

yale medicine magazine

Feeling good

Mental health and its opposite

Spring 2019

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Our fascination with what constitutes mental health (and its opposite) is as old as humankind. From the paintings in the Chauvet cave in southern France that merge animal with human images to discussions of biological versus cultural behavior in Plato's *Phaedrus*, and onward to Freud and Frankl, humans have questioned the meaning of healthy and sick, of consciousness and of conscientiousness. It has been neither an easy path nor a short one, but exciting new research may signal that physical answers are at hand.

In today's world, people are more broadly aware of the difference between wellness and mental illness—and science

has opened up impressive new opportunities to help people live more comfortable and productive lives. These developments have led to a widened definition of mental illness. And as the definition of mental illness has expanded along with opportunities to heal or cure formerly treatment-resistant conditions, the definition of mental health has contracted but become more precise. People know what mental well-being is, and are increasingly able to expect good health, whether it comes through nature, education, or medicine.

Advances in the neurosciences have brought a clearer view of what trauma can do to a brain, for instance. These new insights include the fact that

some individuals can absorb more damage than others (psychological resilience as well as physical ability to absorb concussions), and how that difference shapes what had been viewed as immutable personality traits, like susceptibility to depression and anxiety. Once considered a behavioral problem, the symptoms of traumatic psychiatric injury have been demonstrated to be both physical and treatable. Trauma and mental illness are now treated less as a source of shame (as they once were) and more like problems to be resolved through the attention and ministrations of experts. Even schizophrenia, recently seen as a kind of life sentence, is treatable, especially if diagnosed early.

This issue highlights the ongoing work of some of Yale's leading scientists in the fields of neuroscience and psychiatry. Nevertheless, with so many exceptional achievements accumulating in laboratories and clinics around the university, it is impossible to describe all of them. That is often the case with magazines like this, and I encourage readers who have knowledge of other research and researchers to reach out to us via email or letter. We welcome correspondence and enjoy sharing your recollections with others, both online and offline.

Adrian Bonenberger
Editor, Yale Medicine Magazine

SECOND OPINION BY SIDNEY HARRIS



"LEAD PAINT — THEY'RE BEING RECALLED."

Send letters and news items to

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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 YNH for Yale New Haven Hospital.

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The changing world of mental health

THE SCIENCE BEHIND MENTAL HEALTH has long been one of Yale's strengths. Robert J. Alpern, MD, dean and Ensign Professor of Medicine, talks about the direction of the field today and why society ought to do a better job of taking mental health issues seriously.

What are the key challenges facing people who need mental health treatment?

Mental health care has changed significantly since I entered medicine. Patients with significant mental health disorders were hospitalized for lengthy stays and the public probably envisioned those stays as being something like that described by Ken Kesey in the 1962 novel *One Flew Over the Cuckoo's Nest*. Now, most are treated as outpatients and there's more emphasis on medication, with less emphasis on psychotherapy.

What changed? In the past, mental health was viewed as a problem on the periphery of medicine that most physicians could not fully comprehend and wanted to avoid. An understanding of the neuroscience wasn't really there for drug development, nor was the technology sophisticated enough to image or treat chemical imbalances or physical trauma. We now realize that mental health is central to overall wellness. Mental health is a major concern for this country and the world. We don't treat it well at all and I think we're all aware of that now. We need to make meaningful changes.

Is there anything we can do to fix the system? The entire system is underfunded, to begin with, but the cost that it would take to really treat mental health disorders as they should be treated would be very large. Still, the costs to society of not treating these conditions have been and will continue to be enormous. The question of how serious we want to be about treating mental health is one of the great challenges we face as a country.

Does technology hold any hope for improved accessibility or treatment? The short answer is yes. The longer answer is that technology is always advancing, and the tools we've needed to diagnose underlying biological or chemical causes of mental health disorders are still being developed. Here at Yale we have an outstanding neuroscience program, an outstanding psychiatry department, and an outstanding neuroscience imaging program. I'm confident that our researchers will be playing a major role in making quality psychiatric care more available.

Will mental health be a right some day? It's hard to say that mental health is or will be a right. But I think it's a right to have access to the best mental health treatment. We need to significantly improve our treatments and patient access to those treatments.



New stem-cell cultivation procedure boosts hope for cures

WHEN THE TAYLOR LAB in Yale's Division of Reproductive Sciences extracted stem cells from human endometrial tissue—more commonly known as the uterine lining—the researchers were proud of their accomplishment. They didn't think the find was extraordinary, and they certainly didn't imagine that it might lead to treatments for a neurodegenerative condition. They were wrong—and happily so.

“The best discoveries throughout the history of science have not been predictable, have not always come out the way we anticipated they would, or the way we designed them to,” says Hugh Taylor, MD, HS '92, FW '98, chair and the Anita O'Keefe Young Professor of Obstetrics, Gynecology, and Reproductive Sciences, and professor of molecular, cellular, and developmental biology. “That's the real excitement in science—when it doesn't follow the predicted path, when you get a surprise.”

The surprise, in this case, wasn't finding the multipotent stem cells but finding their proclivity to differentiate into dopaminergic neurons: the brain cells whose loss in

Parkinson's disease leads to tremor, speech difficulty, poor balance, and a host of other symptoms. A reproductive sciences laboratory like Taylor's is not where one would expect to find a treatment for Parkinson's disease.

“There certainly aren't dopaminergic neurons in the uterus,” Taylor says.

Though unintended, the discovery has been serendipitous and is unfolding quickly; so far, the team has demonstrated the neurons' ability to boost fallen dopamine levels

in mouse and primate models of mild Parkinson's disease. In future studies, the team hopes to examine more severe forms of the disease to identify the therapy's effects on physical symptoms beyond improving dopamine levels.

The stem cells' tendency to differentiate into dopaminergic neurons is as yet unexplained, but Taylor and his colleagues have also coaxed the cells into becoming insulin-producing beta cells. Trials in mouse models have used endometrial stem cells to produce beta cells that continued producing insulin and stabilized blood-glucose levels within five weeks when injected into diabetic mice.

Taylor credits the cascading discoveries not only to his team and colleagues in other departments but to the collaborative atmosphere that facilitates the researchers' interactions.

“For each of these applications [of endometrial stem cells], we found the world's expert right in our backyard,” he says. “You have world-leading experts in these diseases right down the hall, or in the building across the street, who are more than glad to help advance colleagues' research as collaborators.” It helps that stem cells are a valuable currency across all of medicine because of their unique ability to produce myriad different cell types—when given the right environment. The endometrium, regenerating month by month for years, is just such an environment.



Hugh Taylor hopes that the new procedure for sustainably harvesting stem cells will lead to extraordinary new developments in personalized medicine, and aid in further medical research into how cells differentiate.

While adult stem cells reside in many different tissues, finding and extracting them in great numbers is challenging and—in all instances but one—invasive. The endometrium is the only tissue from which adult stem cells can be retrieved via a routine office-based procedure without anesthetic. This source is not limited to women of reproductive age, either: estrogen treatment can stimulate endometrial growth in women of all ages. Treatments that use a patient's own cells are attractive because they eliminate the risk of tissue rejection. Taylor envisions tissue banks that would use material retrieved from hysterectomies

to obtain additional stem cells. These could then be used to treat people without a uterus.

“There are tremendous applications in almost all fields of medicine. I think the sky's the limit, really,” Taylor said. “Any disease where cells become defective or die, we can consider using stem cells to replace them.” Parkinson's disease and diabetes are only two of thousands of medical conditions that could one day be treated—or cured—with cell-based therapies.

“Stem cell research has shown potency; it has tremendous potential,” Taylor said. “I think that cell-based therapy can do things that drugs could never do, and I think we'll see a lot more cell-based therapies on the horizon.”

—Natasha Strydhorst



Vectors: An insect variation on viral visitations

Few scientists view the immune system as a binary between human and nonhuman infection. In many cases—dozens known for certain to science, and likely thousands or millions given the variety of life forms in animal bodies—bacteria and viruses have evolved along with more complicated organisms, becoming inextricably linked to health. It may not be accurate to describe these ancient intruders as separable from a “healthy” body—although, strictly speaking, they are undeniably infections.

The human immune system and its bacterial allies aren't the



ONLINE EXCLUSIVE

Surgical residencies based on the methods of William Steward Halsted have long been the gold standard for aspiring surgeons. They've also been very hard on the physicians who go through them, and the idea of single-minded devotion to craft may have contributed to physician burnout and addiction later on in life. Current surgical faculty at YSM are pushing to change how surgical residencies function... for the better.

For more on surgical residencies, visit ymm.yale.edu/surgicalres

only line of defense against hostile diseases, though. As scientists reevaluate what constitutes immunity on an individual level, the health of vectors, the means by which hostile viruses and bacteria are transmitted into human bodies, has taken on a new significance.

“A vector is an organism that serves as a necessary intermediary for human disease, or other animal diseases,” says Leonard Munstermann, PhD, a senior research scientist in epidemiology (microbial diseases) at the Yale School of Public Health. Munstermann focuses on population genetics and taxonomic relationships among the 400 species of South American phlebotomine sand flies, some of which are responsible for spreading leishmaniasis.

Past efforts to control vectors have included wildly destructive assaults on the environment. Alongside developing medical technology, ecological awareness has led to other ways to affect vectors. Most recently these include attempts to strengthen their immune systems against infection. Researchers hope to preserve animals and microbes that may be crucial to the food chain in some manner that isn't understood today while removing the threat that they pose to human populations.

“Especially for the parasitic protozoans, which have few convenient antibiotic cures, targeting the vectors themselves is a promising route for

researchers,” says Munstermann. “Sand flies, mosquitos like the dreaded Asian Tiger *Aedes albopictus*, ticks, tsetse flies, and other arthropods harbor within them a host of debilitating diseases that are anathema to human health.”

A longtime source of illness and debilitation for humans, ticks are a vector that has rebounded as New England farmland has receded and forests have regrown. Sukanya Narasimhan, PhD, FW '93, a senior research scientist in the Section of Infectious Diseases, studies the microbiome of the deer tick in collaboration with Erol Fikrig, MD, FW '92, the Waldemar von Zedtwitz Professor of Medicine (Infectious Diseases), professor of epidemiology (microbial diseases), of microbial pathogenesis, and chief of the Section of Infectious Diseases. Together the two researchers hope to identify ways to reduce the tick's ability to host pathogens that are dangerous to humans and human-adjacent animals.

Narasimhan says that as evidence mounted about the mammalian microbiomes and their impact on human health, “We wondered if ticks might harbor microbiota, and if their indigenous bacteria affect the tick, how it acquires pathogens, and how it passes them on to us.”

She adds, “Tick prevalence doesn't necessarily mean infection prevalence, so there could be parts of the United States where you have a lot of ticks, but infection is not very high. This

is also the case with mosquitoes in India. Many factors, intrinsic and extrinsic, influence infection prevalence—this is complex. We wanted to examine whether the tick gut microbiome might represent one factor, and if shifts in the tick's microbiome might contribute to the tick's ability to host and transmit the pathogens.”

Research conducted by several groups into the lives of African mosquitoes suggests that mosquitoes' gut microbiota influence the survival of their malaria-causing parasites. Articles published in the last decade uncovered correlations between bacteria present in arthropods like *Aedes aegypti* and resistance to such deadly pathogens as (in the case of *Aedes aegypti*) the dengue virus.

Narasimhan and Fikrig's efforts indicate that the microbiome of ticks does play some role in ticks' “health” in the context of how they acquire pathogens and how they molt, but the researchers are still working to establish the precise nature of that role, as well as which microbiota or subset of microbiota observed in ticks might play a significant role.

Ultimately, Fikrig and Narasimhan hope that if we understand how the tick microbiome influences tick-borne pathogens, it may be possible to leverage that knowledge to reduce the prevalence (if not the virulence) of tick-borne diseases.

Serap Aksoy, PhD, FW '88, professor of epidemiology

(microbial diseases) in the Yale School of Public Health, has battled the protozoan parasites that cause African trypanosomiasis (more commonly known as “African sleeping sickness,” which is fatal if untreated) for decades. Her research into the insect vector primarily responsible for spreading the disease—the tsetse fly—has resulted in numerous breakthroughs: most recently, a mechanism that reduces the fly’s ability to transmit disease-causing trypanosomes.

“One of the more interesting characteristics of the tsetse fly is its mode of reproduction,” says Brian Weiss, PhD, FW ’08, research scientist and lecturer in epidemiology (microbial diseases) in the School of Public Health. Weiss, who works in Aksoy’s lab, knows a great deal about the topic. “Tsetse flies reproduce through a process called adenotrophic viviparity, which means gland-fed live birth. In this situation, embryonic and larval stages (one per reproductive cycle) occur within the mom’s uterus, and the larva receives nourishment in the form of milk secreted by a modified accessory gland.” In contrast, almost all other female insects will lay a clutch of fertilized eggs into their environment and hope that a couple of them reach sexual maturity.”

Aksoy and her research team discovered that tsetse milk also contains symbiotic bacteria that mediate numerous aspects of the fly’s physiology. One of these

microbes, the *Wigglesworthia* species (named after the famous British entomologist who first described it) shares an obligate association with its tsetse host. Without *Wigglesworthia*, which produces essential nutrients missing from tsetses’ vertebrate blood specific diet, adult flies present a severely compromised immune system and are reproductively sterile. This research provides useful insights for developing control strategies aimed at reducing tsetse population size and/or inhibiting the fly’s ability to transmit trypanosomes.

Tsetse flies house other symbiotic bacteria that may also reduce disease transmission. “Most tsetse flies harbor a commensal bacterium from the genus *Sodalis* (which means ‘companion’ in Latin) that, similar to *Wigglesworthia*, is passed from mother to larva via milk. This bacterium can live outside of its host and be genetically modified. If we can customize *Sodalis* to produce a trypanocidal protein, and then return these bacteria to the fly, they may become more resistant to infection,” says Aksoy. These characteristics make *Sodalis* an attractive target for research.

“We’ve designated insects that carry genetically modified symbionts as ‘paratransgenic,’” says Aksoy. “And one of these days, they might help wipe out some of humanity’s most prolific killers.”

—Adrian Bonenberger



Turning the page: The transformation of the Medical Library

When John Gallagher, the director of the Cushing/Whitney Medical Library (CWML), arrived at Yale nearly two decades ago, the bustling information hub of Yale School of Medicine actively received 2,600 individual scientific journal titles in print format. The newest journal issues were shelved in the Morse Reading Room, while older issues, bound in volumes, occupied entire floors of space in the journal stacks on the basement level. Researchers photocopied articles and library staff reshelved thousands of bound volumes each week. But there was a digital revolution in the offing: within five years, that list of 2,600 titles had dwindled to around 100. It has continued to drop; these days, the library receives just a handful of print journals. Students and

Part of the effort to stop diseases involves protecting humans from infection. Rather than killing vectors with such ecologically harmful procedures as spraying against mosquitoes or ticks, another approach researched in places like Yale involves protecting those insects from the diseases they carry.



ONLINE EXCLUSIVE

A recent graduate of Yale is working on blended and augmented reality technology in cooperation with YSM faculty, that could revolutionize how patients with problems seeing (such as the blind) interact with their surroundings.

For more on blended and augmented reality technology, visit ymm.yale.edu/blendedreality

researchers, however, have never had greater access to biomedical literature, as they now have digital access to some 23,000 library-licensed journals. The fact that these journals take up virtually no room has been a game-changer for CWML and YSM.

“The transition from print to electronic has freed up an enormous amount of space, and it’s given us a chance to think about the best way to use it,” says Gallagher. “This has been a great opportunity and we’re really excited about it.”

The library teamed with Richard Belitsky, MD, HS ’82, FW ’83, the Harold W. Jockers Associate Professor of Medical Education and deputy dean for education; Michael Schwartz, PhD, associate dean for curriculum and associate professor of neuroscience; and other administrators at the medical school to come up with an innovative project that marries the library’s core mission as a center of learning with ongoing curriculum reform.

Signs bearing the image of “Hard Hat Harvey” Cushing began appearing in the library’s halls and on its website last summer. Since then, the quiet is sometimes broken during the day by Petra Construction Corporation workers tasked with gutting and transforming much-used and now cordoned-off areas of the first floor, basement, and sub-basement. (Many sections of CWML, such as the Morse Reading Room and the Historical Library, are not part

of the renovation.) When the last literal hard hats finish up work in June 2019, the reengineered space will be home to a team-learning classroom that can accommodate 120 students; eight smaller classrooms; a quartet of group-study rooms; and an information commons equipped with 30 computer workstations, a faculty video-production studio, and the offices of several librarians.

“Our students come from an era in which they have rapid access to information, a high reliance on technology, and an emphasis on interactive learning,” says Belitsky, “and the curriculum we implemented in 2015 is designed to reflect that. But if you change your pedagogy, you need different spaces that can better carry out these new ways of teaching.”

The old model—the learned professor standing at a lectern and dispensing wisdom to acolytes frantically scribbling down every fact—has been set aside in favor of the “flipped curriculum” model. This model requires a team-learning classroom in which students gather around tables in groups of about a half dozen. Medical students will have already read and mastered an assignment or absorbed a professor-created video, and they’ll come to class to work with their peers on projects overseen by their teacher, to implement what they’ve learned, and to share and debate their ideas in real time.

“Medicine today is a team-based endeavor,” notes

Schwartz. “Our new curriculum reflects this reality, and the new classroom gives us an effective space for helping our students develop the perspective and expertise to work this way. Learning is less about facts and more about the process of evaluating and applying information, so it makes a lot of sense to center this in the library.”

The renovated spaces also are designed to better implement a team-based interactive approach, and the planners were mindful of crafting a facility that would be flexible and useful to the wider School of Medicine community after the students leave the rooms. “The challenge was adopting the area for teaching while at the same time preserving the history and charm of the library,” says Schwartz.

The result will be a suite of places that can serve as both classrooms and after-class spots for study; such community education opportunities as lectures and seminars; and social gatherings. The library still acquires and shelves books and remains home to one of the world’s most impressive medical-historical collections. “When this is done, we’ll be able to connect people with information in ever more sophisticated and effective ways,” explains the Medical Library’s associate director, Holly Grossetta Nardini, “and we’ll preserve the kind of serendipity that often results when people interact.”

Adds Schwartz: “This is a nice win-win partnership.”

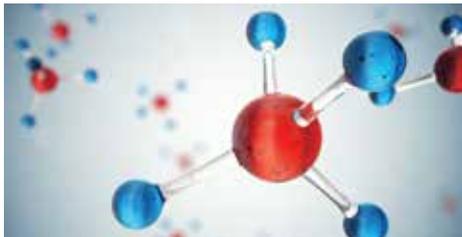
—Bruce Fellman

round up

a collection of recent scientific findings

SUICIDE RISK IN THE GENOME

People have long understood that having a suicide in one's family elevates other members' risk of suicide in ways that haven't always been tangible or understood. Now, scientists at Yale, including Joel Gelernter, MD, the Foundations Fund Professor of Psychiatry and professor of genetics and of neuroscience, and Daniel Levey, PhD, have identified genes linked to suicide attempts in different U.S. populations. They hope to broaden the investigation by evaluating data collected through the Department of Veterans Affairs' Million Veterans Program (MVP). The suicide rate among veterans has grown in recent years, and reducing it is a priority for health care administrators.



ELECTROSPRAY INNOVATION DRIVES SCIENTIFIC ADVANCES

At the University of Minnesota in 1911, physicist John Zeleny, who also worked at Yale during World War I, developed an apparatus called "electrospray" to study electrical discharge in gases. Electrospray involves driving fluid through a tiny aperture; the resulting mist can then be evaluated at the molecular level. Alessandro Gomez, PhD, and Juan de la Mora, PhD, both professors of mechanical engineering and materials science, continue this line of inquiry. One successful collaboration involved working with the lab of Tarek Fahmy, PhD, associate professor of biomedical engineering and immunobiology, to synthesize nanoparticles for the delivery of cancer drugs.



GIVING THE ELDERLY THEIR VOICES BACK

The Department of Emergency Medicine at Yale School of Medicine is working on a project designed to serve a traditionally underserved and systematically exploited population: the elderly. One in 10 Americans over the age of 60 is mistreated in some way, and VOICES (Virtual cOaching in making Informed Choices on Elder mistreatment Self-disclosure), funded by a \$1.5 million grant from the National Institute on Aging, will help victims report physical, emotional, financial, or sexual abuse and seek assistance.



IN-PERSON SOCIAL NETWORKS AFFECT THE MICROBIOME

As scientists investigate the human microbiome, efforts are underway to step back and understand how various human microbiomes affect each other during face-to-face social interactions. Led by Nicholas Christakis, MD, MPH, PhD, Sterling Professor of Sociology, and funded by a \$3.54 million grant from the NOMIS Foundation, the Microbiome Biology and Social Networks in the Developing World project will gauge how our friends' and relatives' health affects our own—on a bacterial level. When Mom said, "Wash your hands before dinner," she wasn't saying it just for your own good, but for hers too!

Feeling good

Mental health and its opposite

THE THIRD EDITION of the *Diagnostic and Statistical Manual of Mental Disorders*, published in 1980, was the first to describe psychopathy as antisocial personality disorder (or APD/ASPD). This diagnosis depended on decades of studies, professional conversations, and advances in neuroscience and technology. Eventually, scientists determined that the condition is neither a moral failing nor (for the most part) a failing of society, but rather the result of a combination of genetic and social influences. Since 1980, the standard by which professional physicians judge whether someone is a psychopath has expanded but not changed fundamentally. Meanwhile, researchers have inched closer to understanding the underlying causes of mental disorders in people previously described as “crazy”... and how to treat those causes.

An evolving idea of what drives mental illness informs mental wellness. And a great many advances in that field are unfolding at Yale School of Medicine. Phil Corlett, PhD, FW '10, and Albert Powers, MD, PhD, HS '16, use research with psychics to better understand the root causes of hallucinations common in schizophrenia. Lynnette Averill, PhD, FW '15, is involved in trials overseeing the prescription of ketamine to heal patients suffering from post-traumatic stress disorder, expanding on pioneering research conducted by John Krystal, MD '84. Emma Lo, MD, a fourth-year resident in the department of psychiatry, takes this research and applies it on the clinical level to a population that disproportionately suffers from mental illness, people experiencing homelessness.

These stories and more examine experts' role in triangulating the causes of diseases and genetic conditions. Resolving biological mysteries is at the heart of contemporary mental health research. So much of what's exciting in the field involves technological advances at Yale that pose new questions and answer old ones.

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Rethinking mental illness

A look at the state of mental health and its inverse, mental illness, from prominent Yale School of Medicine faculty and researchers from the departments of psychiatry and neuroscience.

BY STEVE HAMM

Albert Rivera has had a hard-luck life. As a child, he experienced physical and emotional abuse. Now 38 years old and living in New Haven, he suffers from post-traumatic stress disorder (PTSD) and is in recovery from alcohol and opioid abuse. To top things off, he's in transitional housing—without a dependable roof over his head.

Yet Rivera has hope for his future. He holds a job and he stays on an even keel by participating in two programs run by Yale School of Medicine. One helps people with mental illnesses deal with the stresses of life, and the other enables them to play positive roles in the community. “They help me cope,” Rivera says. “They gave me a purpose and made me part of something bigger than myself.”

The programs are examples of an emerging trend in the treatment of mental illnesses called recovery-oriented care and citizenship. The idea is that helping people cope with their illnesses and live productive lives as valued members of their communities is an essential part of their care—alongside medications, talk therapy, and other treatments.

Recovery-oriented care and citizenship are part of a major rethinking of mental illness and care that is

now underway nationwide. Until recently, the primary focus among mental health professionals has been on identifying therapies that suppress the symptoms of disease and administering those therapies in a clinical setting. Increasingly, though, researchers are focusing on understanding the core causes and mechanisms of mental illness, and clinicians are helping their patients grapple with the social determinants of health while developing a sense of belonging in their communities.

In a sense, mental health care is being redefined—becoming ever more precise and personalized in the biological research sphere and more holistic and patient-centric in the way treatment is provided. “We need to think differently about psychiatry than we have in the past,” says John Krystal, MD '84, HS '88, the Robert L. McNeil, Jr. Professor of Translational Research, professor of psychiatry and of neuroscience, chair of the Department of Psychiatry at Yale School of Medicine, and chief of psychiatry at Yale New Haven Hospital. He believes the department will play a significant role in advancing science, improving care, and training the next generation of leaders in the field.

Progress is sorely needed. That's because the state of mental health in the United States is poor. Nearly 20 percent of the population, or about 60 million people, suffer from some type of mental illness each year. More than 24 million people struggle with substance abuse.

The treatment of mental illness has undergone waves of change over the past 100 years. The field was defined in the early- to mid-20th century by mass institutionalization, poorly informed use of lobotomies, and the dominance of psychoanalysis. Over time, those approaches gave way to deinstitutionalization, rapid proliferation of drug treatments, cognitive behavior therapies, and now psychosocial interventions, including recovery-oriented care.

Understanding of the causes of mental illness has evolved as well. Psychiatry pioneer Sigmund Freud posited that mental illness is caused by conflicts between different parts of the mind resulting from childhood trauma. Later, leaders in the field came to believe that mental illness is the result of disruptions in biological processes. Now psychiatrists increasingly recognize the powerful impacts poverty and other traumatic life experiences have on mental health. "Each view has enriched the picture. They complement each other in explaining mental illness and fostering new treatment directions," says Michael Sernyak Jr., MD, HS '91, professor of psychiatry and CEO of Connecticut Mental Health Center (CMHC).

Yale has long been recognized as a national leader in psychiatry. Today its psychiatry department is one of the largest in the country, with more than 350 faculty members. Yale's partnership with the VA Connecticut Healthcare System has produced numerous advances in PTSD treatment. Its joint venture with the state in CMHC provides psychiatric care for more than 5,000 economically disadvantaged people each year. Yale Child Study Center is renowned for research and clinical care. And the Interventional Psychiatry Service at Yale New Haven Psychiatric Hospital is a leader in providing people with severe mental illness with access to the latest experimental treatments.

NEW DIRECTIONS IN THE BIOLOGY OF MENTAL ILLNESS

Breakthroughs in understanding human biology in the mid-20th century led to the development of medications

for mood disorders and psychosis—alleviating suffering for millions of people. Yet most of the “wonder drugs” introduced during that era addressed the symptoms rather than the causes of disorders.

A new wave of biological research spanning neuroscience and genetics is deepening our understanding of mental illness's underlying biology. This research promises to deliver a new generation of medications and treatments that target causes. “This is opening up a whole host of new treatment options,” says Gerard Sanacora, MD, PhD, HS '98, FW '99, the George D. and Esther S. Gross Professor of Psychiatry and director of the Yale Depression Research Program.

One of the major breakthroughs in this area came in the 1990s when Krystal and colleagues discovered that the drug ketamine, an anesthetic, could provide a fast-acting treatment for depression. Previously, antidepressants had focused on suppressing unruly chemicals in the primitive parts of the brain. But ketamine targets the chemical glutamate in the neocortex, where memory and thought reside. The drug treats a cause rather than a symptom. The hospital now offers experimental ketamine infusion therapy for depression.

These days, research labs within the School of Medicine are using neuroimaging and genetics to probe deeper into the workings of the brain. One lab, run by Ronald Duman, PhD, FW '88, the Elizabeth Mears and House Jameson Professor of Psychiatry, professor of neuroscience, and director of the Abraham Ribicoff Research Facilities at CMHC, has been studying ketamine to better understand the pathophysiology of depression. His team discovered that for some individuals, chronic stress and depression cause atrophy and loss of synapses, reducing connectivity in the brain. Ketamine promotes the growth and vitality of synapses. “We're learning more about how the brain works,” says Duman.

One of the team's primary goals is to discover alternative therapies to ketamine that don't carry the drug's negative side effects, such as hallucinations.

As researchers probe the brain, they're making discoveries that may lead to a reclassification of mental illnesses. Today, psychiatrists refer to the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5) to make their diagnoses. Its classifications of disorders are based primarily on observations of behavior. Increasingly,

researchers find that the phenomena they observe in the brain do not line up with DSM diagnoses. There's too much overlap to separate these phenomena into strict categories. As research advances, it may turn out that many illnesses have the same causes, such as stress and inflammation—leading to new treatment strategies.

Because of the ever-increasing role of neuroscience in psychiatry, the Department of Psychiatry's residency program has evolved to include training in applying neuroscience to clinical practice. "The goal is to help clinicians arrive at more accurate diagnoses

HELPING PATIENTS LIVE IN THE WORLD

In 1977, two women in Madison, Wis., Harriet Shetler and Beverly Young, met for lunch to discuss the challenges faced by their sons, who had been diagnosed with schizophrenia. That fateful meeting marked the beginning of the mental-health patients' advocacy movement, which has pushed the psychiatric community to provide care that respects patients' rights and wishes. Out of that shift in perspective came recovery-oriented care.

The core idea is that people with mental illness can recover even though they're not "cured." They can live

Chyrell Bellamy

“We need leaders with lived experience at the table so that we can together transform health care organizations.”

and to communicate better with patients about what's going on," says David Ross, MD '05, PhD '04, associate professor of psychiatry, who led the initiative.

Rather than relying on traditional lectures, the curriculum includes videos, interactive exercises, and resources for self-directed study.

Ross, working with colleagues at Columbia University and the University of Pittsburgh, discovered that few residency programs around the country were incorporating neuroscience into how they taught psychiatry. To address that gap, Ross' group created the National Neuroscience Curriculum Initiative (NNCI), which offers a comprehensive set of teaching and learning resources, many of which were first implemented at Yale. Today, more than 100 residency programs use the curriculum, and the website has 36,000 registered users from 153 countries.

satisfying lives—holding jobs, enjoying their families, and contributing to society. "These interventions are aimed at the recovery of daily function and life. The focus is on helping a person have the kind of life they want," says Larry Davidson, PhD, FW '92, professor of psychiatry and director of the Yale Program for Recovery and Community Health (PRCH).

His organization does research, training, and policy development aimed at equipping health care and social service agencies to support recovery-oriented care. It also runs experimental programs in New Haven that provide direct support for patients—including person-centered care planning and community-based recovery programs.

The ultimate goal of recovery-oriented care is achieving wellness—improving mental and physical health by expanding awareness and making better choices in all

dimensions of life. Wellness is not the absence of illness or stress; it's making the best of one's situation.

Citizenship adds another dimension, recognizing the rights, responsibilities, roles, resources, and relationships necessary for contributing to community on one's own terms, often through involvement in collective endeavors.

A lot of the work being done at PRCH is practical and utilitarian. The programs help people get jobs and diplomas. CMHC, for instance, provides bicycles for some of its low-income patients, enabling them to get to appointments and jobs on time, and improving their physical fitness and self-esteem.

There's also a strong emphasis on heeding the wishes of the patient. For instance, a person may choose to forgo a medication that suppresses their symptoms because it also makes them groggy, interfering with their ability to work and socialize.

A key element in such programs is the role of peers—individuals who have experienced mental illness and/or substance abuse who advise and guide patients as they navigate their recovery. A peer-support staff member in New Haven, Richard Youins, helps run a weekly discussion group at CMHC and coordinates Magicians Without Borders, which teaches people magic tricks they can use as icebreakers when they tell their stories in public. “When I was in addiction, if somebody had told me I would someday have a job where I was doing good things for other people, I would have laughed. But it happened,” he says. “We're all walking, breathing possibilities.”

Studies of the PRCH programs have shown that peer support reduced hospital readmissions by 42 percent, reduced hospital stays by 48 percent, and improved relationships with health care providers.

The School of Medicine is also helping people in recovery play roles in reforming the mental health care system. Lived Experience Transformational Leadership Academy, a nine-month training program, prepares people to develop and enhance their capacity for leadership. “We need leaders with lived experience at the table so that we can together transform health care organizations,” says Chyrell Bellamy, PhD, MSW, associate professor of psychiatry and director of Peer Services and Research at PRCH.

In order to equip future psychiatrists to provide recovery-oriented care, the Department of Psychiatry has developed a robust social justice and health equity program within the residency curriculum. “We can predict more about a person's health from their ZIP code than their genetic code, so we need to train residents about implicit bias and the roles of communities in mental health,” says Robert Rohrbaugh, MD '82, HS '86, FW '88, professor of psychiatry and deputy chair for Education and Career Development.

The social justice and health equity program takes residents out of the classroom and clinic into New Haven's neighborhoods, where they learn how such factors as housing, employment, transportation, and neighborhood gardens can be barriers to health or help improve it.

For Hana Ali, MD, a second-year resident, the program was a revelation. A guided tour last year of the New Haven neighborhood where she lived took her under the surface to understand the experiences of her neighbors. “It told me there are lived experiences of the patient we take care of that we have no idea about. In order to care for a person, you need to get a full sense of them—what their lives are like,” she says.

Along both vectors where mental illness is being rethought, the biological and the behavioral, researchers and clinicians are gaining knowledge rapidly. “It is wonderfully stimulating to work in a community where the issues arising from basic science, the clinic, and the community converge,” says Krystal.

Huge challenges remain. The mechanisms of the brain are amazingly complex and difficult to interpret. The interactions of individuals with others and society are so varied. There are many stressors in modern life.

Yet School of Medicine faculty members are optimistic that new scientific discoveries and new approaches to treatment will improve the lives of those who suffer from mental illnesses. “We'll have breakthroughs. It's what we are as a species,” says William Sledge, MD, HS '75, the George D. and Esther S. Gross Professor of Psychiatry Emeritus, who was for many years the medical director of psychiatry at the hospital. “We will find a way.” [/yale medicine magazine](#)

Steve Hamm is a frequent contributor to Yale Medicine Magazine.

Armoring the psyche: A brain's resilience

Studies indicate that people whose brains are “wired” for resilience can also receive training that further fortifies them against psychiatric trauma.

By John Altavilla

What makes one human predisposed to suffer from stress and another comparatively immune? Doctors, researchers, and philosophers have wrestled with this question for decades. Answers have been hard to come by, and are anecdotal at best.

Rajita Sinha, PhD '92, the Foundations Fund Professor of Psychiatry, professor in the Yale Child Study Center, and professor of neuroscience, has long been fascinated by the fickle nature of mental fortitude. Her studies focus on the characteristics of the brain that determine resilience.

Sinha believes she has found the answer. Working with colleagues, she assessed the brains of 30 subjects who presented no prior physical or emotional issues. The subjects were exposed to horrific images for a few minutes, then to photos unlikely to provoke an emotive response.

Her study revealed how the brain reacts under stress, and what it does to adapt and be resilient in response. Findings show brains have a specific resilient coping circuit involving a key medial prefrontal region tucked behind the forehead, which slowly activates during stress (such as exposure to grotesque visual images) and helps calm other stress responses. Brains that demonstrated this signal during testing exhibited resilient coping behaviors. Those without the signal tended to engage in nonresilient behaviors for coping, such as avoidance (deferring or evading an unpleasant task or event that evokes previous trauma).

This finding provided an explanation as to why some people may exhibit greater innate resiliency. Those people may be wired to respond effectively to stress, while some others aren't. The benefits extend to training: These brain regions can learn and be trained to increase that capacity.

“There are certain basic things we know that work for the brain, if you think about resilience. We know that having warm, loving parents is absolutely necessary for a developing brain,” says Sinha. “Studies have shown that trauma and neglect, both emotional and physical, are not good for the brain.”

Resilience is one's ability to recover from a horrible injury, tragedy, or exposure to stressors. Those who are resilient are better able to endure hardship. Those without this characteristic are more likely to develop such stress-related illnesses as depression, anxiety, obesity, heart disease, addiction, and even some types of cancers.

Psychological resilience correlates with positivity, and training oneself to think positively increases one's innate resistance to anxiety and depression.



Breaking the cycle of traumatic memories

Trials offering ketamine doses to patients suffering from post-traumatic stress disorder give some veterans hope that they can live a normal life.

BY COURTNEY MCCARROLL

After returning home from active duty, soldier Bassheva Trenk felt as though something significant had shifted inside. Afflicted with intense despair, tortured by lack of sleep and vivid nightmares, Trenk was unable to function in her everyday life. Even a trip to the grocery store left her feeling on edge, hypervigilant, and fearful of anyone standing too closely behind her in the checkout line.

“When I got out of the Army, I was in a state of complete misery. I had no idea how I was going to get through,” says Trenk. Removed from the comfort and familiarity of home and reeling from the effects of trauma, Trenk struggled considerably.

Even under ideal conditions, military service takes a toll on one’s mental health. War, combat, toxic leadership, and other traumas all challenge the wellness of service members and—unfortunately—are not uncommon. Coupled with an individual’s mental makeup prior to enlistment, prolonged periods of extreme mental, emotional, and physical stress can increase the risk of developing post-traumatic stress disorder (PTSD).

Although PTSD can manifest in a multitude of ways, this debilitating anxiety disorder is typically triggered by an especially harrowing event—usually one that the victim experienced directly or witnessed firsthand.

Memories or flashbacks of the event can haunt victims, leaving them feeling endangered, irritable, and afraid. The disorder can be so debilitating that for some, suicide seems like the only recourse. According to the U.S. Department of Veterans Affairs, 20 military veterans commit suicide on an average day—the majority of whom are veterans of the Vietnam War.

In her darkest hour, Bassheva Trenk came dangerously close to enlarging that tragic number. Fortunately, her attempt was forestalled. After Trenk recovered, a close friend begged her to seek help and graciously offered to cover Trenk’s living expenses until she could get back on her feet. This act of generosity allowed Trenk to find her way to Tim Amoroso, a staff affiliate of the VA Medical Center (VAMC) in West Haven.

Down the hall from Amoroso’s office, buried deep within the sprawling VA Connecticut Healthcare complex, flyers and pamphlets adorn the corkboard and visitor seating area, offering relief to veterans afflicted with treatment-resistant PTSD. Funded in part by the multi-institutional Consortium to Alleviate PTSD (CAP) and in partnership with the VA and Yale University, a team of researchers that includes Amoroso investigates a novel approach to treating the

disorder. It is one of the first clinical trials in the country to evaluate the effectiveness of ketamine, an anesthetic most commonly used in veterinary surgery, as part of PTSD therapy.

The CAP study traces back to a significant breakthrough made in the 1990s by John Krystal, MD '84, HS '88, the Robert L. McNeil, Jr. Professor of Translational Research, professor of psychiatry and of neuroscience, and chair of the Department of Psychiatry. Along with his colleagues at the time, Krystal discovered that ketamine has substantial and rapid effects on patients suffering from major depression. Later, Ronald Duman, PhD, FW '88, the Elizabeth Mears and House Jameson Professor of Psychiatry and professor of neuroscience; and George Aghajanian, MD '58, HS '61, FW '63, professor emeritus of psychiatry, found that ketamine's efficacy lies in its remarkable ability to restore synaptic connections in the brain. Dennis Charney, MD, HS '81, conducted a pilot study suggesting that ketamine may also reduce the symptoms of PTSD. With these pieces in place, the present CAP study was born.

Amoroso—a former Army Ranger (2-75th)—is recruiting active-duty personnel and veterans between the ages of 18 and 70 who have been diagnosed with PTSD but have had little success with their prescribed antidepressants. His goal is to enroll 100 participants. After they are cleared for the study, participants are then randomized into three separate groups: a placebo group (which receives a saline infusion); a low-dose group (which receives 0.2 mg/kg of ketamine); and a high-dose group (which receives 0.5 mg/kg of ketamine).

When participants like Trenk attend their infusion appointments at the VA, they are asked to complete a handful of surveys to establish their baseline mood and demeanor that day, participate in an interview, and discuss any notable side effects or adverse events since their last session. Once approved by the VA doctor on staff, their infusion begins; it lasts about 40 minutes.

“Ketamine is safe, well tolerated, and has a relatively minor side-effect profile (compared to the traditionally available antidepressants),” explains Lynnette Averill, PhD, an associate research scientist in psychiatry and member of the VA research team.

“I've seen people change before my eyes after an infusion—the tension in their face changes, their affect changes, and the next day they are hardly recognizable. It's exciting and rewarding work to witness this and be part of their journey.”

Chadi Abdallah, MD, FW '13, assistant professor of psychiatry, and his colleagues are very optimistic about the study thus far and look forward to assessing the comprehensive results in 2020. Ketamine's potential to create positive change in people's lives is enormous. “The success of the [study] may show that ketamine could be safely and effectively administered to veterans suffering from refractory PTSD,” says Abdallah. “It may potentially provide the required evidence to expedite the implementation of this investigational treatment across the VA health system.”

Although no longer in the study, Trenk still undergoes infusions once every month or so (in combination with her antidepressant medications), she credits ketamine with several positive changes. She reports being able to sleep more soundly, has noticed a significant reduction in the frequency and severity of her anxiety, and has even enrolled in a general-studies program at her local community college. With renewed confidence, Trenk has set her sights on a bright future.

“Ketamine has had an obvious impact on my life. When the effects start to fade away and my anxiety and aggression return, that's how I know how big of an impact it has had. I'm not 100 percent recovered, but I'm doing so much better now.” *yale medicine magazine*

Courtney McCarroll is a writer, and works as a program coordinator in Yale's development office.

Post-traumatic resilience

In U.S. veterans, social connectedness, optimism, and a sense of purpose are among the characteristics associated with bouncing back from trauma—sexual and otherwise.

By Ashley P. Taylor

Many think the biggest threat to military personnel is battlefield death or injury. While that is certainly true during wartime, the military spends much of its time training. And for U.S. veterans, sexual assault confers a greater risk of post-traumatic stress disorder (PTSD) than combat.

Robert Pietrzak, PhD, MPH, associate professor of psychiatry and director of the translational psychiatric epidemiology laboratory of the clinical neurosciences division of the National Center for PTSD in West Haven, studies veterans, PTSD, and resilience. According to his research, sexual assault comes with a 26 percent likelihood of developing PTSD if the trauma occurred during childhood and 36 percent if the trauma occurred during adulthood. About 10 percent of veterans have experienced sexual assault, the trauma most strongly associated with PTSD. In comparison, combat of any kind—which about 35 percent of veterans have experienced—comes with an approximately 19 percent risk of developing PTSD. However, this figure increases as a function of the intensity of the combat exposure—the most heavily exposed veterans have a 35 percent likelihood of developing PTSD.

These data about veterans, PTSD, and resilience come from the National Health and Resilience in Veterans Study (NHRVS), which Pietrzak and his colleagues have been conducting since 2011. In the NHRVS, nationally representative samples of thousands of veterans answer survey questions designed to learn about veterans' experiences with trauma, PTSD symptoms, and other factors. Researchers then analyze the data to determine which factors are associated with PTSD and which with resilience, or the ability to “bounce back” from trauma.

In addition to having experienced such types of trauma as sexual and physical assault, other factors that increase the risk of PTSD include being of younger age and female.

Nevertheless, many veterans rebound from their ordeals. Among veterans exposed to high levels of trauma of any kind, 70 percent are psychologically resilient; in other words, they do not exhibit symptoms of PTSD, depression, or anxiety.

“They basically look as if they hadn't been exposed to trauma at all,” says Pietrzak. His research investigates why it may be possible to use that knowledge to help others to bounce back.

Among veterans who participated in the NHRVS in 2011, those who felt they had strong social support and a sense of meaning and purpose in life were less likely to develop symptoms of PTSD, depression, or anxiety. Optimism and gratitude also correlated with greater ability to recover from these symptoms.



Taking psychiatric help to the street

BY STEVE HAMM

Last August, New Haven made the national news in a way no city wants when 72 people were poisoned by an illicit synthetic cannabinoid called AMB-FUBINACA. All over the New Haven Green, people who had ingested and/or inhaled the substance fell to the ground, convulsed, and lost consciousness.

Among those who rushed to help them was Emma Lo, MD, a fourth-year resident in Yale School of Medicine's psychiatry program and volunteer with a street medicine team.

Ambulances, police, and EMTs were scattered all over the green when she arrived. She knelt to aid a man who had just fallen and was seizing. After a moment, she recognized him as a former patient of hers at the Connecticut Mental Health Center (CMHC), where she had completed a residency rotation. Thinking that he was suffering an opioid overdose, she sprayed the emergency antidote naloxone up his nose. It didn't work. "I felt very helpless. I wanted to save him, but we didn't know what was going on," Lo says.

Luckily, nobody died. But stunned city government and health care officials developed a strategy for avoiding a repeat of that awful day. A number of the overdose victims were homeless, so the official response included creating one of the few street psychiatry teams in Connecticut and hiring Lo to spearhead it. "We're developing a program that can be scaled up if it's proven to be effective," says Jeanne Steiner, DO, medical director of CMHC and associate professor of psychiatry at Yale School of Medicine.

Lo has shown a deep concern for people experiencing homelessness ever since she began volunteering to help them as an undergraduate at Haverford College. "In New Haven, we're lucky to have a wealth of resources for people who live on the street, but there's a gap for people who are chronically mentally ill," she says. "There are clinics that offer mental health care but until now there was nobody going out to provide care where the people are."

While national experts estimate that about 25 percent of the homeless population suffers from severe mental illnesses, those who care for them say nearly all have some sort of mental disorder. "Some are homeless because of mental illness, and some are mentally ill because of the stress and trauma of homelessness,"

says Philip Costello, an advanced practice registered nurse who is the clinical director of homeless health care outreach for New Haven's Cornell Scott-Hill Health Center.

Lo had been volunteering on Costello's team for two years as they provided basic medical care for people experiencing homelessness—in parks, at soup kitchens, at shelters, and on the street. Costello says Lo has a low-key style that breaks down the barriers of distrust that many homeless people have for police and health care professionals alike. "These people are so marginalized and they only warm up to somebody who has the persona to be sensitive, genuine, and patient—and Emma is all of those things," says Costello.

Lo credits the residency program's practice of setting aside time for special projects with helping her get to where she is today. She crafted her own residency rotation with the street medicine team. Now, thanks to her, street psychiatry is an elective rotation for other residents.

Her journey is part of a major new emphasis in the psychiatry residency program—where social justice and health equity are increasingly baked into the curriculum. Residents interact with patients and community leaders throughout New Haven's neighborhoods. To raise their awareness, the residents even try to buy healthy meals with the \$2.10 per meal that the government provides for food assistance. "We're exposing the residents to structures in the community that affect health so they better understand the issues their patients face, can help provide more comprehensive patient care, and can advocate for change," says Robert Rohrbaugh, MD '82, professor of psychiatry and residency program director.

"Every resident could benefit from this experience," Lo says. "It has taught me so much about understanding people—not just their physical and mental health but their whole environment, the social determinants of health. Ultimately, you're learning empathy."

/yale medicine magazine

Steve Hamm is a frequent contributor to Yale Medicine Magazine.



Brain bank aids theories on genetics and post-traumatic stress disorder

BY JENNY BLAIR, MD '04



Yale researchers use a massive brain-tissue repository, or “brain bank,” at the VA’s National Center for PTSD to postulate generalizations about the genetic origins of the condition and its physiological characteristics.

The nightmarish experience of post-traumatic stress disorder (PTSD) may be as old as danger itself. Survivors of natural disaster, criminal and domestic violence, and combat or granted formal psychiatric designation only in 1980. PTSD continues to pose a formidable challenge to treatment. Guidelines are derived more often from expert opinion than from trial results and only two medications were FDA-approved as of late 2018.

Now, drawing on a “brain bank” as well as a massive study of veterans, researchers at the School of Medicine are mapping PTSD’s genetic and neurobiological underpinnings. Their efforts could help predict who is susceptible, point the way to better treatments, and perhaps teach people how to cultivate resilience.

The aim of these studies is to move from the art to the science of psychiatry, says John Krystal, MD ’84, HS ’88, the Robert L. McNeil, Jr. Professor of Translational Research, professor of psychiatry and of neuroscience, chair of the Psychiatry Department, and director of the Clinical Neuroscience Division of the VA National Center for PTSD. To date, most PTSD research has been psychological, not biological, so the field has some catching up to do.

“Almost everything that we’re doing is the first of its kind,” Krystal says.

These studies are not merely groundbreaking, they’re vast in scale. So far, some 600,000 veterans have contributed DNA to the nationwide Million Veteran Program (MVP). With this database—one of the world’s largest—researchers can detect subtle signals across thousands of genes.

Joel Gelernter, MD, the Foundations Fund Professor of Psychiatry, professor of genetics and of neuroscience, is co-leading a study of this population to uncover genetic alterations that show up more often among trauma-exposed vets with PTSD. These data could one day help estimate individuals’ risk of PTSD based on their genes, allowing the military to predict that when exposed to combat, person ‘A’ has, say, a 20 percent risk of developing PTSD while person ‘B’ has only a 5 percent risk.

“Should that affect the role that the person is placed in by the military? Is this something we should tell the person, so that he or she can make a decision about the kind of stresses he’s willing to be exposed to?” Gelernter asks. “Those are open questions, but they’re things we’ll be facing—if not in the next year, in the next five years.” Further, he says, “the genetic information will also aid us in understanding the factors that underlie PTSD on the one hand and resilience on the other.”

In 1995, then-faculty member Douglas Bremner, MD, used MRI to discover the first evidence of changes in brain structure in PTSD—a shrunken hippocampus in a group of Vietnam War veterans diagnosed with the disorder. The hippocampus, one of several brain regions involved in PTSD, helps researchers interpret loci in the brain as vulnerable trauma or not.

Thanks to a brain-tissue repository, or “brain bank” of PTSD patients, researchers can now explore the differences between brains from people with PTSD and those without. The National PTSD Brain Bank is housed within the National Center for PTSD (NCPTSD) and the Boston VA Medical Center. The clinical neuroscience division of NCPTSD is based at the VA Connecticut Healthcare System and the Yale School of Medicine;

it serves as the primary research laboratory for the National PTSD Brain Bank.

Instead of studying genetic alterations like Gelernter and his colleagues, Ronald Duman, PhD, the Elizabeth Mears and House Jameson Professor of Psychiatry and professor of neuroscience, is examining the activity of thousands of genes by measuring the mRNA transcripts and proteins those genes express in hotspot brain regions.

By comparing differences in gene expression in the brains of patients who were diagnosed during their lives from PTSD, those who had major depression, and those who did not receive a psychiatric diagnosis, researchers hope to illuminate where PTSD overlaps with other

would actually target these networks and hub genes,” Duman says.

Given how few PTSD medications we currently have, new ones would be no small advance. But as we map the disorder’s genetic and protein correlates, we’re likely to learn more about the origins of resilience, too. In its way, resilience is as big a mystery as the frightening symptoms of PTSD. Why do some people manage to weather terrible traumas and return to a healthy baseline?

“Some of the factors that are going to be implicated in the risk and the vulnerability to PTSD aren’t just going to be things that help people be less anxious. They’re also going to be things that help people to

John Krystal

“PTSD has a lot to do with the capacity to bounce back.”

psychiatric disorders. They also hope to delineate subtypes that might respond differently to treatments.

With the RNA from tissue samples in each of five regions of 200 brains under study, Duman estimates that the project is amassing 50 million data points about the expression levels of 15,000 genes for each brain region of each subject. To analyze this massive amount of data, he is collaborating with the bioinformatics group in the laboratory of Hongyu Zhao, PhD, chair and Ira V. Hiscock Professor of Biostatistics, professor of genetics, and of statistics and data science. The project will gradually untangle networks of genes whose expression is altered in concert with PTSD, as well as identifying so-called hub genes that play an outsized role.

“If we understood the gene networks and biochemical changes that are critical for PTSD pathophysiology, then we could start to think about treatments that

cope and adapt and recover quickly,” Krystal says. “What we find in relation to the genetics of PTSD is likely to have implications not only to PTSD, but ... [for] how people face life challenges and grow from these experiences.”

That too should inform PTSD treatment. When successful, Krystal says, treatment pulls the patient away from rigid thinking—what some people call the “black hole” of trauma or depression—giving him or her the “capacity to approach the world in a much more adaptive and flexible way ... learning to see the world as both dangerous and safe.”

“PTSD,” he adds, “has a lot to do with the capacity to bounce back.” */yale medicine magazine*

Jenny Blair is a frequent contributor to Yale Medicine Magazine.

Computational psychiatry: Modeling the brain's neural circuitry

Alan Anticevic and John Murray have combined efforts in order to understand the biology that underpins the brain's neural system.

BY KATHERINE L. KRAINES

Imagine a mathematical approach to brain research that models the mechanistic basis of brain disorders. Then envision a future in which these models are used to offer personalized medicine to individuals with mental health issues. The field of computational psychiatry, a recent subdiscipline that develops and uses mathematical models of brain function and structure to explain dysfunction in psychiatric disorders, shows great promise in meeting those needs.

Within the Department of Psychiatry's Division of Neurocognition, Neurocomputation, and Neurogenetics, or N3 Division, two researchers are spearheading research in collaborative computational psychiatry with the goal of making inferences about the underlying biology of the brain's neural system. Alan Anticevic, PhD, assistant professor of psychiatry and of psychology, and co-director of N3, leads a clinical neuroimaging laboratory focused on severe psychiatric illness; and John Murray, PhD '13, assistant professor of psychiatry, of neuroscience, and of physics; directs a laboratory that employs computational

modeling to improve understanding of neural function and dysfunction in psychiatric disorders.

Before joining forces, both scientists had observed that many neuroimaging findings, while powerful in mapping the brain, lack a mechanistic interpretation. Moreover, both saw a critical need to translate theoretical findings to clinical research in a principled way. "When we first met, it was obvious to us that a computational-empirical partnership was one of the few ways we could make a practical impact," Anticevic says.

While neuroimaging has come a long way in the last century, spatial and temporal resolutions are still limited; no human imaging can "see" at the level of individual neurons. "Even when we can experimentally manipulate brain function with pharmacology, it's difficult to make inferences about what's happening at the level of neurons," says Anticevic. "Even a single unit of fMRI measurement, a voxel, has a rich circuit landscape made of millions of neurons and kilometers of axons that we just can't see."

To bridge the gap between the seen and unseen, Murray's team creates mathematical models of the brain's electrochemical activity at the cellular level. "The models are used to study how perturbations at the mechanistic level can propagate upward to impact brain-wide functioning," Murray says. "Studying the properties of neurons and synapses allows us to describe those interactions and activity through dynamic equations that resemble equations for resistors and capacitors." Murray's team then builds models that incorporate some of the details that simulate neural activity, which are later evaluated with neuroimaging experiments.

"There are many ideas about what may happen at the neuronal level that drives the cascade of alterations that produce abnormal behavior," says Anticevic. "For instance, one prominent hypothesis in psychosis research is that there may be something 'off' in the way the NMDA receptor is working."

The NMDA receptor, or NMDAR, is a protein molecule that lies within almost all brain-cell membranes and mediates synaptic interactions. Anticevic describes it as a tiny logical gate with two requirements for excitation: first, specific molecules must bind to it; second, it must receive a signal from another cell. When these events co-occur, the channel opens to allow the flow of positively charged ions, thus changing the cell's polarization. "With psychosis, we hypothesize that something goes quite wrong with this core computational machinery," he says. Along with others in the field who are testing this hypothesis, John Krystal, MD '84, HS '88, the Robert L. McNeil, Jr. Professor of Translational Research, professor of psychiatry and of neuroscience; and chair of the Department of Psychiatry, observes that giving healthy individuals low doses of ketamine temporarily blocks a specific kind of NMDA receptor found in cells that calm the brain. The result is a transient state with some of the behavioral symptoms associated with psychosis or schizophrenia.

Anticevic's research includes administering ketamine in order to study the immediate effects of the drug that induce psychosis. "We observe pharmacological effects with imaging and behaviorally," he says. As the behavioral effects of ketamine occur, specific changes in neural activity across the brain are

captured by fMRI. "With evidence from experiments, we can put a hypothesis into a mathematical framework that predicts what would happen if we block NMDA receptors everywhere equally or somewhere more preferentially," says Anticevic.

"Only recently has modeling been able to make experimentally testable predictions for neuroimaging," Murray says. "Being able to design experiments and analyses around models is critical because we need these particular types of data and analyses to iteratively test and refine the models and improve them."

Computational psychiatry hasn't yet crossed the bridge into clinical practice. However, the researchers hope that their work will reveal the diverse mechanisms of brain disorders and provide models that can be used to make predictions at the level of the individual patient. These models in turn will minimize clinical guesswork regarding causes and treatments. The National Institute of Mental Health (NIMH) actively supports research in the field of computational neuroscience.

Anticevic noted that collaborative research within the N3 framework offers a multidisciplinary approach that attracts researchers from physics, mathematics, computer science, computer engineering, neuroscience, psychiatry, clinical psychology, and cognitive neuroscience. "The problem doesn't care about your background," says Anticevic. "There isn't any one skill set that can tackle this challenge. It's bigger than any one lab." [*yale medicine magazine*](#)

Katherine L. Kraines is a frequent contributor to Yale Medicine Magazine.



Why concussions hurt some people more than others

BY SONYA COLLINS

The National Football League's 2017–2018 season brought a stunning first-ever Super Bowl win for the Philadelphia Eagles—and an equally stunning number of head injuries. The 281 reported concussions represent a 13.5 percent increase in such injuries over the previous season and an overall five-year high. While the League's 47 rule changes since 2002 have done little to reduce concussion rates, the steady upswing keeps the issue on the public health radar.

Sports-related concussions are not limited to professionals, nor are their residual effects. The Centers for Disease Control and Prevention estimates that some 135,000 children between the ages of 5 and 18 are treated in emergency rooms for sports-related concussions every year. The National Collegiate Athletic Association sees more than 10,000 of these injuries each year. In all of these groups—youth, collegiate, and professional athletes—a link between concussion and depression is apparent. What's more difficult to tease out is the precise relationship between the two.

“Most athletes after a concussion actually recover quite quickly and don't have these residual symptoms,” says Franklin Brown, PhD, assistant professor of neurology and chief of the Division of Yale Medicine Neuropsychology. “There's been multiple areas of research determining why others don't recover so quickly.”

One such study, published in the journal *Clinical Neuropsychologist* in March 2013, drew on previous research to conclude that 15 to 30 percent of people who suffer a mild traumatic brain injury report lingering symptoms.

An estimated 18 percent of adults develop new-onset depression after a concussion. But definitively “new” cases of depression can be tough to identify after concussion. Depression can often appear to be the result of a head injury when in fact it was only exacerbated by the injury. “The vast majority of people who don't recover quickly usually have preexisting mental health issues,” says Brown. Research shows that pre-existing depressive and pre-existing concussive symptoms are both major predictors of post-concussion depression.

Concussive symptoms don't always mean a history of concussion. Many people in the general population experience such common concussion-like symptoms

as headache, fatigue, and dizziness from time to time. The same is true of depression. Often, people live with these symptoms and never report them. A concussion can draw patients' and doctors' attention to these symptoms for the first time, though they may have been present before.

A small study illustrated the prevalence of “post-concussion-like” symptoms and their overlap with depression in a population with no history of concussion. The healthy study participants completed standard post-concussive and depressive symptom inventories. At least one of the concussive symptoms had been expressed by 36 percent of the respondents in the last two weeks. Up to 15 percent had experienced the more severe symptoms. What's more, the researchers found significant overlap between those who reported concussion-like symptoms and those who reported depressive symptoms. The research didn't establish a causal relationship, but rather underscored the correlation more vigorously.

While researchers don't entirely understand this interplay, they have recognized it for some time. “Neurological and psychiatric symptoms and diagnoses very commonly run together,” says Deena Kuruvilla, MD, assistant professor of neurology. “For example, depression and anxiety are some of the biggest risk factors for developing chronic migraine.”

She adds, emphasizing their physiological link, “Antidepressants can be helpful for treating migraine, depression, and anxiety.”

A recent review in *Neural Regeneration Research* explores a possible mechanism for the overlap, inflammation. The study found a pro-inflammatory state present in the brain in both depression and traumatic brain injury. Each condition can exacerbate the other. “The pro-inflammatory state can persist for months to years after injury,” says Kuruvilla.

Regardless of whether the neurological or the psychiatric symptoms come first, these issues can escalate and multiply if unchecked. “Depression, mood change, headache—these are the things we can treat after concussion,” says Kuruvilla. “If these symptoms go untreated, the patient's quality of life can deteriorate.”

[/yale medicine magazine](#)

Sonya Collins is a frequent contributor to Yale Medicine Magazine.

When researchers listen to people who hear voices

The line between mental illness and genius has long been known to be razor-thin. Yale researchers stumbled upon evidence of this fragile boundary while researching auditory hallucinations in schizophrenia.

BY CHRISTOPHER HOFFMAN

The last thing you'd expect Yale School of Medicine brain researchers to do is hang around with psychics, let alone enlist them in their research. But that's exactly what Albert Powers, MD, PhD, HS '16, assistant professor of psychiatry, and Philip Corlett, PhD, FW '10, associate professor of psychiatry, have been doing since 2014.

Even more surprising, the unusual partnership has produced insights that could one day revolutionize the diagnosis and treatment of schizophrenia.

"The irony is not lost on me," says Corlett, with a broad grin.

Corlett and Powers' unlikely journey into the world of psychics began when they resolved to better understand the phenomenon of schizophrenic patients who experience auditory hallucinations, colloquially known as "hearing voices." The researchers wanted to study people who'd had similar experiences but didn't seek or appear to need treatment. Thanks

to recent research, the pair knew that such people are surprisingly common. As much as 8 percent of the population reports experiencing auditory hallucinations on a regular basis (13 percent hear them at least occasionally), compared to just 1 percent who are diagnosed with schizophrenia. Where to find them? The pair considered charismatic Christians, practitioners of Santeria, practitioners of voodoo, crystal healers, and self-proclaimed druids. None panned out.

One day while riding the bus home, Corlett noticed the large number of storefronts offering psychic readings. *Perhaps people who go to psychics would fit the bill*, he thought. Powers and Corlett reached out to the president of the American Association of Psychics' Connecticut chapter, who informed them they were looking for *clairaudients*—psychics who use voices in their heads to give readings and, the clairaudients believe, communicate with the dead.

Powers started going to association meetings and psychic fairs with another researcher, Adina Bianchi, to talk with clairaudients, Corlett says. Almost immediately, they believed that they had found their study subjects. To confirm their hunch, the researchers asked the psychics to undergo a battery of tests, including brain scans and an extensive survey that included questions designed to unmask fakers. The psychics passed with flying colors, leading Corlett and Powers to conclude that they hear voices much like schizophrenic patients do, but with key differences—the voices are friendly, they can be controlled, and hearers consider them a gift instead of a burden.

The clairaudients have proven enthusiastic participants, Corlett adds. “One of the wonderful things about working with this group is they are delighted that we are taking them seriously,” he says. “We said, ‘We have no interest in debunking. We agree to disagree [on the cause of the voices], but we believe you are having real experiences.’”

One volunteer for the study was Brittany Quagan, who says she first heard voices as a young girl. At 15 or 16, the voices became a serious problem, leading to years of therapy and drug treatment. Her breakthrough came at 21, when a work colleague who was a psychic suggested the voices were evidence of psychic powers, not mental illness. Quagan says she became convinced that her friend was right after Quagan recounted facts about a co-worker’s recently deceased relative to the surprised co-worker.

After her revelation, Quagan says that she quickly gained control of the voices—one is a man, the other a woman with a British accent. She stopped taking medication and turned her life around. She quit her job and began giving psychic readings full time.

“I call them guides,” she says of her voices. “It’s almost like calling a friend, ‘Hey, come here!’ That’s how I connect to them.”

Powers and Corlett’s study subjected the psychics, people diagnosed with schizophrenia, and non-voice-hearers to a simple Pavlovian test devised at Yale in the late 19th century. A light and a sound are paired, with the sound becoming steadily fainter and eventually ceasing. The brain, however, continues to perceive the sound even when it’s not there. Researchers can use

the test to induce a minor hallucination—hearing a sound when there is none—in anyone.

The test results were startling, the patients with psychosis and the psychics were five times more likely than non-voice-hearers to perceive a sound when there was none. Brain scans done during the testing showed that the same parts of the two groups’ brains were activated when they perceived sounds that were not there.

The findings, which Corlett and Powers published in the August 11, 2017, issue of *Science* magazine, have huge potential for the diagnosis and treatment of schizophrenia. Treatments could eventually include devices to short-circuit brain activity that causes hallucinations and behavioral strategies to forestall psychosis, the researchers say.

“I’d say we’ve made a massive leap forward in terms of conceptual understanding, and what we’re trying to do next is turn that into something useful for patients,” Corlett says.

The psychics will remain vital partners in their ongoing work, both men say. Powers has gone a step further, he has hired voice hearer and test subject Quagan, who is in the final stages of obtaining her therapist’s license, as his new lab manager. While Quagan remains convinced that her voices and psychic powers are real, she has come to accept that they may have a neurological component.

“Whether what we [psychics] do is real or not, I’m not going to argue,” Quagan says. “We all have different beliefs. But the underlying narrative for all of us is that we found a way to cope. We found a way to work with our experiences. Because of that, we were able to move away from what could have been a downward spiral.” */yale medicine magazine*

Christopher Hoffman is a frequent contributor to Yale Medicine Magazine.



Speeding treatment blunts the worst of schizophrenia

An interdisciplinary program called Specialized Treatment Early in Psychosis, founded by Vinod Srihari, MD, is helping speed treatment of schizophrenia. How quickly the condition is diagnosed and treated can determine a patient's odds of living a relatively normal, albeit medicated, life.

BY JOHN CURTIS

A few years ago, a young man and his family came to the Connecticut Mental Health Center (CMHC) to seek help. The college student was having troubles that seemed to go beyond the run-of-the-mill concerns of a young adult.

“It was clear to us that the reason he could not keep up in school was not depression or anxiety, but an emerging psychotic disorder,” says Vinod Srihari, MD, HS '03, FW '05, associate professor of psychiatry.

The young man was hearing voices, a classic sign of schizophrenia. The voices commented on whatever he was doing in the moment, disparaged his appearance, and ordered him to do things he didn't want to do.

Srihari's first step was to make the patient feel comfortable with treatment, which included

psychotherapy and antipsychotic medication to quell the voices. He also helped the young man's family understand what was happening.

Between four and five months passed from the onset of symptoms to treatment. This may seem like a long time, but Srihari says average delays in typical care settings can be much longer. Though this pathway to treatment was relatively short, Srihari believes this period, called the duration of untreated psychosis (DUP), is still too long. This is an ongoing area of research, but studies have linked early treatment to better outcomes.

For the past four years, Srihari has led MindMap, a study funded by the National Institutes of Health, to test that theory. Previously, he launched an interdisciplinary program called Specialized Treatment Early in

Vinod Srihari

“Schizophrenia spectrum disorders denote a very diverse group of what are probably many different diseases with distinct causes; nevertheless, this is still a meaningful construct that can tell us a lot about the kinds of experiences people are undergoing, the challenges they are likely to have, and the treatments that will be helpful.”

Psychosis (STEP), which demonstrated that a specialty team-based model of care resulted in better outcomes.

Srihari launched STEP in 2006, after securing approval from the state of Connecticut to provide care to all youth with new-onset psychosis at CMHC, regardless of insurance coverage. The center was already open to those on Medicaid or without insurance, and STEP was permitted to care for those with various commercial insurance plans. STEP reflects a collaboration between the Connecticut Department of Mental Health and Addiction Services and the Department of Psychiatry. “We start a treatment plan that is focused on helping them comply with medication and stabilizing their symptoms, and we start work on getting them back to work or school,” Srihari says.

Each person has at least a one-in-100 chance of developing schizophrenia in their lifetime. Without early and effective treatment, the symptoms can render them unable to work, study, or maintain friendships. “This is a disorder that punches well above its weight in terms of burden, even though it is not as common as other mental illnesses,” Srihari says. Its cause remains a mystery, although researchers have identified genetic and environmental risk factors.

First termed *schizophrenia* by early 20th-century Swiss psychiatrist Eugen Bleuler, it is now considered a group of disorders that share signs (observable by others) and symptoms (subjective experiences) that include hallucinations, delusions, and the inability to

take pleasure in everyday life, trouble focusing, and loss of working memory.

“Schizophrenia spectrum disorders denote a very diverse group of what are probably many different diseases with distinct causes,” Srihari says. “Nevertheless, this is still a meaningful construct that can tell us a lot about the kinds of experiences people are undergoing, the challenges they are likely to have, and the treatments that will be helpful.”

Because schizophrenia strikes when people are young, usually in adolescence or early adulthood, it can be hard to distinguish the symptoms from garden-variety teenage angst.

“They may withdraw socially from their friends. They might struggle in school,” Srihari says. “It can look like depression or anxiety, which they may be experiencing, but psychotic symptoms can be less evident, especially when individuals may feel less comfortable talking about unusual subjective changes.”

Getting patients to treatment can be a challenge. Some may not want to admit that they have a mental illness, or fear that they’ll be locked up. That period between diagnosis and treatment—the DUP—is crucial, Srihari says, because that’s when patients are at the highest risk of aggression, suicide, losing jobs, losing relationships, and dropping out of college.

“There is a subjective journey within which the young person and the family come to figure out this is an illness and professional assistance is necessary,” Srihari says. “It can begin in a jarring manner, with a police officer finding you on the street and taking you to the emergency room or to jail. However, if you’re in a state like Connecticut, you may have a jail diversion officer who says you don’t belong in jail, you need treatment.”

To shorten the pathway to treatment, Srihari and colleagues launched the MindMap study in 2015. MindMap, which covers New Haven and nine neighboring towns, is based on Norwegian research findings that showed earlier access to treatment resulted in better outcomes. MindMap has three prongs: first, a social media campaign raises awareness of psychosis among young people, their friends and family, clinicians, and others; second, the program reaches out to community stakeholders who are in contact with adolescents and young adults—such as mental health providers,

primary care providers, clergy, college counselors, police, and community groups; third, MindMap tracks how many phone calls come into the program and how many calls transpire between first contact and care. There’s no difference in the care provided—the variable is getting patients into treatment quickly.

A control program, which offers treatment but no campaign to reduce waiting time, is underway in Boston. The New Haven program ended in February 2019, but interim results are promising, Srihari says. Two and a half years in, the median delay from onset to prescription of an antipsychotic dropped from about 150 days to 40 days.

“It remains to be seen—if we get our act together and provide early intervention across the U.S.—whether it will change the face of chronic schizophrenia,” Srihari says. “The real gains will be realized over a 20-, 30-, 40-year lifespan, when our hope is that people are less likely to be on disability and will retain their employment, retain their insurance, and retain their families.”

As a success story, Srihari points to the young man who came to STEP a few years ago. After two years, he “graduated” out of STEP and now receives treatment from a community physician. He will need treatment, including antipsychotic medication and psychotherapy, for the rest of his life. Yet his symptoms have receded, and he has a job that involves helping others get rehabilitative services.

“For us, this is an arc that has been fulfilling,” Srihari says. “He has a job, he has commercial health insurance—he is a contributing member of society and does not need intensive or specialized treatment with us anymore.” *yale medicine magazine*

John Curtis is a frequent contributor to Yale Medicine Magazine.

Tackling addiction with treatment and predictive outcomes modeling

Researchers provide insights into the biological profiles the underlying risk of substance use relapse, while treatment methods offer patients new options.

BY ADRIAN BONENBERGER

From the predictive to the prescriptive, advances in the science of addiction treatment are bringing us closer to delivering on the long-implicit promise that functional recovery from substance use disorders is possible. Mapping neural profiles to identify individuals at risk of addiction to certain drugs, investigating the underlying causes of relapse, and expanding the reach of successful behavior modification techniques all give patients with substance use disorders cause for hope.

YOUR OWN NEUROLOGICAL MAP

Researchers in the lab of Kathleen Carroll, PhD, the Albert E. Kent Professor of Psychiatry, combined machine learning and neuroimaging to build a brain-behavior model that predicted cocaine abstinence among a group of 53 people who were entering treatment for cocaine use. The researchers applied this model to neuroimaging data from a group of 45 individuals who were also entering treatment, and found their prediction of who would abstain from cocaine during treatment to be 70 percent accurate. Led by

Sarah Yip, PhD, FW '15, assistant professor of psychiatry, and in the Yale Child Study Center; in collaboration with Dustin Scheinost, PhD '13, FW '15, assistant professor of radiology and biomedical imaging, and in the Yale Child Study Center, the team laid the groundwork for evaluating mechanisms that could guide the treatment of patients.

“We don’t have a good predictor of who will benefit from a course of treatment,” says Yip, “Using these data analysis approaches, we hope to one day be able to tailor treatment to individuals.”

Yip’s research points in the direction of a personalized neural map that may one day save patients valuable time, money, and resources—not to mention heartbreak. Published online in the *American Journal of Psychiatry* on January 4, 2019, the prediction of cocaine abstinence based on the connectome—a complete map of neural connections in the brain—also provides insight into the neurobiology of recovery, which may speed the development of novel interventions to further improve outcomes.

REROUTING THE ROAD TO RELAPSE

While researchers like Yip develop predictive tools to aid in addiction treatment, other clinicians and researchers are focusing on another problem area—the threat of relapse once a patient successfully completes a course of treatment. “Our targets are channels that influence dopamine activity in the brain,” says Nii Addy, PhD ’07, associate professor of psychiatry and of cellular and molecular physiology. “Certain cues can trigger drug relapse—think about the smoker who’s attempting to quit, and then returns to a bar to socialize with friends, only to find themselves smoking again. We’re using rodent models to understand what happens in the brain that allows cues to bring about that relapse. A great deal of research has shown that brain dopamine levels increase in the presence of drug cues. So channels that decrease brain dopamine concentrations could be potential therapeutic targets for drug relapse.”

Addy’s project, funded in part by a grant from the National Institutes of Health, focuses on L-type calcium channels in cells, which are channels that allow calcium to enter the cells. These channels affect how dopamine (the neurotransmitter most responsible for stimulating the reward system within the brain) acts neurologically. At present, scientists mostly understand the roles dopamine plays in motivating reward, regulating mood, and fostering learning. Figuring out when and how to regulate dopamine could allow scientists to develop treatments that short-circuit addictive behavior as well as lower the risk of relapse.

Addy’s interest in the neurological makeup of substance use disorder was sparked when he was an undergraduate at Duke University. He worked in a lab where researchers studied how nicotine could reverse the cognitive deficits associated with schizophrenia and antipsychotic medications.

One discovery that surprised Addy during his most recent research is that blocking the calcium channel decreased the frequency of relapse among subjects but increased dopamine levels. “That was the opposite of what we expected, given current understanding of how dopamine operates,” Addy says.

REPROGRAMMING NEURAL PATHWAYS

Carroll has spent nearly 30 years developing a program called Computer Based Training for Cognitive

Behavioral Therapy, or CBT4CBT. The program takes a model proven to facilitate positive changes in a person’s actions—cognitive behavioral therapy—and offers it online to patients with a substance use disorder. Developed and tested with support from the National Institute on Drug Abuse and the National Institute on Alcohol Abuse and Alcoholism, CBT4CBT makes a standardized, effective form of treatment available to people wherever and whenever they need it; it is particularly promising in reaching underserved populations.

CBT4CBT started when Carroll saw the potential for technology-assisted treatment in the early 2000s. “My daughter loved learning to read while sitting on my lap using the *Clifford the Big Red Dog* program on the Public Broadcasting Service website,” says Carroll. “I realized that CBT could be taught and practiced remotely using those new multimedia tools. We think that by demonstrating cognitive and behavioral self-control skills and strategies in an engaging, fun way—for example, by including a series of videos that show people using the skills in real-world challenging situations—we’ve developed a very powerful tool. Here we are nearly 20 years later, and the technological opportunities for treatment have far exceeded early expectations.”

Asked how CBT4CBT compares to other forms of treatment for substance abuse disorders, Carroll is optimistic. “We spend billions in the U.S. on treatments that haven’t been proven or even shown not to work, like detoxifying people without follow-up,” she says. “We have tested CBT4CBT extensively in over seven randomized clinical trials, and have shown that it can have better outcomes than standard outpatient treatment while costing a lot less. Plus, patients really like it, which is the bottom line.”

There is still much to learn about how bodies respond to treatment for substance use disorders. Yip, Carroll, and Addy are all bringing medical science and the clinical application of that science closer to the day when substance use disorder is seen as a treatable chronic disorder that can be managed, enabling people to resume happy, productive lives. [/yale medicine magazine](#)

Adrian Bonenberger is the editor of Yale Medicine Magazine.



“The Crack-Up,” by Corporal Wayne Seese, uses an unusual palette to depict a public moment of private anguish amid the Pacific campaign during World War II.

The Clements Collard Fry Collection

Clements Collard Fry slowly amassed an astonishing collection of prints and drawings that he bequeathed to the university after his death

By Adrian Bonenberger

He never thought of himself as a collector. He just bought pieces he enjoyed and could share with others who might appreciate medical history, art, or representations of illness. Humorous, serious, valuable, or sad: if a drawing or print caught his eye, Clements Collard Fry (1892–1955), MD, head of the Division of Mental

Hygiene in the Department of University Health at Yale after 1937, made an effort to acquire it.

By the end of Fry’s life, he’d accumulated over 2,000 prints, covering five centuries and the work of hundreds of artists. Susan Wheeler, the Medical Historical Library’s curator of prints and drawings and historical medical posters, knows more about Fry’s collection than anyone else alive, having spent a great deal of time with it. She wrote

a book on the subject—*Five Hundred Years of Medicine in Art*—which was published in 2001.

“Clements Collard Fry developed an interest in collecting fairly early in his life, first focusing on manuscripts and editions of Silas Weir Mitchell, a pioneer in the treatment of nervous disorders and a prominent literary figure,”

said Wheeler. “But as Mitchell’s works became harder to find and more expensive, Fry turned to rare medical prints. Over time that interest developed in sophistication, and what you see in the collection today is the culmination of a lifetime of collecting medical art.”

World War II seemed to be a turning point for Fry as a collector. While working in Washington, D.C., with the National Research Council, Fry became immersed in the

collection of prints and drawings at the National Gallery of Art. An unusual drawing from this time, “The Crack-Up,” portrays a U.S. soldier who has a breakdown during the Pacific campaign. Taken from an event that the artist (Corporal Wayne Seese, U.S. Army) witnessed, “The Crack-Up” was shown as part of a late 1945 exhibition *U.S. Marine Combat Art*, that included 130 drawings by 22 Marines. When Fry contacted the artist to learn the story behind the drawings, Seese replied:

The “Crack-Up” came from a scene I witnessed on the island of New Britain, after the Cape Gloucester campaign ... One night as we sat in our ... tent, bedlam broke out across the street at sick bay. Rushing over there, we came upon the scene I have put down on paper.

Yelling, sobbing, and talking, the kid was held down by a couple of his buddies while the doctor prepared a sedative. The scene was pretty weird with hundreds of fellows drawn by morbid curiosity standing in the darkness ...

The kid was a rugged-looking boy about nineteen or twenty, a messman [entry-level

assistant to the ship’s steward of a merchant marine vessel] at the time. He stepped out of his tent and in the darkness ran into a tree and went to pieces. Rumor was that he had just received a letter that both his sister and father were killed in an accident, but I don’t know.

“Perhaps to a surprising extent, World War II was viewed through drawings made by combat artists,” said Wheeler. She explained that iconic photographs captured the public’s attention, but that handmade illustrations of events still provided civilians back home with powerful visualizations of the war.

The school continues to acquire prints and drawings through gifts and endowments, adding to the collection’s diversity. They reflect Fry’s aesthetic and professional interests.

“The items we have acquired over the past 50 years build on what Dr. Fry’s collection was,” said Wheeler, “and help bring it into the present. Dr. Fry used to show these prints to his colleagues and students—he liked people’s seeing them and delighting in their stories. We do what we can to continue that legacy.”



LEFT Clements Collard Fry’s collection included many period pieces describing scenes or profiles (often satirical in nature) that illuminated a disease or disorder. Relatively few, however, described maladies contemporary physicians would diagnose as mental illness.



ABOVE One of the prints Fry collected on the subject of madness.



LEFT The collection has pieces of historical significance, such as those dealing with 18th- or 19th-century American history.



A well-balanced life: Sharon Weinstein's long career of service

SHARON WEINSTEIN, MD '78, KNEW that she wanted to be a psychiatrist at the age of 10. She read *Nancy Drew* and *The Hardy Boys*, but also *Scientific American* and Freud's books on dreams. She idolized pioneering scientists like Marie Curie, wrote to Jonas Salk, and was thrilled when the discoverer of the first polio vaccine replied. "From early childhood, I have always been interested in how people live their lives," Weinstein said, "learning how they face challenges and overcome adversity to realize their dreams."

Curiosity served her well. The Massachusetts Psychiatric Society recently honored her with the 2018 Award for Outstanding Psychiatrist in Education for her multifaceted teaching and program development in child and adolescent psychiatry.

Weinstein expresses gratitude to those who gave her roots, her family and mentors. Growing up in Hartford, Conn., as the oldest of five, hers was a childhood of stories. "I used to listen to stories about my Jewish grandparents immigrating to the U.S. from Poland to escape

pogroms and find freedom," she recalled. "They came here with little, starting with my grandfather having a pushcart, to establishing a grocery store where people would congregate to ask his advice and share their stories. I listened to family stories of courage and resilience, of my dad's bravery at Normandy on D-Day, and about my mom's dedication to her family."

Service and education were woven into the family's culture. "In Europe, my grandmothers were denied educational opportunities," Weinstein said. "We understood what a privilege education was." Her parents ensured their children engaged with a spectrum of subjects, in school as well as at home and in the community. Weinstein thrived with the multidisciplinary concept—it would in fact become a pillar of her professional focus. "I was fascinated by connections between mind, brain, body, and society," she said. "I think that was fostered by a range of life events in a large, multigenerational family."

In many ways, Weinstein is a product of her environment. Her psychiatry practice exists at the intersection of science and art and of the personal and environmental, where culture, spirituality, and medicine meet. These elements were embedded in her heritage and ignited by her coming of age against the backdrop of a shifting world. In the 1960s, Weinstein attended a "large public high school marked by cultural, ethnic, and socioeconomic diversity," and she began college in an era of political upheaval and social change, particularly for women. Some regarded Harvard's introduction of coeducational housing her sophomore year there as an unwelcome break with tradition. Women were gaining admission to medical schools in greater numbers, but at Yale, Weinstein remembers

some female classmates being told they were “taking the place that a man could have, that they would have children and stop practicing medicine.”

Weinstein challenged biases through evidence-based research—her approach since her first science fair project when she was 12. In college, she disputed the belief that women should not hold key political positions because of “raging hormonal influences” by writing a thesis examining emotions throughout the menstrual cycle. In medical school, her thesis centered on gender differences in depression. “It was an exciting time,” she said. “The whole field of gender and female development was being studied, researched, and radically revised to the good.”

Weinstein volunteered at pregnancy counseling services in Boston and often accompanied women seeking legal abortions to clinics in New York, sometimes crossing picket lines. “I grew up seeing how important it is for a woman’s dignity and self-actualization to have the right to make choices about her own body,” she said.

Weinstein also recognized the connections between environment, biology, psychology, and development, and deepened her appreciation of knowing and treating the “whole person” at Yale School of Medicine. “Yale was renowned for excellence and an innovative, far-reaching curriculum, especially in psychiatry,” she said. “Outstanding faculty



Weinstein is grateful for the foundation and stability her family provided, and she has striven to build the same for her own son, now 23. “It’s such a gift to see the excitement in children when they accomplish their goals,” she said.

taught us a humanistic, compassionate approach to the doctor-patient relationship.”

Weinstein brought the multidisciplinary philosophy to her adult residency and child and adolescent residency at McLean Hospital in Belmont, Mass., and to the Boston Psychoanalytic Society and Institute (BPSI). She ultimately focused on work with children, adolescents, adults, and families, both in her private practice in Lexington, Mass., and in paying forward her family’s educational legacy through teaching at McLean and Harvard Medical School.

The Massachusetts Psychiatric Society award is the latest in Weinstein’s encyclopedic résumé, which includes honors for leadership in clinical work,

education, and advocacy. She is a Distinguished Life Fellow of the American Psychiatric Association and the American Academy of Child and Adolescent Psychiatry; received a Lifetime Achievement Award from the New England Council of Child and Adolescent Psychiatry (NECCAP); and has served several terms as NECCAP president. Over 30 years, she has organized 170 psychiatric conferences and taught thousands of Harvard Medical School students and psychiatric residents.

Looking forward, Weinstein is concerned about a critical shortage of child and adolescent



ONLINE EXCLUSIVE

PA Online students visit Yale twice during their didactic year to get “hands-on” experience with professors and interact with each other. *Yale Medicine Magazine* popped in to see how a recent visit went, and what the students learned from their immersion exercise.

For more on their talk, visit ymm.yale.edu/immersion

psychiatrists. “Nearly one in five U.S. children has a mental, emotional, or behavioral disorder within a given year, and only about 20 percent receive care from a specialized mental health care provider,” she said. “We need more pediatric psychiatrists to meet these needs. It’s a dynamic and rewarding field. With significant advances in research and treatments, psychiatrists can partner with families and colleagues to advocate, help children build on their strengths, and create solid foundations for the future.”

Weinstein finds her work hopeful and embraces the optimism of change and possibilities. “Much of the power of intervention, through education, connection, social action, and multimodal evidence-based treatments is in being able to rewrite your narrative,” she said. “You can see your past through a different lens and rewrite your narrative for the future, knowing that the end of the story has not yet been written.”

As with her family, it all comes back to stories.

—Lauren Johnson



**A study in innovation:
Reinventing substance
use disorder intervention**

The fields of education and psychiatry value researchers who are willing to combine fresh ideas with traditional solutions. That kind of open-minded approach

led Ayana Jordan, MD, PhD, to an epiphany as she sought a better way to help poor people struggling with drug addiction. Though it happened in church, her epiphany was not religious in nature. Jordan realized that the influence and support of the African Methodist Episcopal Zion Church could provide the transformative experience people needed when they didn’t have much trust in health care. Through her positions as assistant professor of psychiatry and director of the Yale Global Mental Health Program, she was able to draw on colleagues and church leaders to break new ground in addiction interventions.

Raised in Pittsburgh, Jordan began her award-studded academic life with an undergraduate degree in biology from Hampton University in Virginia, a school steeped in Black history and culture with a progressive mandate. She embarked on an MS in pathology at Albert Einstein College of Medicine of Yeshiva University in the Bronx, then stayed on for an MD/PhD program.

Completing the combined degree program is a rare accomplishment for any student. The number of Black women who achieve it is miniscule. “I planned to go into internal medicine and infectious disease,” she said since she earned her PhD in immunopathology. But during the program, she did clinical work in psychiatry in the South Bronx. “I had never seen that level of

poverty in the U.S. It really struck me,” she said. This experience changed the trajectory of her career. “I realized I could make a bigger impact in the underserved and marginalized communities. There is such a big mistrust in those communities around mental health and mental illness.” The existing interventions weren’t working, and she felt compelled to find a solution.

“To improve outcomes for marginalized populations, we need to involve them from research to clinical interaction—every step of the way,” Jordan explained. This kind of community-based participatory research wasn’t an option in most residency programs. At Yale, she found an environment that supported her vision to integrate the cultural and religious aspects of people’s lives while also addressing the disparities that can hold them back from improved mental health. Jordan also discovered a community in need: According to the National Institutes of Health, Connecticut is among the top 10 states for overdose deaths from opioid abuse. She arrived in New Haven in 2011, as the rate of opioid deaths in the state started to climb dramatically.

During her residency, she served as program-wide chief resident in psychiatry; completed a fellowship in addiction psychiatry; amassed a dozen awards, including the Resident Recognition Award from the American Psychiatric Association (APA); and found an innovative

approach to community intervention. When Jordan arrived in New Haven, one of her top personal priorities was to find a Black church. She joined Varick Memorial AME Zion Church, which has a long tradition of participation in studies at Yale. Knowing that the Black church had been instrumental in changing how people thought about HIV, Jordan realized the church community could help with another stigmatized epidemic: mental illness, specifically substance use disorder. She approached the pastors to propose a pilot of a community-based treatment program within the church.

While it may sound a bit like 12-step meetings held in church halls, which Jordan acknowledges can help many people, this program is quite different. “Here we are focused on being Black, being spiritual, [and] the church itself is involved in the care,” she said. “It’s not about bringing people to Jesus, and participants are often not part of the congregation,” she explained. “It’s about a safe place where people can get help.” The pilot program was held in Dixwell Avenue Congregational United Church of Christ. It included evidence-based computerized cognitive behavioral therapy, and received an overwhelmingly positive response.

At the same time, Jordan hoped to bring a faith-based initiative to members of the Black community with opioid use disorders throughout the state. That

led to a collaboration with Chyrell Bellamy, MSW, PhD, associate professor of psychiatry, on a program called Imani Breakthrough (*imani* means “faith” in Swahili). With input from peer facilitators and church leaders, they added the traditions and values of the church to a curriculum based on the Citizens-Community Enhancement Project, an intervention shown to be effective for people with serious mental illness that includes substance use disorders.

The foundation of Imani Breakthrough is the 5Rs model from the Citizens’ Project, created by Michael Rowe, PhD, professor of psychiatry, and his colleagues. The model emphasizes the “rights, responsibilities, roles, resources, and relationships” of community members. Imani Breakthrough also incorporated a support system that encompasses spiritual, social, financial, emotional, environmental, intellectual, physical and occupational aspects of life—the “Eight Dimensions of Wellness,” as outlined by the Substance Abuse and Mental Health Services Administration of the U.S. Department of Health and Human Services.

Imani Breakthrough aims to help people gain independence without relying on perennial attendance at meetings. The program involves 12 two-hour weekly meetings and refers patients to medication-assisted treatment and wellness counseling when appropriate. It also includes one-on-one

support to address such factors that might compromise success as issues with housing, jobs, and transportation.

When the program launched, hundreds of people came. The success led to further funding for another year. Jordan and Bellamy are now expanding the program by designing a version for the Latinx community. “The next challenge is preparing a large randomized controlled trial to determine if partnering with the faith organizations works better than traditional substance use clinics,” Jordan said.

While Jordan has won many awards and accolades, one of her favorites was bestowed at Yale’s commencement last June: the Faculty Diversity Award. “I wanted to recruit residents and faculty that are reflective of the population, to make sure all kinds of people are at the table—race, gender, point of view, where we trained, and more. You can’t be an excellent physician unless you are aware of the cultural identity that patients bring into the room and take that into consideration in the treatment plan. Yale psychiatry is starting to reap the rewards of being focused on inclusion.”

Jordan said she hopes to help everyone find a path to recovery, regardless of past failures. “My ultimate dream is to open up a substance abuse wellness center that not only deals with the biological aspects of substance use, but equally addresses the social determinants of health,” she said.

—Elena Rover

The biochemical basis of human mood

DURING HIS FIRST SUMMER IN COLLEGE, John Krystal, MD '84, HS '88, chair of Yale's psychiatry department, traveled from the University of Chicago to help patients at a methadone-dispensing addiction clinic in Boston. In a biochemistry class that autumn, he learned about the discovery that the body makes opioid-like molecules called endorphins that act via the same receptors in the brain as drugs like heroin and methadone. An idea clicked. "That suggested to me that the problem of addiction might have a scientific underpinning," Krystal, the Robert L. McNeil, Jr. Professor of Translational Research, professor of psychiatry, and of neuroscience, said, "and that the complexity and unpredictability of clinical psychiatry work could be grounded in discoverable, scientific principles about brain-behavior relationships."

The direct link between biological processes in the brain and a person's behavior is widely accepted today, but it seemed radical three decades ago. When Krystal was an undergraduate, the late Yale psychiatry professor Daniel X. Freedman, MD, directed him toward the lab of Richard J. Miller, PhD, a pioneer in opiate-receptor research. Since then, Krystal has built a career bridging basic science

with clinical understandings of depression, alcoholism, post-traumatic stress disorder (PTSD), and schizophrenia.

In this *Yale Medicine Magazine* interview, Krystal discussed a deep and wide range of topics from across his roles, which also include chief of psychiatry at Yale New Haven Hospital, editor of the journal *Biological Psychiatry*, director of clinical neuroscience at the Department of Veterans Affairs National Center for PTSD, and numerous advisory responsibilities.

Statistics generally show an upward trend in rates of depression, anxiety, and addiction. Are we dealing with an actual increase or just talking about mental health more openly? There is a lot of activity in the sphere of public mental health. First, the numbers of people diagnosed with anxiety and depression are going up. Second, the rate of serious consequences of inadequately treated mental illness, like disability and suicide, are going up. Third, we have a very serious shortage of psychiatrists and psychologists. We've tolerated this shortage because society has traditionally viewed mental illness as something that can be treated if there are resources available, a sort of add-on to health care. Many people, including myself, believe that we need a new model whereby mental health is a core element of primary medical care. In our society, more than two-thirds of people are routinely screened for various forms of cancer—but more than two-thirds of people are not screened for mental illness or addiction. We need to change that statistic.

To nominate a subject for Q&A, contact
Yale Medicine Magazine, 1 Church Street, Suite 300, New Haven, CT 06510, or email ymm@yale.edu.

Neuroscience research is progressing rapidly. Why might the public still think of mental illness as shrouded in mystery?

The symptoms of mental illness—including changes in mood, patterns of thought, or behavior—can be confusing or even frightening. Providing a scientific foundation for understanding these symptoms that guides the processes of diagnosis and treatment could have profound implications for how society thinks about these problems.

What changes do we need in how mental illness is treated? I think we need a new model. As a society and as a medical specialty, we need to take responsibility for the outcomes of mental-illness treatment. To do that, we have to measure the outcomes of treatment and use this information to inform clinical practice. The current model has some parallels to the way we treat infection, in that the most commonly used treatments are not always the most effective. We save the most effective treatments for “treatment-resistant” symptoms. But that is not what we do in cancer. There, we initiate

definitive treatment as soon as the problem is diagnosed. We need to offer more care like that. If we diagnose depression, we need to make sure you get a comprehensive array of services. Also, when people fail to respond to established cancer treatments, a high percentage of patients will enroll in a research study to test new treatments. That is not the way we deal with mental illness or addiction, where only a small fraction of patients participate in research.

Which mental health trend disturbs you most today, and which trend gives you the most energy? The trends that disturb me most also energize me the most: the increase in opiate-related deaths and the increase in suicide. Psychiatry is unique in that mortality from psychiatric illness is increasing, whereas mortality from practically every other diagnosis is decreasing. Cancer mortality, diabetes mortality, and heart-disease mortality are going down. But suicide and addiction-related deaths are going up. We have to do things differently—and not just as a department or health care system but as a country.

What is a dream you have for the future of psychiatry? We are working toward an era of precision psychiatry. By that I mean having tests that diagnose risk or disease processes for individuals and that enable us to engage specific prevention and treatment interventions. We envy cardiology, where one can diagnose and treat hypertension and thereby prevent myocardial infarction. We may be able to use genetics to identify people at risk for problems, but then we also may need to deal with the societal issues that increase risk, such as childhood exposure to violence, abuse, neglect, and maternal depression and addiction. Future treatments may involve gene- or cell-based therapies or procedures only imaginable on shows like *Star Trek*, where a scan is performed that tells us how to stimulate the brain to alleviate symptoms. Who knows what will come? *Cure* is not a word that we use in psychiatry, but that too is simply a reflection of the limits of our knowledge in comparison to the enormity of the challenge of understanding the brain.



A stimulating book on hormones

By Cathy Shufro

In 1902, two English physiologists, William Bayliss and Ernest Starling, undertook gruesome experiments on a dog to prove that hormones are essential to canine digestion. As Randi Hutter Epstein, MD '90, MPH, recounts in her new book, those experiments confirmed that the glands scattered in the body—whether canine or human—have something in common: they produce hormones. The field of endocrinology was born.

The next year, animal rights activists watched Bayliss and Starling cut into a dog's throat at a demo for medical students. Epstein tells how anti-vivisectionists protested the dog's treatment and erected a statue of a canine in South London that read, "In Memory of the Brown Terrier Dog Done to Death." Medical students, in turn, mobbed the streets, shouting, "Down with the Brown Dog!"

This interweaving of science and story is characteristic of *Aroused: The History of Hormones and How They Control Just about*

Everything. While tracing the history of endocrinology, Epstein includes accounts of hucksters, eugenicists, and murderers. She writes about how hormones affect those going through menopause, are intersex, are gender transitioning, or experiencing fluctuations in weight.

Epstein hopes these tales will attract a broad audience. "I'm trying to hook in the reader who would say, 'I never thought I'd read a book about the history of medicine—and I don't know a thing about chemistry—but I really understand it, because the stories are so great.'"

One such story: In 1960, when a doctor predicted that 7-year-old Jeff Balaban "might never make it past four feet," his mother took action: she recruited pathologists to donate 156 human pituitary glands from cadavers each year to supply growth hormone for Jeff. As Epstein writes, "It would take a graveyard of bodies to make him grow." Balaban proved lucky; since 1985, more than 226 other people treated with glands obtained from cadavers have died

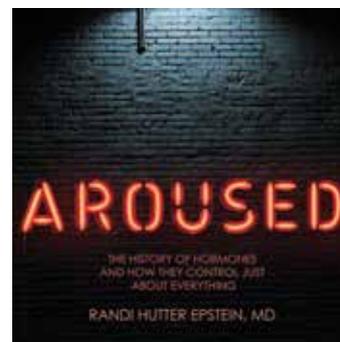
from iatrogenic Creutzfeldt-Jakob Disease (iCJD) which is transmitted by prion-contaminated growth hormone. Physicians now use synthetic growth hormone.

One of Epstein's favorite stories is that of Rosalyn Sussman Yalow. Born in 1921 to Jewish immigrants, she found a spot in physics graduate school only after male students left for the military. "They had to go to war so I could get a PhD," Yalow declared. In 1959, she and colleague Solomon Berson developed a way to measure hormones in the body. The radioimmunoassay (RIA) detects hormones down to one-billionth of a gram per milliliter of blood. As Epstein writes, "That's like being able to measure the extra water in a swimming pool after one swimmer sheds a tear." RIA can detect various biological substances and is fundamental to fertility treatments and detecting HIV. Pediatricians have used RIA to virtually eliminate the thyroid deficit that causes congenital

hypothyroidism; they routinely prick the heels of newborns to spot the deficiency.

Epstein describes the barriers that Yalow had to breach. She ignored a rule at the Bronx Veterans Administration Hospital requiring pregnant women to resign in the fifth month. Journals repeatedly rejected her first groundbreaking article. In an interview, Epstein described Yalow's advice to a group of third-graders: "'Hold onto all your rejection letters, because you can display them during your Nobel awards ceremony.' Which Yalow did." She received the Nobel Prize in physiology or medicine in 1977 for inaugurating "a new era of endocrinology."

Epstein said that during five years of researching and writing the book, she saw a pattern in how people have responded to discoveries about hormones. "Here are these chemicals that seem to control us, and we ask, 'How can we control *them*?' That's human nature. We learn something about health or wellness or disease, and then we want to take control."



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Going once, going twice

THE AUCTION IN CAFÉ MED on the evening of December 6, 2018, was the 26th in an annual series that has raised money for New Haven organizations that provide services to those in need. This year's auction raised \$15,306 for four of the 28 organizations that applied for funding: Cornell Scott-Hill Health Center; Integrated Refugee and Immigrant Services (IRIS); Love Fed New Haven, which makes healthy and affordable food available through community gardens; and Youth Continuum, which serves homeless youth in the city.

Noting the auction's long-standing tradition, organizer and second-year student Melanie Zheng said, "It's a great event because it allows us to help the community we were meant to serve."

The auction began at 5 p.m. with music from the Railboys, a jazz ensemble made up of medical students. At 6 p.m., William Stewart, PhD, who has taught anatomy to generations of Yale medical students, took to the lectern as the first of several auctioneers. He would, he said, dispense with the kindness and understanding he displays in the anatomy lab. "My one job is to get into your wallets, so I am not going to show any mercy at all."

As in past years, Stewart offered one of his signature bow ties, provoking the traditional rivalry between students in the Physician Associate Program and medical students. The PA students won with a bid of \$2,080.

—*John Curtis*