, will help in the understanding of the public health risks associated with the continuing legalization of marijuana use across the United States, Gelernter said.



INVESTIGATING DISEASE PATHOGENESIS IN ATAXIA

Spinocerebellar ataxia type 1 is a neurodegenerative disorder that primarily affects the cerebellum, a brain region involved in the control and coordination of movements. The disease ultimately robs patients of their ability to walk properly. Janghoo Lim, PhD, associate professor of genetics and neuroscience, and colleagues used single-nucleus RNA sequencing to determine how gene expression changes within specific types of cerebellar cells throughout the course of the disease. These results, published in *Neuron* in November 2023, illuminate the cellular and molecular basis of this disease. The Yale researchers are the first to study changes in gene expression in the postmortem tissues of patients with ataxia at the level of single-cell resolution.

IMPROVING RECOVERY AFTER ICU CARE

In the first few months after receiving ICU care for a critical illness, such as sepsis, older adults suffered a threefold increase in symptoms like shortness of breath, fatigue, and others that restricted their activity and threatened their quality of life, according to a study published in the *American Journal of Respiratory and Critical Care Medicine* (December 2023). The study emphasized that the first month following ICU hospitalization is a critical time for such interventions as medications and exercise. These measures could improve patients' recovery and prevent hospitalizations, said lead author Snigdha Jain, MD, MHS, assistant professor of medicine (pulmonary, critical care, and sleep medicine).

EQUITABLE TREATMENT FOR SICKLE CELL DISEASE

Gene therapy, recently approved by the FDA to treat sickle cell disease (SCD), could be an equity-enhancing treatment, according to research conducted by George Goshua, MD, MSc, assistant professor of medicine (hematology), and his colleagues. Although the gene therapy, projected to cost $2.45 million, did not meet traditional cost-effectiveness standards, it did satisfy distributional cost-effectiveness standards—an approach that takes health equity into quantitative consideration. In the United States, SCD primarily affects historically marginalized patient populations. The research was published in the *Annals of Internal Medicine* in May 2023.

OPPOSITE PAGE: SELVANEGRAIMAGE; THIS PAGE (CLOCKWISE FROM TOP LEFT): HALFPOINT IMAGE, KATERYNA KON PHOTO, GRAPHICSCOCO

FROM HYSTERIA TO EMPOWERMENT

Women's health through the ages.

BY ISABELLA BACKMAN

IN ANCIENT GREECE, physicians practicing in the Hippocratic tradition commonly diagnosed women suffering with such vague symptoms as pain, heavy menstrual bleeding, depression, anxiety, and fatigue—and even infertility—with "hysteria," a term derived from *hystera*, the Greek word for uterus. The physicians posited that their patients developed hysteria because they were not fulfilling their womanly duty to marry and bear children, which caused the uterus to become displaced and wander around the body. The cure, the doctors advised, was to get married and have children quickly.

Throughout history, medical treatments for these "female problems" ranged from hanging women upside down and shaking them to return the uterus to its rightful place to putting leeches in the vagina to giving suppositories of bull urine. Women were accused of madness, witchcraft, or demonic possession, and forced to undergo exorcisms, burned as witches, or confined in mental institutions.

Stories of misdiagnosis and mistreatment aren't just curiosities of ancient and medieval history. Longstanding claims that Victorian-era doctors performed "pelvic massage," in which they stimulated female patients until they reached orgasm, as a treatment for hysteria have now been called into question. However, neurologist Silas Weir Mitchell's 19th-century rest cure, which included six to eight weeks of forced bed rest and isolation, was often prescribed for hysteria.

"For centuries, hysteria has served as a dramatic medical metaphor for everything that men found mysterious or unmanageable in the opposite sex," wrote Mark Micale, PhD, a former assistant professor of history at Yale and professor emeritus of history at the University of Illinois Urbana-Champaign, in a 1989 article published in *History of Science*.

FEMINISM AND WOMEN'S HEALTH ADVOCACY

But in the mid-19th and 20th centuries, change was brewing. In 1848, the so-called "first wave" of feminism emerged with the women's rights agenda promulgated at the Seneca Falls Convention. A year later, Elizabeth Blackwell, who was born in England and moved with her family to Cincinnati, became the first woman in the United States to graduate from medical school, earning her diploma from the Geneva Medical College after being rejected by 29 other medical schools. Several decades later, Mary Ware Dennett, who had once been prosecuted for mailing a pamphlet that she had written for her sons titled *The Sex Side of Life*, founded the National Birth Control League, an organization that advocated legalization of contraception.

The 1960s and 1970s gave rise to the "second wave" of feminism, ushered in by the Women's Health Movement, which largely focused on reproductive health. The groundbreaking book *Our Bodies, Ourselves* (1970) covered topics that were considered taboo at the time, including contraception, women's sexuality, and postpartum depression.

Feminist health advocacy was strengthened when the Supreme

Court's 1973 landmark *Roe v. Wade* ruling granted American women the constitutional right to abortion. Two years later, a protest at the U.S. Food and Drug Administration's (FDA) headquarters—in which women demanded accurate information about the risks of birth control pills—led to the birth of the National Women's Health Network, which remains a driving force in women's health advocacy today.

The 20th century also saw the development of products that dramatically improved women's quality of life. Menstrual pads reached the market in the 1920s, while tampons grew in popularity a few decades later. Birth control pills and intrauterine devices (IUDs) became available shortly thereafter.

WOMEN'S HEALTH: MORE THAN REPRODUCTIVE MEDICINE

Recent years have also brought new challenges. Although the longstanding stigma around menstruation has largely dissipated, many women still feel shame around talking openly about their periods. Activists continue to challenge these attitudes as well as those related to other historically taboo subjects through such movements as #MeToo, which has empowered women around the world to speak out against sexual violence.

Most recently, state-level bans following the overturning of *Roe v. Wade* in 2022 are hindering many women's access to safe abortions, and new legal risks to doctors are putting women's lives in danger as they encounter delays in getting care for complications during pregnancy. Researchers are monitoring the long-term effects on public health in the post-Roe era.

There is also growing recognition of the many health disparities that affect women. Today, women still suffer from autoimmune diseases, chronic pain syndromes, and disability at higher rates than their male counterparts, but these conditions attract less funding for medical research.

Women are also significantly underrepresented in clinical trials and research. A 2021 study published in *JAMA Network Open* that examined over 20,000 clinical trials between 2000 and 2020 reported that women were underrepresented in clinical trials in a range of areas including cardiology, oncology, neurology, immunology, and hematology.

WOMEN'S HEALTH AT YALE

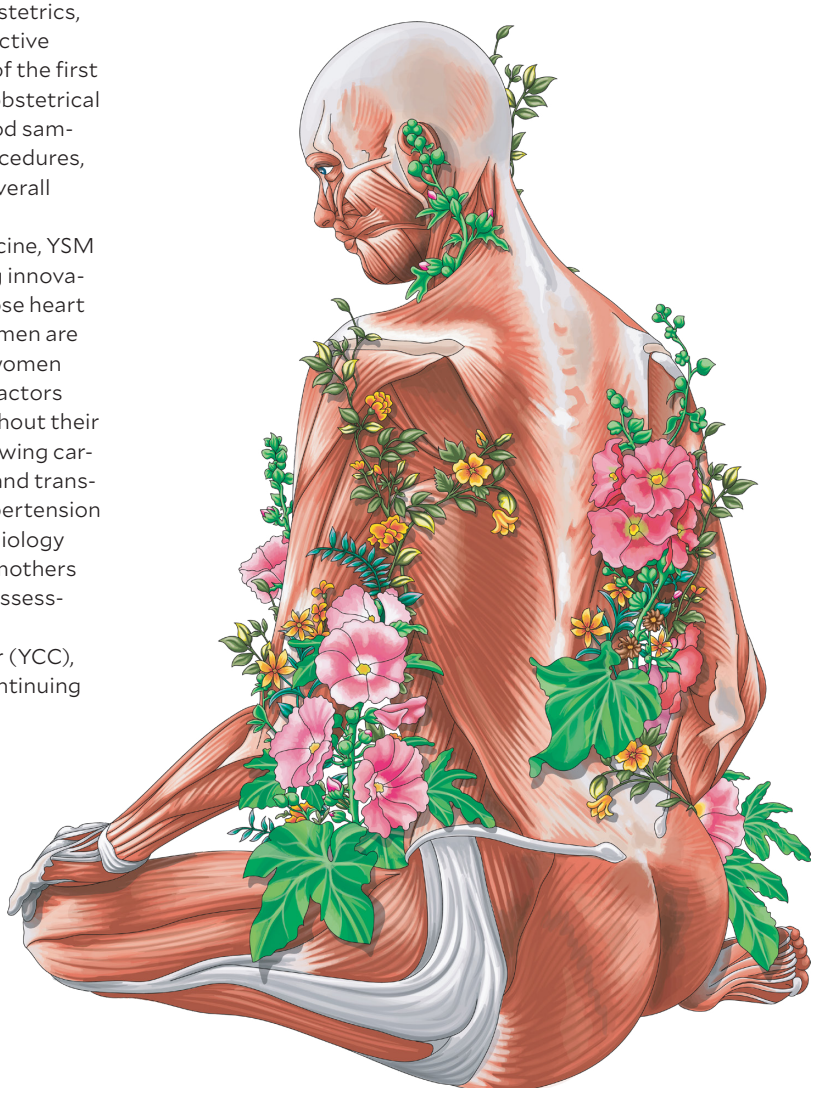
Researchers and clinicians at Yale School of Medicine (YSM) have been at the forefront of groundbreaking innovations in women's health. As early as 1822, Nathan Smith, MD, YSM's first professor of materia medica and surgery, developed an improved method of oophorectomy—the surgical removal of one or both ovaries used to treat such conditions as ovarian cancer and endometriosis—a condition now more deeply understood than ever before, thanks in large part to Yale-led research. YSM's Department of Obstetrics, Gynecology and Reproductive Sciences was also home of the first fetal echocardiography, obstetrical ultrasound, and fetal blood sampling and transfusion procedures, contributing to today's overall clinical excellence.

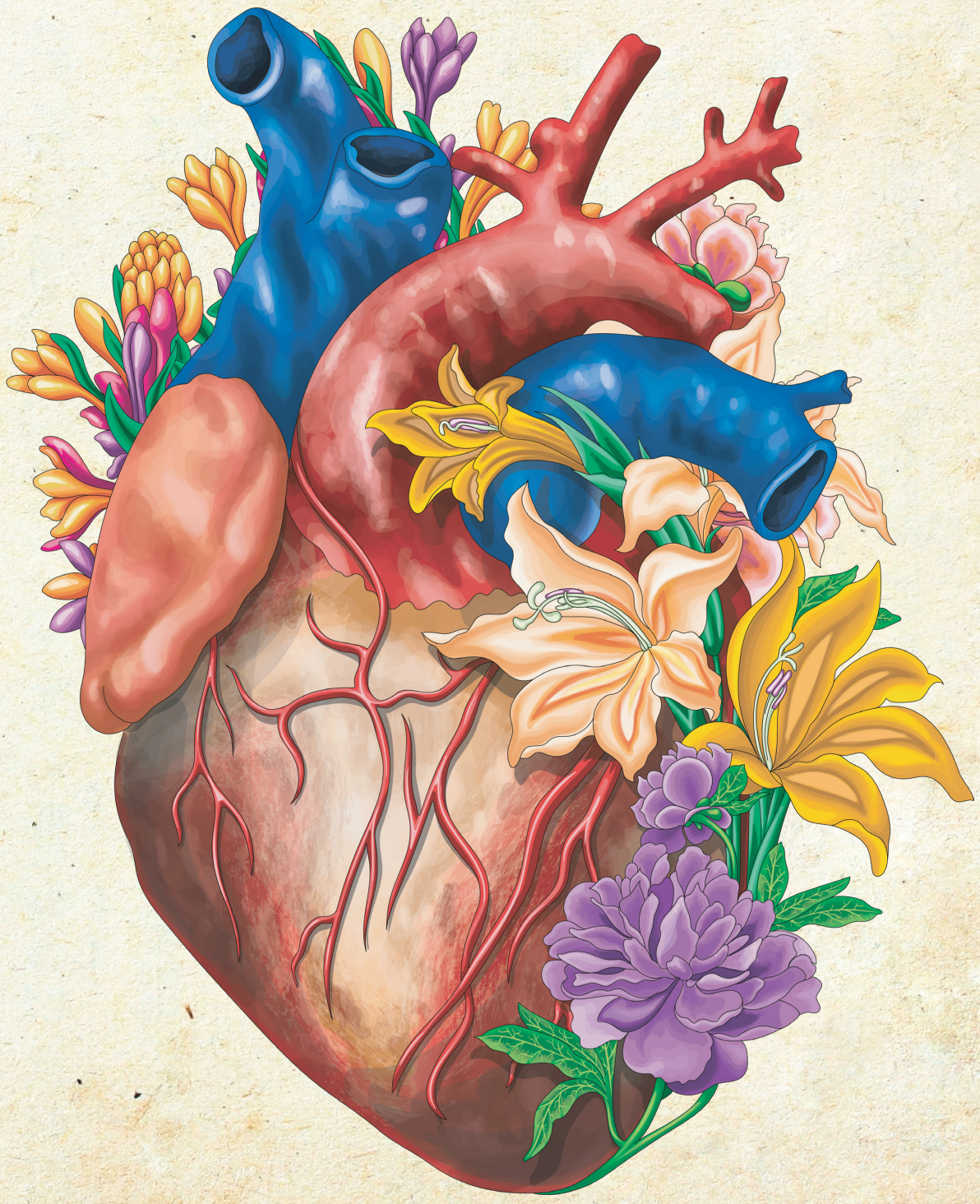
In cardiovascular medicine, YSM specialists are identifying innovative techniques to diagnose heart disease so that fewer women are overlooked, supporting women with cardiovascular risk factors and heart disease throughout their pregnancies in YSM's growing cardio-obstetrics program, and transforming post-partum hypertension care through a novel cardiology clinic that provides new mothers with cardiovascular risk assessment and management.

The Yale Cancer Center (YCC), now in its 50th year, is continuing its tradition of breakthrough research and innovative treatment that includes a dedicated focus on breast cancer. Along with that, YCC has launched a new program to eliminate disparities based on gender identification, race, sexual orientation, and other factors that affect women's cancer diagnoses and outcomes.

Women's Health Research at Yale (WHRY), founded 25 years ago by Carolyn Mazure, PhD, has launched over 110 studies dedicated to women's health across a wide range of specialties, including cardiovascular disease, cancer, autism, obesity, and addictive behaviors. (To read about Mazure's newest role, see page 34.)

Ongoing research in these and other areas is leading the way to new insights into female biology that will help women live longer, healthier lives.





HEART DISEASE IN WOMEN

How bias compounds sex-linked biological differences.

BY RACHEL TOMPA, PHD

CODEX ANATOMICUS ILLUSTRATION

IN THE 1960S,

doctors in the United States sounded the alarm that heart attacks were on the rise.

That is, heart attacks in American men were on the rise. Something was going on with women too, but it wasn't as clear-cut. Like men, more women were having cardiac symptoms, but many of these cases didn't look like a "typical" (that is, a man's) heart attack—the women's arteries were clear.

Doctors puzzled over this phenomenon. In 1973, it was dubbed "cardiac syndrome X"—a term that would stand for several decades, to be replaced only recently with more descriptive diagnoses. Cardiac syndrome X referred to the fact that many people, mostly women, were having symptoms identical to those of a standard heart attack but with no evidence of blockages in their coronary arteries.

Arterial blockages are still the most common cause of heart attacks in both women and men, but we now know that heart attacks without arterial blockages can happen—80% of these kinds of attacks occur in women, and they're just as dangerous (or possibly more so) as attacks involving the arteries. But at the time, doctors believed that cardiac syndrome X was benign; they would often send patients home without treatment.

"The field was calling it [cardiac] syndrome X because we had no name for what women experienced when they had the same cardiac symptoms as men, just without blockages," says Samit Shah, MD, PhD, assistant professor of cardiovascular medicine and director of the VA Connecticut Cardiac Catheterization Laboratory. "It's so vague and nondescriptive and, to the patient, really not a helpful diagnosis."

While cardiac syndrome X is a real biological phenomenon, brushing it off as benign was a societal response, akin to the many other documented instances of understudied or undertreated health conditions in women. Today, effective treatments exist for heart disease, including the forms available to women, and researchers know a lot more about the biological and societal factors that increase women's risk of heart disease. But getting the message to the public and clinicians is the sticking point. Despite the fact that heart disease is the number one killer of women, there's a persistent misconception, even among many medical professionals, that women rarely have heart attacks.

"Women don't receive as aggressive heart care as men do, and that is a significant problem," says Lisa Freed, MD, assistant professor of cardiovascular medicine and director of the Women's Heart and Vascular Program. For instance, doctors are less likely to recommend statins—a class of cholesterol-lowering drugs—to women than to men with the same cardiovascular risk profile. Women also refuse statins and other life-saving treatments more often than men do, in part out of fear that these medications haven't been thoroughly tested on women. "You shouldn't undertreat yourself, and you shouldn't let anyone undertreat you. That's been a long-standing story in women's health, and it's something that I work against every day," says Freed.

WANING ESTROGEN

While women of any age can and do have heart attacks, higher levels of estrogen before menopause help protect against plaque formation and blockages. Estrogen raises HDL cholesterol, lowers LDL cholesterol, and keeps artery walls flexible. After menopause, when estrogen levels wane, those protective effects disappear. Even though some research has shown that women who take estrogen (hormone therapy) closer to the onset of menopause may have a lower risk of developing cardiovascular disease, those findings have not been consistently demonstrated in other trials. Recommendations from the American College of Cardiology state, "At this time, there is no role for menopausal hormone therapy (MHT) for cardiovascular disease prevention." To address menopausal symptoms with the use of MHT, the American College of Cardiology, the American Heart Association, and the North American Menopause Society support an individualized risk assessment for women contemplating MHT, rather than an absolute recommendation.

OTHER RISK FACTORS

There are many other sex-linked risk factors for heart disease, according to the American College of Cardiology, some of which can influence disease risk even decades after the fact. Polycystic ovarian syndrome (PCOS), which affects 6% to 12% of U.S. women of reproductive age, is tied to a higher risk of heart attacks, perhaps due to the syndrome's effects on sex hormones. Women make up nearly 80% of patients with autoimmune disorders—conditions that are themselves often linked to heart disease. The leading cause of death among women with lupus is cardiovascular disease, and rheumatoid arthritis nearly doubles a woman's risk of heart attack. Endometriosis, an underdiagnosed condition that affects at least 10% of women, increases the risk of heart disease and stroke. (To read more about endometriosis, see page 24.) Mental disorders like post-traumatic stress disorder (PTSD) and depression—both more common in women than in men—also increase the risk. (Read more about PTSD and depression in women on page 45.)

Adverse events during pregnancy like preeclampsia, a pregnancy-related form of hypertension, increase the risk of heart disease even decades after giving birth. So too does gestational diabetes, as well as certain kinds of pregnancy loss related to blood flow disorders or dysfunctions of the endothelium, the thin tissue that lines blood vessels and organs. (To read more about pregnancy loss, see page 31.)

While current guidelines from the American College of Obstetrics and Gynecology state that anyone with preeclampsia should visit a cardiologist soon after delivery, that doesn't always happen—women are often so busy with a new baby that even regular post-partum checkups fall by the wayside, says Erica Spatz, MD, MHS, associate professor of cardiology, associate professor of epidemiology (chronic diseases), and director of the Preventive Cardiovascular Health Program. Because high blood pressure is tied to so many other adverse health outcomes, Spatz and her colleagues are looking for new ways to reach those at risk, including newly post-partum women.

Spatz is part of a study at Yale, led by Rafael Pérez-Escamilla, PhD, professor of public health (social and behavioral sciences), and Heather Lipkind, MD, MS, of Weill Cornell Medicine, that recruits women with preeclampsia in hospital delivery wards, giving them blood pressure cuffs for home use to transmit data to the study coordinators.

"Hypertension is the most modifiable risk factor for heart disease," Spatz says. "We've been trying to flip the script, and not wait for people to come in for care but reach them where they are."

BETTER DIAGNOSES

Even if a woman with cardiac symptoms seeks care, accurate diagnoses and treatments can still be hard to obtain. Shah is working to bring better diagnoses to patients with what was formerly called cardiac syndrome X and is now described as ischemia/angina with no obstructive coronary arteries (INOCA/ANOCA). Two related but different conditions, coronary microvascular disease and coronary vasospasm, can both result in heart attacks without blockages in the coronary arteries; both of these conditions are also much more common in women. The prevalence of these conditions in women partially explains why women's heart attack symptoms are different from those that men experience, Shah says. Chest pain or pressure is by far the leading symptom of a heart attack in both men and women, but women are also more likely to experience less recognized symptoms, like nausea or pain in the jaw or back. These symptoms can sometimes occur without chest pain in women.

In microvascular disease, small blood vessels that feed the heart don't work as they should, either due to problems in the vessel lining or damage to the vessels themselves, which can decrease blood flow. In vasospasm, the vessels spontaneously narrow when they should open, shutting off blood flow to the heart—this may result from problems in the blood vessel lining or from genetic factors. Vasospasm can cause chest pain or other cardiac symptoms at rest because the spasms happen at random, while arterial blockages and microvascular disease tend to trigger symptoms during exertion.

It's not clear why these conditions are so much more common in women, but their risk factors are similar to those for other kinds of heart disease, including smoking, high cholesterol, and diabetes. Heart attacks resulting from these syndromes are just as dangerous as an attack due to arterial blockage. These vascular disorders require different treatments; but luckily, effective treatments exist. Accurate diagnoses, however, have lagged behind.

In work presented at the 2023 American Heart Association's annual meeting, Shah and his colleagues showed that coronary function testing, a cutting-edge set of methods that can diagnose and distinguish microvascular disease and vasospasm, resulted in correct diagnoses more often than the standard-of-care testing—coronary angiography, which images only the arteries. The methods include dosing a patient with the neurotransmitter acetylcholine, which induces spasms in someone who has coronary vasospasm and inserting tiny wires into blood vessels to check for decreased blood flow. Patients who received accurate diagnoses were also more likely to change medication, receiving more individualized treatment. Shah is now leading a multisite trial to evaluate these diagnostic methods in more patients, as well as to better understand the risk factors for these disorders and patient outcomes.

In another project, Shah and his colleagues conducted detailed interviews of women who have cardiac symptoms without blockages. Many less recognized symptoms of heart attacks, such as nausea, dizziness, or arm pain, are not captured in standard screenings, Shah says, but a better understanding of symptoms in women could help doctors detect unrecognized heart disease.

Shah sees physicians' lack of awareness as a huge stumbling block to women's heart health, especially in the conditions that he treats. His study also found that for patients without an arterial blockage, their average time from onset of symptoms to an accurate diagnosis was a startling 6.5 years.

"Even if all the tests are normal, take your patient who has new-onset cardiac symptoms seriously," he says. "We have to figure out what the diagnosis is. It's not in their head."

A TROUBLING TREND

While heart disease risk rises in postmenopausal women, heart disease is also a leading cause of death in adult women younger than 65. Even though heart attacks have been declining in many groups over the past few decades, the decline in younger women has been minimal. And perhaps most concerning,

women under 55 who have a heart attack are more likely to die from it than are young men. This could be due to lack of awareness—women are more likely to dismiss symptoms of a heart attack or may not recognize subtler symptoms, such as unexplained jaw pain or extreme fatigue, and may not seek treatment until symptoms become more severe. Additionally, when younger women arrive at the hospital, their wait time to be evaluated is, on average, about 10 minutes longer than that of younger men. And with heart attacks, every minute counts to prevent permanent damage.

A team of Yale researchers is studying what happens to these women after their heart attacks—and why their outcomes might be different from those of men. A recent study from the group showed that women 55 and younger have twice the rate of rehospitalization after a heart attack as young men. Many biological factors were similar in the men and women in the study, but several social factors differed. The women in the study with poor outcomes not only had higher rates of depression, but also were more affected by health inequity issues, such as lower income and education levels, than their male counterparts. They also had higher rates of disorders that raise the risk of heart disease, like diabetes and hypertension.

"It turns out that psychosocial factors such as stress, depression, [lack of] social support, whether they can get to the hospital to access health care, all these factors are impacting the outcome of young women," says Yuan Lu, ScD, assistant professor of medicine (cardiology), and one of the leaders of the cardiac outcomes study. "This has not been a main focus of research in the past, but now we really need to think about tailored intervention for these women. We need to raise awareness that young women with heart attacks have worse outcomes than men, and that their clinical and social risk factors may be different from those of men, so clinicians need to pay special attention to these characteristics."

As in the study providing home monitoring to women with preeclampsia, Lu and Spatz think strides can be made through community outreach. Spatz is leading a new multicenter study partnering with community organizations in Black, Hispanic, and low-income communities to address hypertension in both men and women, pairing community health workers and remote blood pressure monitoring so that people can participate in the study without disrupting their normal routines.

"The idea is to meet people in spaces they feel comfortable in, that they already trust," Spatz says. "We think that this is going to be effective for women—especially women who may not have otherwise come to the clinic or attended to their health if they weren't part of this program." */yale medicine magazine*

ERICA SPATZ, MD, MHS //

> "The idea is to meet people in spaces they feel comfortable in, that they already trust."

BREAST CANCER RESEARCH

Treatment victories and remaining questions.

BY JENNY BLAIR, MD '04

For most women diagnosed with breast cancer, there's plenty of good news to report. Steady declines in the death rate for this type of cancer have furthered overall progress in cancer mortality in the United States. Notably, about nine in 10 women with breast cancer survive for at least five years after diagnosis.

But breast cancer can also be tenacious. For 6% of patients diagnosed with the disease, the cancer has already spread to distant parts of the body when it is found. Of that group, only 32% survive to the five-year mark. This statistic makes breast cancer the second deadliest (after lung cancer) for women in this country. Breast cancer can also sometimes recur in distant parts of the body many years after an apparent cure.

"Most people think, 'It's breast cancer, and it's so common; just get treatment and you're done,'" said Sandy Cassanelli, a Yale patient who has lived with metastatic breast cancer since 2015. "But Stage I could come back 10 years later, and once it spreads, you're in treatment forever. People don't realize how deadly breast cancer is and how much research is really needed."

While significant advances have been made in breast cancer treatment, Eric P. Winer, MD, director of the Yale Cancer Center (YCC), president and physician-in-chief of Smilow Cancer Hospital, and Alfred Gilman Professor of Medicine and Pharmacology, envisions an even brighter future. "I really hope we get to the point where the vast majority of women with breast cancer can say that even if they have to live with it on an ongoing basis, it's unlikely to ever take their life because we'll have enough treatments to keep it at bay. And the majority of people who are diagnosed with anything other than the most advanced disease will actually be able to be effectively cured. We are so close!"

To accomplish this, Winer is leveraging his more than 30-year career as a breast cancer researcher and clinician, which included leading a breast cancer program at Dana-Farber Cancer Institute for over two decades, to help

CODEX ANATOMICUS ILLUSTRATION

build on the significant strengths of the YCC Breast Cancer Center and advance it to become a world-class program.

In the meantime, a great deal remains to be understood. From bench scientists to pathologists to trial doctors to epidemiologists, Yale breast cancer researchers are sharing research tactics and findings, listening to patients, and working toward a future in which breast cancer is no longer a killer. Here are a few of the many questions being studied—and a look at the promising work under way.

WHO IS AT INCREASED RISK OF BREAST CANCER?

It was over a decade ago that the actress Angelina Jolie announced that she had undergone a preventive double mastectomy after learning she had a mutation in the *BRCA1* gene that put her at high risk of breast cancer. Genetic sequencing of genes like *BRCA1* or *BRCA2* often uncovers mutations known to increase the risk of breast cancer in women and men, as well as ovarian cancer and—to a lesser extent—such other malignancies as prostate and pancreatic cancer, as well as melanoma.

Thousands of mutations have been identified in genes associated with breast cancer. These include not only *BRCA1* and *BRCA2*, but others such as *PALB2* and *ATM*. These mutations can inform surgical decision making, cancer risk-reduction strategies, targeted breast cancer treatment (particularly for patients with *BRCA1* or *BRCA2* mutations), and hereditary cancer testing in families, explained Veda N. Giri, MD, director of the Cancer Genetics and Prevention Program and professor of internal medicine (medical oncology).

However, genetic testing can also report many variants of uncertain significance (VUSs). These are genetic variants where it is currently unclear, based on available evidence, whether they are disease-associated or benign. VUSs do not currently inform the management of breast cancer risk or treatment and can be confusing for patients who receive these results, said Giri. Furthermore, VUSs are reported at higher rates in minority populations whose genetic data are limited—which points to the need to engage more diverse populations in genetic studies.

"We often don't know if these variants are pathogenic or benign, and that's frustrating," said Ryan Jensen, PhD, an associate professor of therapeutic radiology and pathology who studies DNA repair and genome instability. "They're a problem for precision medicine."

Jensen is working to characterize those variants one by one, introducing them into human cell lines and then testing how they react to cancer drugs like cisplatin and PARP inhibitors. The goal is to develop a lab test that can give patients useful information about their particular mutations.

"I've studied *BRCA2* for the past 20 years, but if someone tells me [they have] a specific amino acid missense mutation, I usually have no idea what that's going to do to the protein functionally," said Jensen. Nor could any existing software predict it, he added. "I would have to take that variant into the lab and put it into cells and then see what it does. That's the only way to do it for unique variants lacking genetic linkage studies."

DO PATIENTS GET THE MOST EFFECTIVE THERAPIES?

Highly efficacious cancer drugs typically work in some malignancies but not others, and determining which cancers will respond is not always straightforward. For example, deciding which patients with metastatic breast cancer are eligible for trastuzumab deruxtecan requires an assay that quantifies the HER2 protein. This antibody-drug conjugate, which links a cytotoxin to an antigen-specific antibody, is FDA-indicated for patients with positive or low levels of HER2, but not for those in whom it is zero.

Yet the traditional immunohistochemical assay is not sensitive enough for every individual, according to research by David Rimm, MD, PhD, Anthony N. Brady Professor of Pathology and Professor of Medicine (Medical Oncology), and director of Yale Pathology Tissues Services.

"A lot of the 'zeros' may actually have signals that are missed because of this faulty testing," said Maryam Lustberg, MD, MPH, director of the Center for Breast Cancer and an associate professor of internal medicine (medical oncology), who is collaborating with Rimm. "Not accurately characterizing breast tumors may deprive potentially eligible patients from receiving this important therapy."

An alternative test using different technology might detect additional patients who stand to benefit. With Rimm and Patricia LoRusso, DO, Amy and Joseph Perella Professor of Medicine (Medical Oncology) and associate cancer center director for experimental therapeutics, and others, Lustberg is planning to conduct a clinical trial of the drug in patients deemed HER2-zero by the traditional test.

"It's an important study that builds on the emerging thought that maybe a lot more patients actually benefit from these more targeted HER2-antibody-drug conjugates than we thought before," Lustberg said.

WHY DO GOOD DRUGS STOP WORKING?

In recent decades, the group of powerful drugs called PARP inhibitors has revolutionized the treatment of certain cancers. These drugs target malignant cells while leaving healthy cells untouched. Susceptible tumors are those in which a mutation has damaged a DNA repair pathway called homologous recombination—a mutation in *BRCA1* or *BRCA2* is commonly involved. The *BRCA* proteins are involved in DNA repair in many tissues, which is why these tumors can occur not only in the breast but also in other organs, including the ovaries, pancreas, and prostate.

"A germline mutation in [one copy of a] *BRCA* [gene] is what gives you the high cancer risk. In the tumor, you've also lost the functional-copy allele, so the tumor is essentially *BRCA*-null—there's no functioning *BRCA* protein. That's why the tumor cells are so sensitive to PARP inhibitors," Jensen explained.

As a cancer continues to evolve, additional "reversion" mutations in *BRCA2* can result in the protein being expressed once again, restoring the homologous recombination repair pathway, even if imperfectly. Then the tumor may no longer be sensitive to PARP inhibitors. These resistance pathways are particularly important in advanced breast cancer when ongoing effective therapies are needed to control the disease.

"We are continuing to search for better therapies that can be translated from the bench to the clinic," Lustberg said. "When a patient is told that the cancer has progressed on a drug which is no longer helping, that is difficult news to hear. To be able to understand resistance pathways and develop either better drugs or better interventions that address the underlying biology of the cancer is absolutely key to improving our existing therapies."

Yet, Jensen said, we still lack a clear understanding of the roles of the *BRCA* proteins in homology-directed DNA repair, how tumorigenesis is initiated in the absence of *BRCA1* or *BRCA2*, and why PARP inhibitors can specifically target *BRCA*-deficient tumors.

"The more we learn about DNA repair pathways, the more we're going to understand how resistance develops in these tumors," Jensen said. "If we can understand how PARP inhibitors work, maybe that'll help us come up with ways to prevent that resistance in the first place by targeting other mutagenic repair pathways that are causing those secondary reversion mutations."

ERIC P. WINER, MD //

> "We have real potential in breast cancer treatment at Yale to provide truly unsurpassed care. … We've got the right team in place. I think we can do something special."

WHAT CAN BENCH SCIENTISTS AND CLINICIANS LEARN FROM ONE ANOTHER?

Plenty—and cancer center leaders like Qin Yan, PhD, see to it that everyone gets opportunities to interact regularly, including in two monthly meetings focusing on either basic and translational research or clinical research. Yan, co-director of Translational Research at the Center for Breast Cancer and a professor of pathology, recalls how one such conversation steered him, earlier in his career, as he was designing a study of metastasis before he had gained much experience with breast cancer.

Yan had planned to compare primary breast tumor tissue with metastatic tissue from lymph nodes. But his colleague David Rimm explained that lymph node

metastases are in many respects very similar to the primary tumor, while those occurring at other body sites are different.

"Because I wanted to identify drivers of distal metastasis, which is the major cause of breast cancer–related death, comparing primary with lymph node metastases would not have given us much information," Yan explained.

Rimm not only advised him to study distal metastases instead but also helped arrange access to these rare and hard-to-obtain samples. Ultimately, Rimm, Yan, and their collaborators identified an important protein called CECR2 that is upregulated in distal metastases.

Surgeons also play a pivotal role in translational research. "Surgeons are members of the cancer team resecting these cancers, with hands-on access to tissue in the operating room," said Rachel Greenup, MD, MPH, co-director of the Center for Breast Cancer and associate professor of surgery (oncology, breast). "This tissue can then be shared downstream with the biobanking lab and can be critical for basic and translational researchers."

Having that kind of access to tissue samples is crucial, according to biochemist Megan King, PhD, an associate director of basic science at the cancer center who studies how PARP inhibitors induce the death of cancer cells.

"The ultimate experiment is always happening in patients—genetic diseases or failed therapy are the data. You need basic scientists to engage with that data to say, 'What hypotheses can I pull out of these patient data? What are the open questions that have clinical implications?'" King said.

Rather than doing, say, a CRISPR screen with cells in a plastic dish, King added, "I serve everyone better by actually trying to use clinical samples to make those discoveries. It's a better experiment at the end of the day, and it's much more likely to be relevant for what's happening in a patient."

Winer sums up the value of translational research succinctly. "These days, there's no clinical research without translational research—you take what you learn clinically to the lab to understand how it works and where it doesn't work … and in the reverse direction, translational research figures out how to bring lab findings to the clinic."

Jensen, whose lab is "just down the hall" from the cancer center, enjoys interacting with colleagues who run clinical trials.

"It's so much fun to see Pat [LoRusso] in the hallway, bring her to the lab and show her what we're doing, running proteins on the gel, explain how we're trying to figure out if these variants are significant or not," he said. "She sees these patients all the time, and the patients have to make these serious life-impacting decisions. It's very satisfying from my side to be able to hopefully make a difference in some patients' lives."

HOW CAN WE ENSURE THAT PATIENTS CAN PARTICIPATE IN RESEARCH?

Breast cancer death rates have long been higher in non-Hispanic Black women, one of many appalling disparities in American cancer care.

"There are huge disparities in outcomes based on race, ethnicity, financial status, education, sexual orientation, and gender identification," said Tracy Battaglia, MD, MPH, associate director of YCC's newly established cancer care equity research.

"If you're a 20-year-old Black woman living in the United States," she said, "you have twice the chance of dying from breast cancer before you're 50 compared to the 20-year-old white woman sitting next to you. Cancer inequities are pervasive and may even get worse if we are not intentional about ensuring that new discoveries are representative of all patients and reach all patients equally. This requires a community-engaged approach where we address root causes of inequity, such as social determinants of health, as well as biologic differences."

The evidence suggests that clinical trial participation is associated with better outcomes, yet such participation is out of reach for many people. The data have demonstrated that these barriers can be disproportionately greater for people in minoritized subgroups.

"They want to go on a trial, they want the treatment, but staying on it is overwhelming, and sometimes they can't," LoRusso said. "'Who's going to babysit for my kids when I'm on the trial and I have to spend all day in a clinic? How am I going to get back and forth? Who's going to pick my kids up at school? Who's going to take care of my mother—I'm her caregiver and she's living with me. How do I pay my rent if I have to take days off work to be on these trials?' These are real-life issues that many of these patients are facing that interfere with their ability to participate in clinical research."

So LoRusso and others are helping to spearhead what LoRusso calls a "logistical overhaul" to make early-phase trials available closer to home for the patients by bringing the early-phase trials program to Smilow Cancer Center's community sites.

"With our new YCC director, Dr. Winer, there's an increased commitment to the needs of patients who are underrepresented or face barriers because of social and structural determinants of health," said LoRusso.

Cassanelli recalls driving to New Haven for a trial three days in a row from her home in Glastonbury. "It's a lot physically and mentally, but also financially. And what if you're a mom?" she said. "If you can go to a satellite office in your backyard, it's a game-changer."

Traveling to participate in a clinical trial is just one aspect of the overall financial hardship of a cancer diagnosis. "There are obviously major disparities based on women's socioeconomic status at the time of a breast cancer diagnosis," said Greenup, who is also a health services researcher. "But even women who are well insured and well resourced are at risk of having cancer treatment impact their job and financial security."

LoRusso added, "Providing broader access to trial participation is not only fair and just, but also improves our understanding of how the drug works for a variety of people—and may even accelerate FDA approval. If you can minimize the timelines because you're maximizing recruitment and retention, you can theoretically get an effective and safe drug to market that much sooner."

CAN OTHER CANCERS BENEFIT FROM THESE LESSONS?

Given the shared mechanisms underlying so many cancers, what we learn about breast cancer treatments—and failures—can be applied to other cancers. PARP inhibitors, a cornerstone of breast cancer treatment, were initially approved to treat ovarian cancer and are now being used for prostate and other cancers. A similar process is under way for the antibody-drug conjugate sacituzumab, whose FDA approvals have expanded from breast to bladder cancer. Research into drug resistance will also apply to many tumor types.

And many researchers have developed expertise that's broadly applicable, King pointed out.

"One of the reasons why we basic scientists are great partners for translational and clinical scientists is that we're disease-agnostic," King said. "I study genome integrity. It turns out that breast and ovarian cancer are the cancers you get when you have a deficiency in [the DNA repair mechanism] homologous recombination. So these are cancers where we know that genomic integrity is particularly important, and that's a good home for our work. But we're realizing *BRCA* mutations are also tied to prostate and pancreatic cancers.

"In fact, much of what we've learned about breast cancer and ovarian cancer is relevant to a subset of those other cancers—the mechanisms play out in different places—and so as researchers we're very flexible. We can actually help people who are interested in multiple diseases," King added. "In an institution where you have collaborations, I can go into five different rooms and be five different people because I work on something really fundamental."

WHAT DOES THE FUTURE HOLD?

Yale has big ambitions for breast cancer research and treatment. It is one of four types of malignancy that the cancer center plans to emphasize in the coming five years, in addition to prostate, liver, and lung cancer. Plans are under way to become a Specialized Programs of Research Excellence (SPORE) site—a National Cancer Institute initiative to translate basic science into clinical practice quickly, said Winer, who previously served for a decade as the principal investigator of a SPORE site in breast cancer. There are also plans to secure a broad-based National Institutes of Health Program Project P01 grant to fund further research into DNA damage and repair.

In the meantime, many more studies are in the works. One Yale group is investigating whether giving an antihyperglycemic drug can improve the effectiveness of chemotherapy, based on promising Yale findings showing targets within the oncometabolic pathways. Another study is exploring the use of blood tests to monitor whether patients are taking a drug correctly and to watch for recurrent disease. Researchers are examining how to safely reduce aggressive therapies in slow-growing cancers. They are looking to better understand patients' experiences with symptoms and financial burdens during active disease. And they are studying the life changes survivors face following a cure, including anxiety about recurrence.

Amid so many efforts to comprehend the origins, treatment, and social context of breast cancer, what does the future hold? "We have real potential in breast cancer treatment at Yale to provide truly unsurpassed care," said Winer. "We already do great research, and we can play a leading role there. We've got the right team in place. I think we can do something special." /

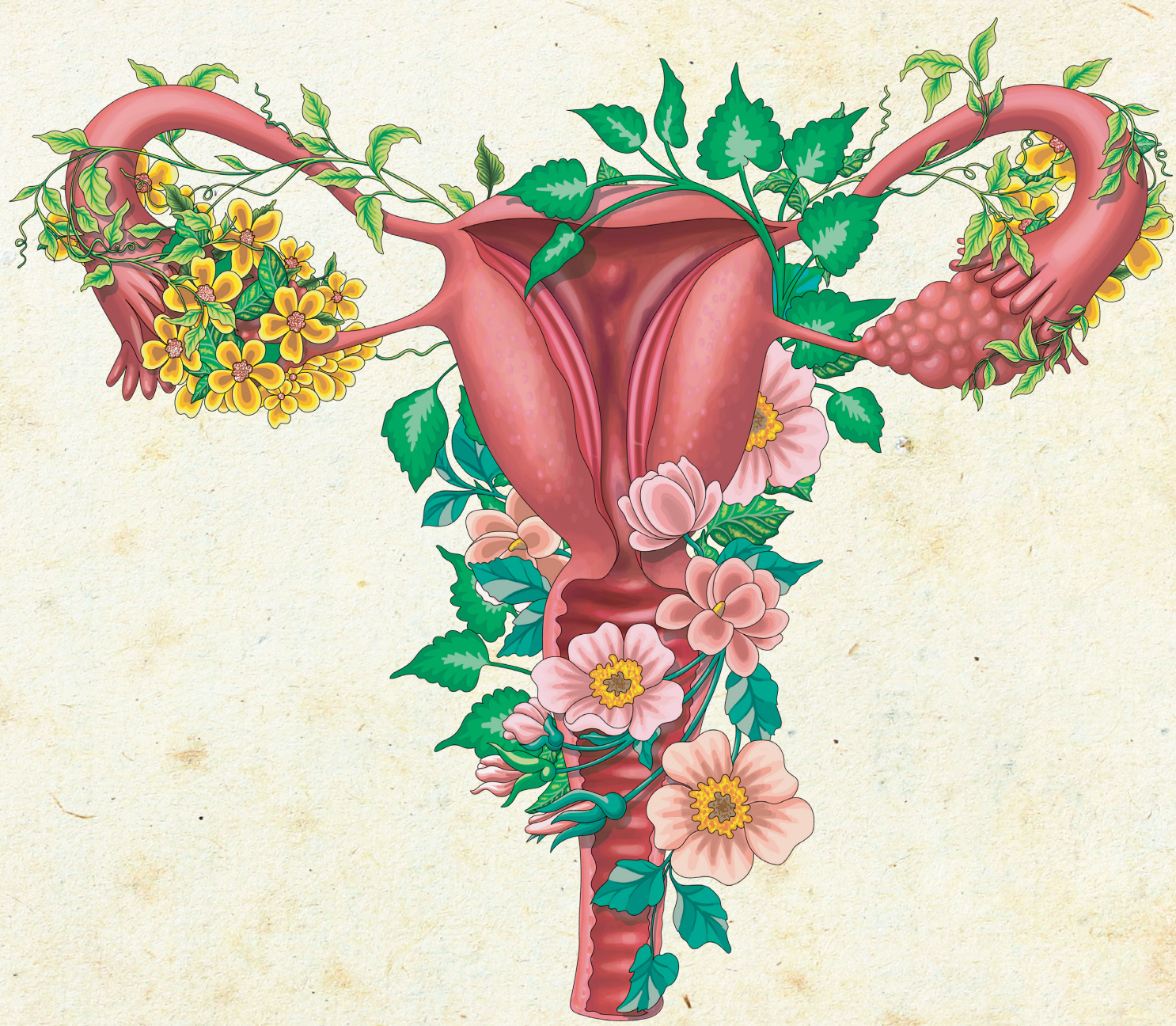
yale medicine magazine

ENDOMETRIOSIS

Changing the trajectory of a painful systemic disease.

BY ISABELLA BACKMAN

CODEX ANATOMICUS ILLUSTRATION



Even though endometriosis—a condition in which tissue similar to that lining the uterus grows outside the uterus—is among the most common gynecological conditions, it remains one of the most misunderstood and misdiagnosed.

Time and again, as far back as the age of Hippocrates, physicians have failed to recognize endometriosis as a real disease with underlying physical causes and often blamed women for the debilitating symptoms they experienced.

"The now-discredited mystery disorder presumed for centuries to be psychological in origin, was most likely endometriosis in the majority of cases," wrote Ceana Nezhat, MD, and his colleagues in a 2012 article in *Fertility and Sterility*. "If so, then this would constitute one of the most colossal mass misdiagnoses in human history, one that over the centuries has subjected women to murder, madhouses, and lives of unremitting physical, social, and psychological pain. The number of lives that may have been affected by such centuries-long misdiagnoses is staggering to consider, likely involving figures in the multiple millions."

While one might assume that the ancient perspective on endometriosis and chronic pelvic pain is a relic of the past, that's not necessarily true. Researchers estimate that over 10% of all women of childbearing age live with endometriosis—over 190 million adults worldwide. While initial complaints often include painful periods and/or infertility, in reality the disease has a vast number of other symptoms, many of which extend beyond the pelvis to other regions of the body. For some women, the pain correlates with their menstrual cycle; for others, symptoms are constant. And too many patients with endometriosis suffer severe, debilitating symptoms that drastically reduce their quality of life.

Unfortunately, the dismissive and demeaning attitudes of physicians toward endometriosis is not just something that used to happen; it remains prevalent today. On average, it takes women 10 years to receive an accurate diagnosis of endometriosis, and many see at least four or five doctors before their pain is taken seriously.

Now, emerging research has demonstrated that endometriosis is a chronic, systemic disease with multiple manifestations affecting the entire body. At Yale School of Medicine (YSM), Hugh Taylor, MD, Anita O'Keeffe Young Professor of Obstetrics, Gynecology, and Reproductive Sciences and professor of molecular, cellular, and developmental biology, and department chair, specializes in identifying the dozens of symptoms of endometriosis, explaining why these symptoms occur, and advocating for recognition of the severe pain caused by the disease.

"Menstrual cramps are the only pain that we as human beings accept as normal," says Taylor. "Any other pain would prompt one to seek medical attention, but here we have pain that we've normalized. Thus, the pain of endometriosis is too often underappreciated and underrecognized by physicians, other health care providers, and even by patients and their families."

MISPLACED ENDOMETRIAL CELLS

Researchers currently think that most cases of endometriosis result from what they call "retrograde menstruation." This condition occurs when cells from the uterus and other menstrual debris flow backward out of the fallopian tubes and settle in the abdomen, where they implant and grow.

The pain of the disease may be caused by several different mechanisms. The cells may implant around nerves, irritating or compressing them. The endometrial cells may also produce inflammatory molecules that irritate and inflame the surrounding tissue. Over the long term, this inflammation can lead to scarring and adhesions, which create further pain. "Endometriosis can eventually lead to the pulling and twisting of tissues," says Taylor. "This distorted anatomy can also cause pain."

Sometimes, physicians even find endometrial cells outside the abdominal cavity, lodged within the lungs or even in the brain, for example. Taylor's lab was the first to describe that some cases of endometriosis may also originate from stem cells. Usually, stem cells are mobilized to repair areas of inflammation or injury in the body. His group has found, however, that they also deliver certain molecules that promote the growth of endometriosis lesions. "The lesions of endometriosis may be perceived by the body like an injury," says Taylor. "The stem cells are drawn there to repair the body, but in reality, they're helping to promote the endometriosis."

New research is revealing that endometriosis is not just a gynecologic disease, but rather a widespread inflammatory disorder. Taylor's lab has found that the disorder communicates with the body in numerous ways. The disease, for example, secretes small RNA molecules called microRNAs that travel to organs beyond the pelvis,

where they can alter gene expression. Endometriosis can also activate macrophages and other immune cells that induce whole-body inflammation. Based on these insights, Taylor's team is currently exploring new anti-inflammatory therapies, including repurposing drugs used for other inflammatory conditions.

GENETICS: COMPLEX AND POORLY UNDERSTOOD

Studies on twins show that genetic factors account for approximately 50% of a woman's risk of developing endometriosis. But the disease itself can't be attributed to a single gene or two. "There's certainly a familial tendency toward endometriosis. But it's not like breast cancer where you can find a gene such as *BRCA*—which causes breast cancer in a large percentage of women living with it—and identify who is going to develop it," says Taylor. "We believe endometriosis is polygenic with multiple genes that all have a net contribution." In future studies, Taylor hopes to better understand the multitude of genes that interact to cause endometriosis so that his team can identify targets for potential therapy, "but we're not there yet," he says.

Furthermore, studying the genetics of endometriosis may also help researchers better understand its association with comorbid conditions. For example, a January 2023 *JAMA Network Open* publication has identified gene aberrations in women with endometriosis that overlap with psychiatric conditions. In other words, genetic commonalities may partially explain why endometriosis patients also have higher incidences of depression, anxiety, and eating disorders. "The epidemiological associations between endometriosis and these psychiatric traits are not only due to experiencing chronic pain, but also underlying biological and genetic mechanisms," says Dora Koller, PhD, a postdoctoral fellow at YSM and first author of the study.

SYMPTOMS EXTEND FAR BEYOND THE PELVIS

Endometriosis typically begins to manifest as extremely painful periods. This pain, however, may extend to the intervals between periods and occur in places outside the uterus. Symptoms may include pelvic pain, back pain, bladder pain and frequent urination, painful bowel movements and other gastrointestinal issues, and fatigue. But doctors often fail to consider endometriosis when women seek help for their specific range of symptoms. For instance, a urologist or gastroenterologist may not immediately associate their patients' bladder or digestive symptoms with endometriosis. "It's like the blind men with the elephant analogy," says Taylor. "Everyone looks at their own aspect of the disease rather than the big picture."

Endometriosis is also linked to depression and anxiety. Unfortunately, many doctors blame the pain women experience on these mental symptoms. However, when Taylor's laboratory team induced

DORA KOLLER, PHD //

> "The only way to obtain a definitive diagnosis is through surgery, which is unheard of for such a common disease."

endometriosis in mice, the animals shortly developed depression and anxiety. "Depression and anxiety are directly caused by the disease," he emphasizes.

In some women, the first sign of endometriosis is difficulty getting pregnant; they experience no pain, but infertility brings them to a doctor who ultimately diagnoses endometriosis as the reason they've been unable to conceive or carry a child. In other cases, women who had been previously dismissed when they go to the doctor with painful symptoms finally receive a diagnosis of endometriosis when they struggle with infertility down the road. "Many times, women only get taken seriously when they are unable to get pregnant," says Koller.

New research is now revealing that endometriosis causes more health challenges than initially thought. Studies show that having endometriosis is linked to a greater risk of heart disease later in life. Other research has found that the disease can cause changes in metabolism, including difficulty maintaining a healthy weight. While these associations were already known, women themselves were once again often blamed, rather than the disease.

"Physicians used to say that being thin was a risk factor for developing endometriosis," says Taylor. But his lab was the first to prove by using mouse models that the disease caused mice to be thinner, not the other way around. Furthermore, doctors used to attribute heart disease to the hormonal medications that endometriosis patients take and the surgeries they often undergo. Once again, Taylor's lab disproved this assumption. "We induce endometriosis in mice, and they develop heart disease," he says. "It's cause and effect."

WOMEN WAIT YEARS FOR A DIAGNOSIS

Unfortunately, women spend years seeing doctor after doctor for their symptoms, and often, says Taylor, they are dismissed or initially misdiagnosed. This delay is due, in part, to the old clinical standard for diagnosis being laparoscopic surgery. "Although that is still the definitive way to identify it, we can have a very good idea if someone has endometriosis just by her symptoms alone and start some easier treatments to alleviate the pain," says Taylor. But he also blames the delay on sexist attitudes that are still common among physicians. "I often hear demeaning, horrible comments from doctors who believe that women with endometriosis are just anxious and complain too much, or are overly sensitive to pain."

HUGH TAYLOR, MD //

> "Our goal is to recognize this disease early enough that we don't ever need to do surgery to diagnose it."

This lack of early intervention has tragic consequences, especially because the disease often first strikes when women are in school or in the early stages of their career. "The debilitating pain can change their life trajectory," says Taylor. "At times, it keeps them from performing well or forces them to miss work or

school. It holds them back, and you just don't get a 'do-over' on your early education."

TREATMENTS: HORMONES AND SURGERY

The majority of available treatments for endometriosis today are hormonal therapies. The standard first-line treatment is a class of synthetic hormones called progestins, typically in the form of birth control pills. This treatment, however, fails to relieve pain in a third of patients, while others will experience adverse side effects, including weight gain, mood changes, nausea, and irregular bleeding. In total, hormonal therapy is not optimal in about half of patients.

When medications fail, women may also choose to undergo laparoscopic surgery. "The only way to obtain a definitive diagnosis is through surgery, which is unheard of for such a common disease," says Koller. This procedure involves removing the endometrial lesions, and it can be very effective in reducing pain. Surgical excision, however, is not a cure—it does not prevent reoccurrence of the lesions, among other downsides. "The decision to perform surgery often means that one has waited until they feel bad enough that they want to undergo a surgical procedure," says Taylor. "It's not a good option for early recognition and treatment of the disease."

Another treatment is a GnRH agonist called leuprolide acetate (Lupron®). The injectable drug works by suppressing estrogen levels to zero and putting a patient in temporary menopause. Once administered, it doesn't take effect for several weeks. "Lupron is an extreme therapy," says Taylor. Physicians typically offer their patients supplemental hormones to mitigate the side effects, including hot flashes and fatigue. But unlike taking a pill that can be discontinued immediately, if a patient decides the side effects aren't worth the benefits, she must wait months for the drug to wear off.

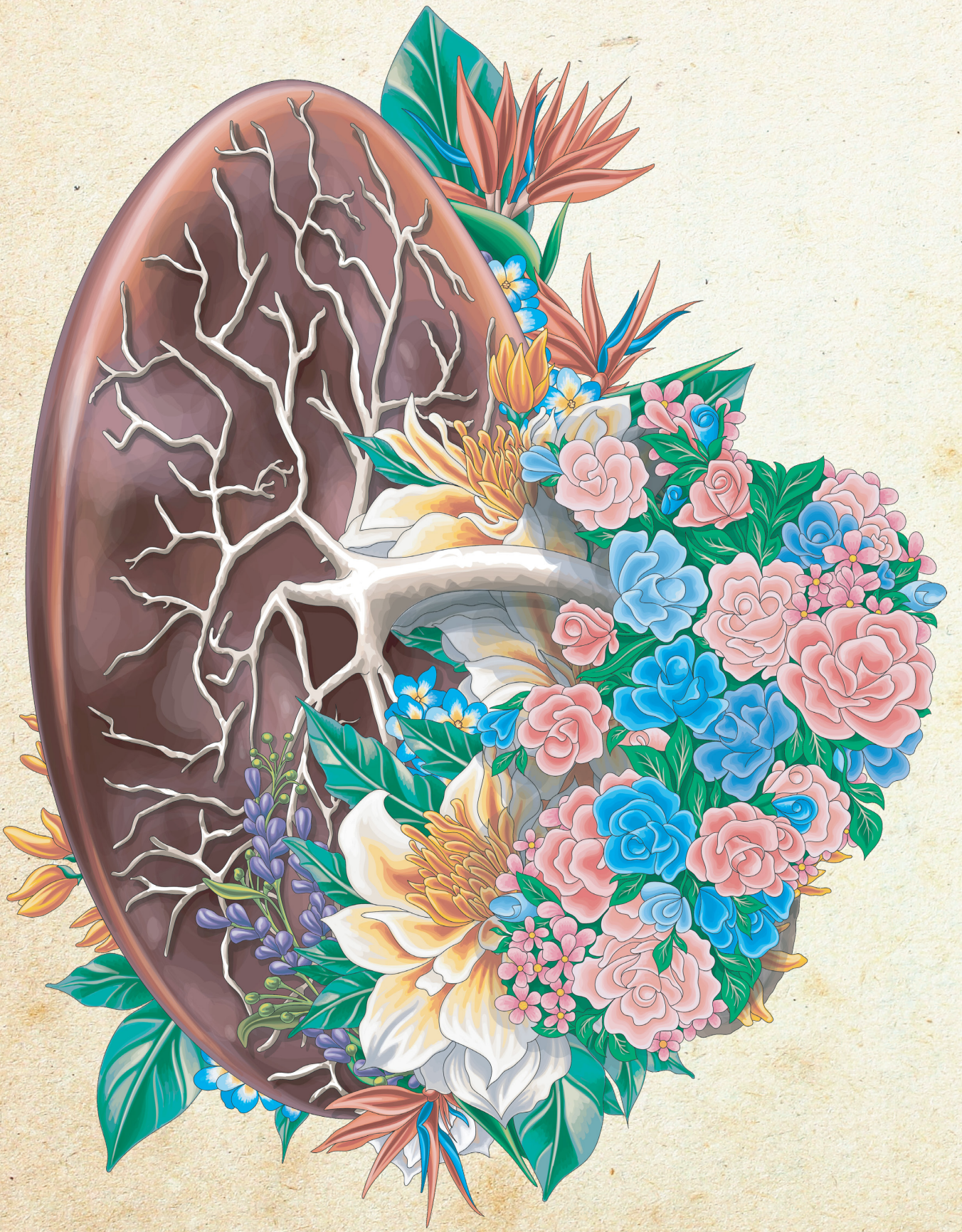
Over the past few years, researchers have developed an alternative to Lupron called GnRH antagonists. These oral therapies target the same receptor and have numerous benefits. They start lowering estrogen levels in the body in as little as 24 hours, and the doses can be titrated. This allows doctors to prescribe smaller doses that avoid full-blown menopause. "These have been a game changer because they are so much gentler, kinder, easier to use, and just as effective as the old-fashioned medications," says Taylor, who was the leader of the clinical trial published in *The New England Journal of Medicine* that led to the approval of elagolix (Orilissa®), the first GnRH antagonist in the United States. These drugs have become the most commonly used second-line therapy when birth control pills fail.

THE FUTURE OF ENDOMETRIOSIS CARE

Taylor and his team are working hard in the lab to improve the diagnosis of endometriosis, including developing a diagnostic blood test that looks for molecular biomarkers of the disorder, such as microRNAs, as a way to prevent the need for surgery. "Our goal is to recognize this disease early enough that we don't ever need to do surgery to diagnose it," he says. "And if we recognize it early enough, before the scarring and adhesions form, we may never need surgical therapy."

As researchers continue to learn more about the molecular biology and pathophysiology of endometriosis, Taylor also hopes to see more treatment options beyond hormonal medications. Because research shows that inflammation plays a significant role in the disease, his team is interested in repurposing drugs currently used for such inflammatory conditions as Crohn's disease and rheumatoid arthritis to see whether they also relieve the symptoms of endometriosis. Other key options include targeting the circulating microRNAs secreted by the disease by using specific microRNA inhibitors. Animal models are already showing promising results in both these areas of research.

Exciting progress is already being made, but half the battle will be convincing the medical community and beyond to recognize endometriosis as the complex disease that it is. "The more we understand and embrace that complexity, the sooner we're going to get to better therapies that treat the entire disease," says Taylor. "That requires getting people to start taking women's pain seriously, being unafraid to talk about menstrual cramps, and treating endometriosis sooner before it gets to a stage where a woman needs surgery." ***/yale medicine magazine***



WHY PREGNANCIES FAIL

Understanding the genetics of pregnancy loss—and the overlooked role of the placenta.

BY JENNY BLAIR, MD '04

In an era of high-profile debates and legislation surrounding abortion, it can be easy to overlook another widespread but less talked-about reproductive issue: the many obstacles some people face trying to get and stay pregnant. Among women of childbearing age, as many as 1 in 4 have trouble either becoming pregnant or carrying a pregnancy to term.

That figure translates into a lot of miscarriages. About 20% of the 5 million or so pregnancies that occur each year in the United States end in miscarriage at or before 20 weeks. Losses that happen past the 20th week of pregnancy are called stillbirths; these add another 20,000 to the total. One in 10 women will miscarry during their lives.

"These are just the losses where there was a heartbeat," said Harvey Kliman, MD, PhD, a research scientist in the Department of Obstetrics, Gynecology, and Reproductive Sciences at Yale School of Medicine (YSM). Kliman is also the director of the Reproductive and Placental Research Unit.

In addition to miscarriages and stillbirths, another 1 to 2 million pregnancies too small to detect on an ultrasound also end spontaneously before the fifth week.

Pregnancy loss can result in anguish as well as grief borne in isolation, as the losses are often written off as unavoidable by the general culture. This pain is magnified when the losses recur. And about half the time, such standard diagnostic measures as placental inspection and/or genetic testing after a miscarriage do not provide a clear explanation—which is all the more distressing for potential parents who often blame themselves.

The vast majority of early pregnancy losses are due to genetic abnormalities. But hearing that is often no consolation, Kliman said.

"On an emotional level, almost 100% of the women I take care of with pregnancy loss feel it's their fault," he said. "[They hear things like] 'You need to take more vitamins. Maybe you need more sun. Maybe you're eating [wrong],'"

CODEX ANATOMICUS ILLUSTRATION

Part of the problem is that it's usually a mystery how the genetic factors went askew.

Evidence of many abnormalities does not show up on such routine prenatal tests as the 10-week blood test of fetal DNA that screens for chromosomal anomalies like Down syndrome.

Likewise, if genetic testing is performed after a miscarriage, it only "scratches the surface," said Reshef Tal, MD, PhD, an assistant professor of obstetrics, gynecology and reproductive sciences at YSM, who is an expert on reproductive endocrinology and infertility. Tal is also a principal investigator of an NIH-funded basic science research lab.

"We think that there are many subtle genetic abnormalities—even variants in single genes—that can lead to recurrent pregnancy loss. These are things we are not currently testing for as part of the workup for recurrent pregnancy loss," Tal said.

Kliman and Tal are among a group of Yale researchers seeking to better understand miscarriage by studying how genetic factors influence pregnancy, as well as how genetic changes affect the placenta and its role in pregnancy. What they're discovering suggests not only such potential future therapies as bone marrow transplant but also finer-grained genetic checks before in vitro fertilization and closer monitoring of high-risk pregnancies.

AN INTRICATE GENETIC DANCE

Pregnancy proceeds step by step. A fertilized egg begins dividing and becomes a blastocyst, which travels to the uterus and begins to settle there—a key event called implantation. Then begins what Tal calls "cross-talk" between the embryo and the endometrium, or lining of the uterus. Cells in the endometrium adapt in response to the embryo in part by engaging new cells from far afield in the mother's body that help support the pregnancy.

Over many years of research published in journals that include *PLoS Biology*, *Biology of Reproduction*, and most recently *JCI Insight*, Tal has painstakingly demonstrated that a pregnancy recruits cells from maternal bone marrow, summoning them to the pregnant uterus via a molecule called CXCR4. There, the bone marrow cells differentiate into cells involved in embryonic implantation.

In their recent study, Tal and his colleagues showed that adult mice without a functioning CXCR4 receptor have such problems as smaller litter sizes and miscarriages. Their placentas have immune cell abnormalities and develop inflammation and abnormal blood vessels. Pregnancies proceed normally, though, in knockout mice that receive a bone marrow transplant from other mice with normal CXCR4 function. The bone marrow transplant introduces normal immune cells into the placental microenvironment. These cells are able to correct the abnormal placental inflammation and blood vessels, thus rescuing the pregnancy.

It's too soon to say how this finding translates to human pregnancy losses. If the gene for CXCR4 is involved, it isn't the only one. But the notion that a bone marrow transplant can rescue placental function in mothers with abnormal pregnancy genes is an important proof of concept, Tal said: "That's definitely something that we foresee as a future therapy for patients."

A "CHECK ENGINE" LIGHT IN THE PLACENTA

Kliman is taking a different approach to the mystery, scrutinizing placentas from both healthy pregnancies and miscarriages under a microscope to look for telltale differences.

In a 2023 study published in *Reproductive Sciences*, which examined 1,256 placentas from previously unexplained miscarriages and stillbirths, Kliman reported that an abnormality that could explain the pregnancy loss emerged in nearly 92% of cases. Most of the miscarried placentas contained a type of abnormal folding that is a red flag for genetic abnormalities.

Placentas from stillbirths, meanwhile, were usually very small. That insight could allow for preventive efforts. Kliman has developed a formula to estimate placental volume from easily measured parameters during prenatal ultrasound. If used routinely, estimated placental volume might allow obstetricians to flag higher-risk pregnancies for closer monitoring and treatments that could reduce the risk of stillbirth.

These results underscore the importance of a more thorough inspection of the placenta after pregnancy loss—something Kliman has advocated for years.

The abnormalities Kliman sees in placentas from miscarriages are called trophoblastic inclusions. Under a magnified cross-section of the placenta, these microscopic anomalies resemble circular islands of cells, but they are actually infoldings—as if you were to poke a finger deep into a ball of clay, then remove your finger and slice across the tube-shaped space left behind.

Trophoblastic inclusions are harmless per se. Some are found in every placenta, but there are far more in

placentas from miscarriages. Large numbers of them are also associated with such abnormalities as low birthweight and swelling of the placenta.

When many inclusions show up in the placenta, they are "the 'check engine' light that is saying there's a problem in the pregnancy," Kliman said.

AN EXPLANATION FROM EVOLUTION?

Kliman's findings have led him to hypothesize that evolutionary pressures that favor increased brain folding in human beings might also be driving vast numbers of pregnancy losses.

Broadly speaking, building a baby from a cell involves basic developmental processes or tools.

For one, there is proliferation; one cell must become many. In addition, there is migration: cells must travel to and develop in new locations in the embryo or fetus. Cell death also needs to occur in the right spots—so that, say, fingers emerge from a webbed proto-hand.

Another crucial tool is folding. That includes both infolding, as with the finger hole poked into clay; and branching, as if one were to mold protrusions from the clay. A host of anatomical structures develop using this tool, including the lung, kidney, brain, and heart.

Folding is a complex process involving many genes, so there are many ways it can go wrong. If it does, the developing fetus winds up with anomalous tissues or organs. The consequences vary in severity: misfolding of the brain may result, for example, in developmental disabilities.

During evolution, human beings have developed more complex brains than those of our primate cousins; the evidence is visible in our highly folded cortex. Nature increases cognitive capacity in part by increasing these deep folds, possibly because this may allow a larger cortex to fit into a head small enough to pass through the birth canal. If intelligence can confer a survival advantage, there may likewise be an advantage to genes that result in revved-up folding during development in the womb.

But folding also illustrates the Goldilocks principle; it needs to be "just right." Genes that promote a little extra folding may well result in a more highly folded brain. But too much can result in an unwelcome side effect: a malformed and nonfunctional heart. While a fetus can survive to term with a variety of organ defects, a nonfunctional heart is lethal.

Trophoblastic inclusions are not only more common in pregnancy losses, they also appear in large numbers in the placentas of children on the autism spectrum, whose brains have been found in some studies to exhibit extra folding. Kliman is now searching for the inclusions in the placentas of children with congenital heart disease—who, perhaps not incidentally, also have a higher incidence of brain abnormalities.

MORE LIGHT ON GENETICS

So far, Kliman's explanation remains a hypothesis that requires more research. Yale's Genomic Predictors of Recurrent Pregnancy Loss (GPRPL) study is currently recruiting 1,000 couples with unexplained recurrent pregnancy loss and scrutinizing their genomes, as well as the genomes of the miscarried fetuses. This analysis allows fine genetic detail to emerge, including errors that correlate with pregnancy loss.

The study should shed more light on the genes that are essential to early embryonic development and implantation—and it should translate immediately to prenatal care, Tal said.

That is because, at least for in vitro fertilization, a technology called preimplantation genetic testing is already used in the clinic to screen for chromosomal abnormalities and single-gene disorders to help clinicians select unaffected embryos. A more complete understanding of gene abnormalities associated with miscarriage will allow providers to better screen embryos before implantation for maximal chances of a successful pregnancy.

For a doctor specializing in infertility, that success is deeply gratifying, he said.

"I cherish the opportunity to be involved in the journey of the couples that I treat, helping them navigate what is a frustrating journey at the beginning, but then ultimately witnessing those miracles of life and the patients' joy of starting or expanding their family," Tal said. "You are really dealing with the secrets of life, the very origins of humankind."

Kliman for his part hopes that for people coping with the loss of a wanted pregnancy, understanding the genetics of miscarriage—and the ways in which it might exist within our very humanity—could help ease the anguish.

The work, he says, is "an effort to be able to give grieving would-be parents a more satisfying explanation than 'These things just happen.'" */yale medicine magazine*

MAZURE CHAIRS NEW WHITE HOUSE INITIATIVE

LAST FALL, PRESIDENT JOE BIDEN ANNOUNCED the first-ever White House Initiative on Women's Health Research. Carolyn M. Mazure, PhD, founder and director of the Yale School of Medicine's Women's Health Research at Yale, was named chair of the initiative.

Led by first lady Jill Biden and the White House s Gender Policy Council, the initiative draws on Mazure s decades long work in the field of women s health to advance research into health issues that are unique to women, affect women disproportionately, or manifest dif ferently in women than in men.

Looking back, biomedical research grew exponentially in the last half of the 20th century. Researchers, however, largely excluded women from clinical tri als, believing that their hormonal fluctuations would complicate studies of the outcomes of clinical interventions. Instead, research ers assumed that the data gen erated from men could also be applied to women. "There was a paradox embedded in this way of thinking," says Mazure, who is the Norma Weinberg Spungen and Joan Lebson Bildner Professor in Women s Health Research and professor of psychiatry and of psychology at YSM. "If women are ruled out because we re different from men, how could we apply the findings of men to help women?

In 1986, the National Institutes of Health (NIH) established a guide line recommending that women be included in clinical trials. But in 1990, an investigation found little evidence that women were being included in research despite the new recommendation. As a result, a provision was placed in the NIH Revitalization Act of 1993 and signed by President Bill Clinton that required not recommended that women be included in clinical research. By 2000, the number of published articles in the scientific literature that included women, as well as men, began to increase.

Women s health research today is still a young field, but sub stantial progress has been made. Sometimes, I hear people saying, We don t know anything about women s health.' But that s not true at all," says Mazure. "For too long, the knowledge base was so low that sometimes we didn t recognize the gains being made.

Even though there is still a long way to go in advancing the health of women, the increased recogni tion of the importance of women s health will spur more research.

In February, the initiative announced its first major accom plishment securing $100 million in federal funding to support sci entists engaged in breakthrough women s health research. "The fact that this has been elevated to a national level by the president and first lady of the United States is an extraordinary event," says Mazure. "I m both privileged and honored to be a part of it.

Isabella Backman

ERIN SCOTT, OFFICIAL WHITE HOUSE PHOTOGRAPHER

On a mission

BY MARY ANN LITTELL

AS A CHILD GROWING UP ON SAINT THOMAS, one of the U.S. Virgin Islands, Marcella Nunez-Smith used to sprawl on the floor of her maternal grandmother's house and listen to the adult conversation around her. "My grandmother's home was a gathering spot—a place where people came to discuss everything from politics to community service," she says. "She'd cook lots of food. People would come by, have something to eat, and talk."

ROBERT A. LISAK PHOTO

Overhearing these conversations opened Nunez-Smith's eyes to the realities of life in the Virgin Islands. She grew up witnessing the juxtaposition of unparalleled beauty among the people and the territory's turquoise-blue waters alongside the challenges confronting a small island—including access to high-quality health care.

"It was a dominant theme I heard early on," says Nunez-Smith. "Young people with debilitating illness were unable to get the care they needed. Or their care was delayed, which essentially is care denied. Too many people were dying young."

Then Nunez-Smith's father had a stroke that left him partially paralyzed. "He had to navigate through life with a severe disability because his hypertension was never diagnosed or treated," she says. "This wouldn't have happened if he'd had proper care. I became obsessed with thinking about the role I could play as a physician to change this narrative."

Now, she is doing just that. As inaugural associate dean for health equity research and C.N.H. Long Professor of Internal Medicine, Public Health, and Management at Yale School of Medicine (YSM), Marcella Nunez-Smith, MD, MHS, is laser-focused on eliminating inequities among marginalized people. "Disparities in health care are persistent and prevalent," she states. "They've been at a crisis point for many years, but until now, no one talked about them. When I was a medical student, the term health equity didn't exist. We talked about differences in outcomes. But there's been an evolution in thinking. We've gone from a place where disparities were not talked about, to where they were talked about, sometimes ridiculed, and usually dismissed, to now being a topic in newspapers and on news shows."

Nunez-Smith's mother, a retired professor of nursing, instilled in her a steadfast commitment to improving health equity. Maxine Nunez had earned a doctorate from the Johns Hopkins School of Public Health, "one of the first women of color to do so," says her proud daughter. "She had a stellar career in clinical care and was also a department chair and dean at the University of the Virgin Islands. She and my grandmother are my inspiration."

Her mother filled the family home with books. "She said we

would read together any book that I could reach," says Nunez-Smith. "The medical textbooks were on the top shelf, so I'd go up on a ladder to grab them. I was fascinated by human anatomy." While in second grade, Nunez-Smith brought one of the books to school. "I held court at recess: 'Look! This is our body! Isn't it amazing?' I got detention for that."

Graduating from high school at 16, Nunez-Smith enrolled at Swarthmore College, near Philadelphia. After she earned her undergraduate degree in 1996, Nunez-Smith returned home to help her mother and grandmother, who was very ill at the time. "I taught biology and physiology at my old high school," she says. "Unexpected experiences shape you, and I found that I loved teaching and mentoring. I was able to start a dissection lab and launched our first science fair. I realized teaching really is the family business."

Returning to the mainland after a year, Nunez-Smith went to medical school at Thomas Jefferson University (which merged with Philadelphia University in 2017) and completed an internal medicine residency at Boston's Brigham and Women's Hospital. Following a fellowship in Yale's Robert Wood Johnson Foundation Clinical Scholars Program, she joined the Yale faculty after completing her MHS in 2006.

At Yale, Nunez-Smith wears many hats—professor, scientist, clinician, administrator, teacher, mentor, and director of several research centers. Her research focuses on promoting good health and health care equity for marginalized people, with an emphasis on community engagement. She is the principal investigator on many NIH- and foundation-funded research projects, including one to develop a tool to assess patient-reported experiences of discrimination in health care. Nunez-Smith also leads other studies in workforce diversity, development, and inclusion.

The year of 'triplets'

Given Nunez-Smith's keen interest in global health and health policy, she is the founder and director of the Eastern Caribbean Health Outcomes Research Network (ECHORN), a collaborative consortium that conducts research in chronic diseases, including identification of risk and protective factors, across four groups of islands in this region.

Nunez-Smith is also the director of Yale's Equity Research and Innovation Center (ERIC), which she founded in 2013. "I always say that's the year I had triplets," she says with a laugh. "I had a set of twins and gave birth to ERIC, with strong support from the School of Medicine. It is a home for my research and for the research programs of other junior and mid-career faculty."

The twins, a boy and a girl, are 10 years old now. She and her spouse, a professional equestrian, also have a 14-year-old daughter. Their younger daughter has complex medical needs, requiring the assistance of care providers and other helpers. "When I talk about people who influenced me, I'm grateful to my mom, my grandmother, and all my other mentors. But right now, my best life coaches are my children."

Like those of busy families everywhere, the Nunez-Smiths' world changed with the arrival of COVID-19 in 2020. "Going to [the children's] school in early March to clean out their lockers, I remember saying, 'We won't be back here for a while,'" says Nunez-Smith. She was at Yale New Haven Hospital when the first COVID patient arrived. "The ER team called saying that they had a patient with possible SARS-CoV-2 infection," she recalls. "I remember sitting with the house staff, planning our next steps. Even then, we started thinking about issues of testing and testing access."

As significantly higher rates of COVID-19 cases, hospitalizations, and deaths afflicted minority communities throughout the United States, the pandemic shone a spotlight on health disparities. Examining this issue further, Nunez-Smith, Cary Gross, MD, YSM professor of medicine and epidemiology, along with other colleagues published a pivotal research paper in the *Journal of General Internal Medicine* in August 2020 that outlined the alarming lack of COVID data stratified by race and ethnicity. "We were among the first to say that these

disparities are real and underestimated," she notes.

Because of Nunez-Smith's involvement with COVID-19 response efforts and research, she was asked to be part of Connecticut Governor Ned Lamont's Reopen Connecticut Advisory Group, chairing its community committee. This group's mandate was to ensure public safety as businesses, stores, recreational facilities, and other entities resumed operations.

"As the government advised 'stay home and stay safe' measures, it took us some time to figure out how to maximize safety for people who didn't have the luxury of staying home," says Nunez-Smith. "[Such as] people with economic pressures, who have service jobs or work deemed essential, who take public transportation, who live in homes that are crowded and multigenerational. We got up to speed quickly. Investing incredible resources, the state of Connecticut developed plans for supported quarantine and isolation." This support has included public programs providing financial incentives and other services that facilitate quarantine.

In recognition of Nunez-Smith's expertise, she was tapped by the president-elect to co-chair the Biden-Harris Transition COVID-19 Advisory Board, and later to chair the Presidential COVID-19 Health Equity Task Force, which was created to address COVID-19-related health care and social inequities. "This appointment presented an opportunity to create policy on a national level," she says. "I used many of the lessons learned from Reopen Connecticut. One of our biggest challenges was fighting misinformation, disinformation, and limited trust. Our strategy was to use trusted messengers and tailor our messages to demonstrate our commitment to helping all people."

Nunez-Smith adds: "If there is one lesson learned from COVID-19, it's that we rise and fall as a collective. When it comes to wellness, opportunity, and economic recovery, we will only achieve and thrive as much as the least among us. Equity must be part of every conversation."

Health equity at Yale

To expand health equity research efforts across Yale, the Office of Health Equity Research was established with support from Nancy J. Brown, MD, the Jean and David W. Wallace Dean of YSM and C.N.H. Long Professor of Internal Medicine. "This effort will help us ensure that our work addresses health and health care disparities in everything we do," says Nunez-Smith. "To be centering health equity research here is extraordinarily exciting."

Part of Nunez-Smith's mission is to ensure that the next generation of physicians and health providers are trained to understand and address the root causes of health inequity. "Training and mentoring are at the core of everything we do," she says. "At any given time, ERIC is host to Yale undergraduates, medical students, and public health students who serve as student research interns." The ERIC program places interns into established research teams at ECHORN as well as at Yale, providing opportunities for experiential learning.

Taking this training one step further, student interns are invited to join the Alderfer Scholars Program, established in honor of Clay Alderfer, a former Yale faculty member who died in 2015. The program is co-directed by Nunez-Smith and David Berg, PhD, an organizational psychologist presently serving as a clinical professor of psychiatry. "The focus of the program is power in organizations, organizational change, and intergroup relations," explains Nunez-Smith. "If we're tackling issues of equity and causes of disparities, how do you do that from within an organization?

"We are tackling health inequity on many fronts," sums up Nunez-Smith. "What I do is extremely rewarding, in large part because of the extraordinary people I work with across different teams and different spaces here at Yale. So much of our work is problem-solving, and there are many smart people here to do that. There is also a lot of opportunity for vision-setting." She adds a caveat: "We've raised awareness; we've got people talking and thinking about disparities. But we can't rest on our laurels. There's more to do."

The power of collaboration

BY DAVID FREEMAN

Multidisciplinary team science seeks to solve biomedicine's big problems.

"ONE OF THE THINGS THAT I LIKE TO SAY about Yale is that from the outside it looks like an Ivy League institution, and from the inside it feels like a small pond," says Michael Caplan, MD, PhD, C.N.H. Long Professor of Cellular and Molecular Physiology and professor of cell biology.

This, of course, makes Yale School of Medicine (YSM) the perfect setting for the cross-disciplinary tapestry known as team science.

"Everybody knows everybody, and the ethos is that people work together," says Caplan, a member of several science teams at YSM. "If I call up somebody and say, 'I'm working on X and you're working on Y, and let's see what the cross-product Z looks like'—everybody does that."

But if an openness to collaboration is one factor in the popularity of team science at YSM, it's not the only one. The explosive growth of medical knowledge, along with the rise of genomics and sophisticated technologies that require expertise across multiple domains, are other key factors in the expansion of collaborative research at YSM.

As scientific knowledge has accumulated and research tools and technologies have grown more complex, Caplan and other YSM faculty members say that it's not surprising that individual scientists found it difficult to pursue their research without creating interdisciplinary teams.

"When I started in science in the '80s, there were a lot of publications where there were two or three authors, the student, and then the principal investigator," says Peter M. Glazer, MD, PhD, Robert E. Hunter Professor of Therapeutic Radiology and professor of genetics. "Now, that's very rare, and mostly you see a dozen authors on a typical paper."

Glazer says that science teams form easily at YSM, in part because of its right-sized pool of researchers. "It's kind of in a Goldilocks-size range, where it's not so small that you don't have enough of a scientific critical mass," he says, "and it's not so large that it gets too fragmented and silos develop."

A leg up in funding

The National Institutes of Health and other major sources of extramural funding have moved in recent years to promote team science by giving preferential treatment to grant proposals from science teams. And for good reason. Studies show that for complex problems requiring a more convergent research approach, teams tend to be more successful than scientists working on their own, according to Stephen M. Fiore, PhD,

Pegasus Professor in the Department of Philosophy and director of the Cognitive Sciences Laboratory at the University of Central Florida, and a past president of the International Network for the Science of Team Science (INSciTS).

"You're trying to bring people together to solve a problem much more rapidly than you would before," Fiore says, adding that "when we talk about team science, we tend to be describing the more interdisciplinary, more integrative approach to doing science, where you're creating something new, something that didn't really exist until that collaboration unfolded."

Team science at Yale has gotten a major boost from Nancy J. Brown, MD, the Jean and David W. Wallace Dean of YSM and C.N.H. Long Professor of Internal Medicine. She founded the school's Office of Team Science not long after arriving at Yale in 2020. Its aim is to provide logistical support and act as a nucleus for multidisciplinary teams working to solve some of biomedicine's big problems. Led by Kathryn "Kakie" Mashburn, director of interdisciplinary research initiatives, the office also provides research teams with preliminary financial support of up to $200,000 through its Program for the Promotion of Interdisciplinary Team Science (POINTS).

Such seed money is often critical to a team's success,

ANGELINA BAMBINA ILLUSTRATION

"Everybody knows everybody, and the ethos is that people work together."

MICHAEL CAPLAN

"I couldn't have advanced our work without [Mark Saltzman]'s delivery expertise."

PETER GLAZER

according to Caplan. "You can have all of the creative people that you want and lock them in one room for as long as you want," he says. "But if they can't afford to do the experiments or pay the salaries of the people who are going to do the experiments, you're not going to make as much progress as you'd like." Adds Mashburn, "The idea is to really encourage people to come together to bring their separate resources, their separate expertise, and to really contribute to a much larger goal to bring infrastructure to the institution."

Team science in action

The Office of Team Science isn't the only initiative promoting this form of collaborative research at Yale. The Yale Center for Clinical Investigation (YCCI) maintains a Team Science Program, which not only promotes an academic and clinical culture that supports interdisciplinary research, but also seeks to advance what experts call the "science of team science." Or, as James McPartland, PhD, Harris Professor in Yale's Child Study Center and the co-director of the program, explains, it's about figuring out "how we can understand the functionality of team science ... studying processes and developing outcomes to see how team science succeeds at Yale."

McPartland, who says that he and Mashburn stay in touch to share information and look for synergies between the two programs, also collaborates on studies focusing on autism. As part of the center's autism research, Flora Vaccarino, MD, Harris Professor in the Child Study Center and director of the center's program in neurodevelopment and regeneration, recently developed a pair of brain organoids that may help scientists identify different subtypes of autism, which so far remains diagnostically undifferentiated despite the marked heterogeneity of its symptoms, explains McPartland.

Glazer, who is an expert in gene editing, has been collaborating with Caplan on research in mice to discover ways to use these technologies to fight polycystic kidney disease. Another team focusing on polycystic kidney disease, including Caplan along with Stefan Somlo, MD, C.N.H. Long Professor of Medicine (Nephrology) and professor of genetics, and Lloyd Cantley, MD, C.N.H. Long Professor of Medicine (Nephrology) and professor of cellular and molecular physiology, as well as other principal investigators and dozens of Yale researchers, discusses recent findings and proposes new ideas every other week at the Anlyan Center for Medical Research and Education. In addition, the team meets informally and holds video chats. It has been "really productive in terms of developing new

insights into disease mechanisms, new animal models, and new therapeutic directions," says Caplan.

All those meetings and hard work are paying off. Led by Cantley, the polycystic kidney disease team recently obtained a grant of more than $11 million from the Department of Defense. That's one of the largest grants ever awarded to YSM researchers.

Glazer is also pursuing joint research on cystic fibrosis and other diseases with W. Mark Saltzman, Goizueta Foundation Professor of Biomedical Engineering and professor of cellular and molecular physiology and of chemical engineering at the Yale School of Engineering. Saltzman is an expert in nanoparticle drug delivery. "He has a technology for delivery that needs a cargo, and we had a cargo that needed a delivery vehicle," Glazer says. "It was a well-made match," he adds, "and I couldn't have advanced our work without his delivery expertise."

The next challenge for the team, which also includes Marie Egan, MD, professor of pediatrics (respiratory) and of cellular and molecular physiology, is to move the experimental gene-editing technique from the laboratory to clinical practice, says Saltzman. "We've not made that leap yet, but I hope we will" within the next decade.

Other research teams at Yale include those devoted to elucidating the body's energy metabolism; developing a nasal spray vaccine for COVID-19; and identifying genetic mutations that could be exploited to develop treatments for brain tumors, leukemias, sarcomas, and other malignancies.

But all these successes don't mean there aren't occasional challenges. "There are lots of teams that have crashed and burned because the people who participate don't have that commitment or don't have those communication skills" needed for success, Caplan says. Emotional intelligence and the ability to listen well are essential, he says. So is being able to keep one's ego in check, as band members do. "When you are playing in a band," he explains, "each one of you gets to take the solo at various times. But you can't be Mick Jagger all the time."

The good news is that everyone involved in team science at YSM is working toward the same goal. "We want to increase the impact of our science and the benefit that it has for humanity—both in medicine and more generally for the scientific enterprise," says Anthony Koleske, PhD, Ensign Professor of Molecular Biophysics and Biochemistry and of Neuroscience, and the deputy dean for basic science research at YSM. "We have a world-class faculty that we can build into teams," he adds, "and they are doing really transformative work." And this is the epitome of team science.

"We want to increase the impact of our science and the benefit that it has for humanity—both in medicine and more generally for the scientific enterprise."

ANTHONY KOLESKE

"It's about … studying processes and developing outcomes to see how team science succeeds at Yale."

JAMES MCPARTLAND

The evolution of psychiatry

MENTAL ILLNESS HAS HISTORICALLY been underdiagnosed and undertreated in the United States, says John Krystal, MD, Robert L. McNeil, Jr. Professor of Translational Research and professor of psychiatry, of neuroscience, and of psychology at Yale School of Medicine (YSM). In recent years, the COVID-19 pandemic has substantially accelerated the use of mental health services.

Yale Medicine Magazine spoke with Krystal—a leading psychiatrist who specializes in the pharmacotherapy of psychiatric disorders and a pioneering researcher into the fast-acting antidepressant effects of ketamine—about the evolution of the field of psychiatry.

How has the field of psychiatry changed since you began to practice?

Early in my career, we were tweaking existing medication types to improve tolerability and safety. For example, when I was a psychiatry resident on our Clinical Neuroscience Research Unit in the 1980s, we tested some of the first selective serotonin reuptake inhibitors (SSRIs)—the prototype being fluoxetine [brand name Prozac®]. These medications acted via mechanisms similar to older tricyclic antidepressants introduced in the late 1950s but were better tolerated.

As a result, many more people decided to pursue treatment for depression than in the past. When I joined the faculty in 1988, my first project was studying a new antipsychotic medication called clozapine. While similar in many ways to antipsychotic medications introduced in the 1950s, it had a reduced propensity to cause motor side effects, and it was a little more effective. These advances in tolerability helped to encourage many more people to seek medication treatments for problems like depression, anxiety, and psychosis.

To move from incremental advances in treatment to fundamentally novel treatment mechanisms, we had to change the way that we thought about the neurobiology of psychiatric disorders. Most of the medications that psychiatrists prescribed targeted the monoamine systems, such as norepinephrine, serotonin, and dopamine, which comprise only a few percent of the synaptic connections in the brain.

To move forward, my colleague Dennis Charney and I reasoned that we had to better understand how the monoamine systems were related to the rest of the synaptic connections in the brain—particularly glutamate and GABA neurotransmission, which constitute more than 90% of the synapses in the cerebral cortex.

This change in perspective about the biology of depression led my colleagues and me to test the effects of very low doses of ketamine in depressed patients in the mid-1990s. Ketamine, in higher doses, is an anesthetic medication. In the 1980s, it had been shown to block the NMDA subtype of glutamate receptor in the brain. Our initial study shocked us. While traditional antidepressants may take months for patients to recover from depression, some of our initial patients achieved this within 24 hours of a single ketamine dose. Further, the beneficial effects of a single dose lasted up to two weeks.

Our study and subsequent replications led Johnson & Johnson to develop the s-isomer of ketamine (esketamine; Spravato®) into the first mechanistically novel antidepressant approved by the FDA since the 1960s. In addition to their

distinctive rapidity of action, these medications are remarkably effective for depression symptoms that have not responded to other antidepressant treatments, are effective for suicidal patients, and are quite effective in preventing relapse to depression.

Two large studies published in 2023 suggest that for treatment-resistant symptoms, adjunctive esketamine is more effective than adjunctive antipsychotic medication, and similar in efficacy to electroconvulsive therapy (ECT). Recent findings regarding long-term effects of esketamine suggest that when compared to standard treatments, it reduces suicide attempts, death by suicide, and all-cause mortality (i.e., it reduces the chances of dying from medical problems that are worsened by depression).

Esketamine is approved by the FDA and limited to clinic-based administration. Ketamine is not yet approved by the FDA for the treatment of depression, and ketamine treatment is generally not reimbursed by insurance. As a result, some practitioners have developed the practice of prescribing ketamine for take-home use.

However, ketamine is an abused substance, and "take-home" ketamine may be associated with risks associated with misuse of this drug. The widely publicized death of [the actor] Matthew Perry makes this case. He was known to have substance use problems. At the time of his death, he had more than 10 times the amount of ketamine in his blood than that needed to treat depression—enough to anesthetize him and to contribute to his drowning. At Yale, we limit both ketamine and esketamine treatment to the clinic.

In addition, there are two new medications approved for the treatment of post-partum depression: brexanolone (Zulresso®), approved by the FDA in 2019, and zuranolone (Zurzuvae™), approved by the FDA in 2023. Both are thought to work by replacing a progesterone-derived neurohormone called allopregnanolone (ALLO). ALLO levels drop rapidly after childbirth, depriving the brain of a natural mood resilience mechanism.

These drugs restore ALLO in the body and brain, reducing post-partum mood symptoms. Brexanolone involves a 64-hour intravenous infusion, and it is impractical to use in many treatment settings. However, zuranolone is an orally administered drug and may be used more broadly.

We also are making progress in developing new treatments for psychotic disorders like schizophrenia. Since the 1950s, all antipsychotics have produced therapeutic effects by blocking the dopamine D2 receptor. These medications are helpful for many people with psychosis symptoms, but other symptoms of schizophrenia may not respond well. Further, dopamine D2 receptor blockade may make people feel dulled, and may cause tremor, restlessness, and other motor side effects.

The first two drugs to treat psychosis without blocking the dopamine D2 receptor seem to be emerging. The first medication, KarXT, is a combination of two drugs that stimulate muscarinic cholinergic receptors in the brain but block muscarinic receptors in the body. It produced very encouraging results in clinical trials and has been submitted to the FDA for approval.

The second medication, emraclidine, is a selective muscarinic M4 positive allosteric modulator. One index of how important these new drugs may be for psychosis treatment is that the companies that made these new drugs were acquired by large pharmaceutical companies. Karuna, which makes KarXT, was acquired by Bristol Myers Squibb, while Cerevel, which makes emraclidine, was acquired by AbbVie.

What are your longer-term expectations for the use of such drugs as ketamine, which have fast-acting antidepressant effects? When ketamine was first introduced, it was originally reserved for the most severe forms of depression. At Yale, we initially reserved ketamine and esketamine for patients who had failed ECT. Now, ketamine and esketamine are generally provided to patients before they are treated with ECT. It seems like these treatments are being used for a larger group of patients, as the data support evidence of greater efficacy for a broader range of conditions.

I also expect ketamine treatment to evolve based on what we are learning about potential synergies between ketamine and esketamine and particular forms of psychotherapy, as well as the potential for next-generation versions of ketamine that may provide either greater tolerability or efficacy.

How have attitudes about ECT evolved? ECT, which involves the application of brief electrical pulses to the brain, was highly stigmatized based on depictions of it in movies like *One Flew Over the Cuckoo's Nest*. It's taken a long time for the

public to appreciate that the actual practice of ECT is nothing like what they saw in the movies. It remains an extremely effective form of antidepressant treatment, and it's been helpful when public figures like Kitty Dukakis and our own Sherwin Nuland, a distinguished surgeon who was on the faculty here at YSM, spoke out and wrote about their positive experiences with it.

For many people, this may be the only treatment that works for them. When we suggest that a patient consider ECT, we often spend a lot of time explaining to them and to their family that they won't be awake, they won't have a visible seizure, and that there's a good likelihood that the treatment will be effective for them. The most common side effects are headache or difficulty recalling what happened right before the treatment was delivered. Some people may have relatively mild memory impairment that can persist for a while, but this risk can be reduced by administering the therapy on one side of the brain at a time rather than both sides at the same time.

What role will psychedelics play in treating psychiatric conditions and for end-of-life care? Psychedelics are being intensively studied at this point. There are now two Phase 3 studies that have been published for psilocybin [the active ingredient in *Psilocybe* mushrooms], that suggest that this hallucinogenic substance is rapidly effective and has a fairly robust antidepressant effect in patients with major depression.

That's very exciting, because no treatment works for everybody, and we need a diversity of rapid-acting and highly effective treatments for patients with depression. Psilocybin is also being tested for a variety of other conditions, such as end-of-life existential distress, and there are some encouraging data reported there. It can be a deeply comforting and inspiring experience for people who are in that stage of life.

MDMA, also known as Ecstasy, which is not hallucinatory, is being tested in post-traumatic stress disorder (PTSD). It seems to be robustly effective in the published data so far. A second Phase 3 study was completed, and while we haven't seen the results, the group that conducted the trial—MAPS, the Multidisciplinary Association for Psychedelic Studies—has submitted an application to the FDA for approval of MDMA as a treatment for PTSD.

Psychedelics are striking drugs because of the profound experiences that people report during the treatment sessions. The administration of the drugs is somewhat burdensome to go through. Psilocybin and MDMA treatment sessions last between six and eight hours. And, generally, people have several psychotherapy sessions before each treatment to prepare, and several after to process what they experienced. It's a very intensive process, but many people find it meaningful and helpful.

How will interventional psychiatry be incorporated? Interventional psychiatry, which was a term we started using around 2009, is now a mainstream idea. It is based on the principle that treatment options don't stop when a patient hasn't responded to the usual medications that we commonly prescribe for mood, anxiety, and psychotic disorders. We have other options that can often be very effective.

Together, in partnership with our patients, we can often produce better clinical outcomes by using these more interventional kinds of treatments, which include ketamine, esketamine, ECT, and transcranial magnetic stimulation—a more subtle kind of brain stimulation than ECT. Psychedelics and MDMA are just two examples of drugs that will very likely become part of the interventional psychiatry package after they're approved by the FDA. So interventional psychiatry is a growing field, in part because its options seem to be increasing every year.

What are the most important changes occurring in the treatment of alcoholism? While I am not aware of a new medication coming to the FDA for approval in the near future, research on alcohol use disorder is extremely active. Our center, called the NIAAA Center for the Translational Neuroscience of Alcohol, identified one promising strategy in early studies that involves the combination of an opioid receptor blocker and a glutamate receptor antagonist. We are currently evaluating a negative allosteric modulator of the metabotropic glutamate receptor-5 (mGluR5). In other centers, an anti-inflammatory drug called apremilast has shown some promise. There is also tremendous interest in the potential role that ketamine, psychedelics, and MDMA might play in the treatment of alcohol use disorder.

What's being done to address the disproportionately high rate of mood disorders in women?
Depression is about twice as common in women as in men. In the post-partum period, the rate of depression in women doubles over the usual elevated rate. Women are at greater risk for most mood and anxiety disorders relative to men, and that's one of the reasons why it's important to understand the unique factors contributing to these increased rates. Some of the clues come from understanding hormone levels in the body. But we are beginning to develop a more fundamental understanding of the neurobiology of depression.

These insights are coming from studies on the genetics of depression and from analyses of post-mortem brain tissue from men and women. This work has revealed that the biology of mood disorders, such as depression and PTSD, are somewhat different in women and men. In other words, when you look at specific cells in specific parts of the brain and look at the profile of the genes that are expressed, you find some differences in the alterations of men's and women's brains. It's possible that these new insights into sex differences in the biology of depression will lead us toward more specific mood and anxiety treatments for women, as well as for men.

How is the relatively new field of reproductive psychiatry helping women? Reproductive psychiatry focuses on mood disorders associated with female reproductive health. The range of clinical conditions includes menstrual cycle–related mood disorders, post-partum or peripartum mood disorders, and menopause-related mood and anxiety disorders. Addressing these issues is extremely important because they affect so many women, and are associated with distress and disability.

Historically, these conditions did not receive the kind of research that general mood disorder symptoms got in terms of psychiatry research. As a result, the researchers working in this area, including Dr. Ariadna Forray, associate professor of psychiatry at YSM and director of the Center for Wellbeing of Women and Mothers, have been specifically testing treatments that target women who are experiencing these mood symptoms related to their reproductive health.

That's where new treatments, such as brexanalone and zuranolone, come into play. Clinicians may use distinctive medication treatments that are not commonly used in other areas of psychiatry, and the people who work in this field are also dedicated to studying the causes and mechanisms of these reproductive-related mood disorders.

How has telehealth affected the practice of psychiatry? Within two weeks of the emergence of the pandemic, all of our ambulatory service was converted to telehealth. We were concerned that we would not be able to deliver effective psychotherapy via telehealth; that did not turn out to be the case. And what we discovered is that attendance in psychotherapy increased when we switched to telehealth. Because people could attend their appointments more easily, fewer were cancelled, and patients benefited from that.

Our hope is that we will be able to maintain telehealth as a part of an overall set of treatment options for patients. We are concerned that some of the payers are reducing their reimbursement for telehealth visits, which makes it financially disadvantageous to offer telehealth relative to in-person visits. We hope that will not persist, because for many patients, it's the most viable form of treatment.

Over time, it is likely that telemental health might be augmented by digital health. This would include computerized psychotherapy-like programs that people can use at their convenience to work on issues that they're also addressing in their face-to-face therapies. Treatment could also be augmented by data that can be collected easily and in an automated way. For example, there are wearable devices that inform us about a person's quality of sleep or daily activities. These kinds of data are relevant for understanding both the symptoms that people have and how they're responding to treatments.

What other predictions do you have for the future of psychiatry?
This is an extremely exciting moment in the field of psychiatry. The science is better than it has ever been, and we are now beginning to see the emergence of treatments from our understanding of the neurobiology of psychiatric disorders. I predict that the next generation of new treatments will target very fundamental mechanisms underlying the biology of psychiatric disorders.

Digital pathology

BY JOHN CURTIS

A faster, more powerful way to 'see' disease.

IF THE WORK OF PATHOLOGISTS evokes images of physicians hunched over microscopes examining pink-stained glass slides, it's time to update that vision. With the acquisition of two digital scanners that produce whole slide images of histology slides, Yale School of Medicine's Department of Pathology has entered the booming field of digital pathology. Those images are the fundamental tool that pathologists use to investigate bodily fluids and tissues.

Whole slide image (WSI) scanners produce digital high-resolution images that can be reviewed on monitors instead of microscopes. These images, coupled with rapidly evolving artificial intelligence (AI) algorithms, provide clinical data that can mean faster and more accurate diagnoses, as well as the ability to predict the course of disease. The applications and benefits of digital pathology include informing treatment for an individual patient, ensuring safety in hospitals, providing high-quality standardized care in multihospital networks, and providing access to health care in underserved parts of the world.

"We see this as really transformative. It's almost impossible to quantify it right now," said Chen Liu, MD, PhD, Anthony N. Brady Professor of Pathology and chair of the Department of Pathology. "It's my prediction that any academic department that doesn't have a digital pathology practice will be obsolete in the next 10 years."

Forging ahead

The current digital pathology boom started in earnest in 2017 after the Food and Drug Administration (FDA) approved the marketing of WSI scanners for rendering primary diagnoses. Until then, the scanners' predominant applications were nonclinical, like archiving and research. The technology has its roots in telepathology, which starting in the 1960s sought ways to transmit scans of tissue slides electronically. Efforts were also under way to improve the quality of scans; by 2000, WSI could produce scans equal in resolution to those of the original slides.

But those developments don't mean that the entire process has gone high-tech. The essential first step to scanning still requires making histology slides the old-fashioned way.

"In anatomic pathology, we get tissue from patients; we dice it up, embed it in paraffin, and cut very thin sections from it. Next, it goes on glass slides and gets stained. Then we look at it under a microscope and make a diagnosis," said Sudhir Perincheri, PhD, MBBS, assistant professor of pathology and director of digital pathology. "It was possible for a long time to take snippets—put one area under the microscope and take a picture. Now, we can not only image the whole slide, but also do it in a way that allows us to zoom in, zoom out, and basically replicate our work over the microscope."

Speed, AI, and portability

The department's new scanners can image a slide in two to three minutes and run up to 450 slides at a time. Before WSI, scanning a single slide could take up to 24 hours. "Technologically, it has become feasible to digitize slides at a large scale for clinical workflows and make them available for

review rapidly," Perincheri said. "If there was a lung biopsy done today, it will go in the scanner at three in the morning, and it'll be ready for the pathologist to review at eight in the morning."

And, Perincheri added, because AI can "see" things missed by the human eye, it can unearth surprisingly large amounts of information. "Because these are gigantic files, there's a lot of unmined data," he said. "One of the strengths of AI algorithms is pattern recognition. If you take a big enough data set of slides and feed it into the algorithm, and you tell the algorithm this is how these patients' conditions behaved over time, the algorithm is able to pick out patterns that predict disease behavior over time."

Digital pathology also brings huge gains in accessibility and portability. Because slides no longer need to be shipped by courier to a path lab, waiting time is reduced, as is the likelihood of lost slides. A pathologist with a laptop and a Wi-Fi connection can access high-resolution scans during conferences, in the classroom, or at a tumor board meeting.

"I see the opportunity for workflow efficiencies, including quicker patient diagnoses, that are really great gains, especially in the cancer care setting," said

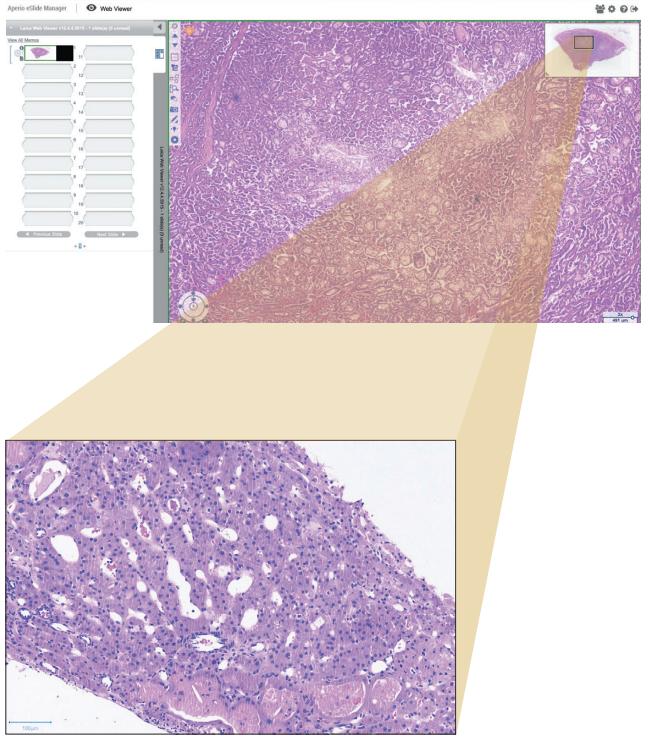
Angelique W. Levi, MD, vice chair and associate professor of pathology, and director of Pathology Reference Services. "The physical slide no longer has to travel, so as we collaborate with YNHHS delivery networks across the enterprise, and grow and expand beyond the [Yale] system, we can share case images, and more pathologists can have access to patient specimens or 'slides' in a central place, digitally. We have so many opportunities for clinical and educational case-sharing, second-opinion consultation, quality control review of cases in-house, and many more sets of eyes with subspecialty expertise."

Digital pathology plays an important role in a hospital system, she said. "Hospitals use pathology to guide patient safety and inform safety data, and digital pathology can efficiently standardize care and subspecialty expertise across a system."

In a multihospital system, like Yale New Haven Health, said Liu,

Histology glass slides are being converted into digital whole slide images, which benefits the work of Yale pathologists, including Mina Xu, MD, professor of pathology, director of hematopathology, and director of the Expert Consultation Practice at Yale Pathology.

ANTHONY DECARLO PHOTOS



Sudhir Perincheri, PhD, MBBS, assistant professor of pathology and director of Digital Pathology, leads the transformation into digital pathology at Yale.

digital pathology is critical to maintaining a high standard of care across different institutions. "This will allow all pathology units systemwide to come up with the same quality of diagnostics."

That standard of care, Levi added, can travel around the world. "Part of what excites me is not just improving the standard of care here at Yale but having that extend into communities beyond academic institutions. This increases the access to this technology in a way that can have the greatest impact and extend this care, perhaps, in other countries where there isn't subspecialty expertise or training, or even a pathologist."

A powerful educational tool

When it comes to teaching pathology, Perincheri sees an exciting time ahead. Pathologists and their residents or other physicians don't need to be in the same room hunched over a multiheaded microscope to view a slide. "The image is sitting in a server somewhere, so it doesn't matter if I'm here and my colleague is in New York or Boston, we can all see the same thing."

Residents will also learn how to mine data from the slide. "There are tools now where we can point out details and say, 'If you look at this tissue biopsy, it has a, b, and c features; hence, we render a particular diagnosis.' We can annotate slides; we can enrich them with all sorts of data, such as demographic data and outcome data."

The fundamentals of histopathology and morphology will not change, said Levi. But now residents can learn from digital scans rather than glass slides. "They are becoming more and more comfortable looking at tumor board cases that have been scanned or accessing scanned images, and getting their feet wet in that way," she said. "It's like we're creating a digital library of our interesting entities that they would otherwise have learned about in a book or an atlas or a glass slide set."

Extending WSI's reach

Yale's pathology department has scanned about 130,000 whole slides since 2022—roughly 10% of the cases that come its way. "We don't have the ability to scan everything, but we have prioritized cases that we want to scan, such as lung and thoracic biopsies," said Perincheri. "Right now, the barrier is cost—hardware, image management software, storage, high-resolution monitors. And there is no insurance reimbursement for that."

However, that could change. A billing code has been created for digital pathology, even though insurers are not yet offering reimbursements. "If historical precedent is any sort of indicator," Perincheri said, "we think that in about three or four years, probably less, we should start seeing reimbursement for digital pathology. This is the future. If you don't become digital, you become obsolete."

ANTHONY DECARLO PHOTO; SCANS COURTESY OF SUDHIR PERINCHERI, PHD, MBBS

Brenda Cabrera-Mendoza, Valerie Tornini, and Jiun-Ruey Hu (l–r) were named as 2023 STAT "Wunderkinds."

ANTHONY DECARLO PHOTO

Yale researchers hailed as STAT 'Wunderkinds'

Three Yale researchers are among 28 North American early-career scientists who were recently celebrated as the "next generation of scientific superstars" by STAT, a health, medicine, and life sciences news service that named the 2023 "Wunderkinds."

Brenda Cabrera-Mendoza, MD/PhD, a Yale postdoctoral fellow in psychiatry, studies the genomes of people with mental illness in the hope of identifying genetic variants associated with suicidality for each major mental health disorder.

Cabrera-Mendoza, who received her doctoral degrees in psychiatric genomics from the Universidad Nacional Autónoma de México, focuses on people of Latin American, Asian, and African descent because these populations have been underrepresented in the past in genomic databases. "To diversify our genetic databases, and thus better understand the whole of humanity, we need to diversify our research workforce," she says. "Diverse researchers are best able to reach diverse communities and can provide different and useful perspectives."

Jiun-Ruey Hu, MD, MPH, a Yale clinical fellow in cardiovascular medicine, has developed a suite of computational tools to help physicians who treat cardiovascular and kidney disorders improve their decision-making. The tools make use of the large quantity of new research published daily in medical journals. Hu, who received an MPH from the Johns Hopkins Bloomberg School of Public Health and an MD from Vanderbilt University School of Medicine, modeled his suite on the decision-making processes used by specialist consultants and on clinical practice guidelines issued by national subspecialty societies.

"The goal of good computing is not to replace health care professionals but to provide them with tools that amplify their capabilities, allowing them to make more accurate diagnoses and evidence-based treatment decisions," says Hu, who adds that he was drawn to investigate the heart and the kidneys because there is much yet to be learned about the interaction of these organs.

Valerie Tornini, PhD, a Yale associate research scientist in genetics, uses zebrafish models to study the roles of small and still-mysterious genes and proteins in vertebrate neurodevelopment. She hopes to better understand how brain cell development might differ in people with neurodevelopmental disorders.

Tornini, who received her PhD in cell biology from Duke University School of Medicine, says zebrafish are excellent models for basic neurological research. The processes she monitors in humans occur in similar ways in these fish and are easily observable because the transparent fish develop relatively quickly compared to humans and other mammals. "You can screen for effects of hundreds of genes and prioritize them rapidly by mutating them in zebrafish," she points out, reflecting on the nature of the fish and the power of sequencing, the use of fluorescence microscopy, and whole-organism phenotyping.

—*Cristina Deptula*

yale medicine magazine YALE UNIVERSITY, 50 DIVISION STREET, 2 SCIENCE PARK, NEW HAVEN, CT 06511
ymm.yale.edu ISSUE 172