yale medicine magazine

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

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FW for the final year of a fellowship,
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Yale SCHOOL OF MEDICINE

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To commemorate and observe its accomplishments over the last century,

the Department of Pediatrics hosted a number of events, ranging from a centennial kickoff picnic to three symposia on cardiology, endocrinology, and neonatology. The programming, which brought together faculty, staff, students, and the community, included initiatives with and through the Yale School of Public Health, Yale Child Study Center, and many of the departments in which pediatricians often work.

— Adrian Bonenberger

Preparing for the next century of pediatric excellence

YALE SCHOOL OF MEDICINE’S Department of Pediatrics has played an integral role in establishing and boosting the medical school’s culture of cooperation, diversity, and interdisciplinary research. Nancy J. Brown, MD, the Jean and David W. Wallace Dean of the Yale School of Medicine and the C.N.H. Long Professor of Internal Medicine, discusses the present and future of pediatrics.

What role does pediatrics play in driving interdisciplinary work and collaboration at Yale? Increasingly, the medical community has focused on understanding the importance of early life in determining health outcomes across a person’s lifespan. That requires collaboration in terms of clinical care and in terms of research. From Ob/Gyn to pediatrics to adult medicine, our goal is to understand the genetic and environmental determinants of health. It all springs from a life’s beginning.

One of the keys to tracking health care is at the transition in care between pediatrics and adults. We’ve made impressive progress treating diseases, such as cardiac anomalies and cystic fibrosis, that were once fatal in children; now, those same children live into adulthood. How do we bridge that and care for those patients as they lead successful and fruitful lives? It requires a great deal of collaboration between fields and physicians who in the past may not often have worked together.

Similarly, in mental health, many diseases become manifest in childhood. They reflect the environment and genetic factors. There’s a need to work with our community partners as well as with adult psychiatry. Those are a few examples.

Which research initiatives stand out as being areas of strength for Yale School of Medicine’s Department of Pediatrics? The Department of Pediatrics has a robust history in the area of type 1 diabetes, both in understanding disease mechanisms and in developing new treatment paradigms, such as closed-loop insulin pumps. Pulmonary work around cystic fibrosis is a strong area. And the work we do with our Department of Genetics in terms of identifying rare disorders early, sometimes as early as in the neonatal intensive care unit, is quite robust.

What are your general thoughts about pediatrics at Yale and the arc of pediatrics in the United States? Pediatrics as a specialty has always been about the whole human being. It’s about normal development as much as it is about disease— caring for our children in a way that maximizes their chance of leading a healthy, long life and succeeding; reaching their potential in school and eventually as fully formed adults. Pediatrics has a collaboration with Yale Child Study Center that is unique to Yale. That is a mission for pediatrics, and Yale has excelled at this. And, recently, in a more intentional way, the department is considering and promoting health equity.

What are some of the initiatives and plans the School of Medicine has for the Department of Pediatrics? The Department of Pediatrics is adding to its academic excellence. Recruiting superb leaders in areas including immunology, oncology, neonatology, and neurology has been extremely important. Along with an emphasis on leadership, we have a commitment to grow the cadre of young physician-scientists in the department who are contributing to discoveries.

JENNIFER STOCKWELL ARTWORK

In June 2022, volunteer aid workers deliver medical supplies donated from the United States to a hospital in Kramatorsk, Ukraine. The aid workers are a collective of people who pay their own expenses to help in Ukraine.

SCOTT OLSON/GETTY IMAGES

Support for Ukraine's trauma victims

DOCTORS AND RESEARCHERS at Yale School of Medicine (YSM) with friends and family in Ukraine have organized to raise funds and equipment for overwhelmed hospitals in the embattled country.

The Russian invasion of Ukraine left doctors at YSM who have Ukrainian roots feeling distraught and frustrated. Instead of stewing, they acted, forming an organization to channel desperately needed medical supplies and equipment to their overwhelmed Ukrainian colleagues. Doctors United for Ukraine (DU4U) has so far delivered more than $1 million in medical and mental health aid to the embattled nation, said DU4U's Vice President Andrey Zinchuk, MD, MHS, assistant professor of medicine.

"We were lucky to find people who shared our worry and shared our hope that we can ameliorate some of the war's effect on people," said Zinchuk, who came to the United States as a boy with his family in 1992. "It's also an action for self-preservation. If you make a difference, you are not hopeless. What you do matters."

The group's major focus is providing medical supplies and equipment to treat acute war injuries—everything from shattered limbs to severe abdominal and chest wounds. Needs range from basic tools like drainage tubes and fixators to repair broken bones to more sophisticated items, such as wound vacuums and field ventilators, to keep patients alive until they reach a hospital.

"These women and men [Ukrainian health care workers] have done an impressive job with the resources they have," Zinchuk said. "They are incredibly grateful for the resources from charitable organizations. We are not the only ones."

DU4U operates differently from some charitable organizations, which typically send pallets of materials to warehouses managed by Ukraine's Ministry of Health.

Zinchuk and his fellow physicians talk directly with Ukrainian critical care doctors and military hospitals to learn their specific needs. DU4U then buys the equipment and supplies in Ukraine or Poland, and ships them directly to where they are needed. The group has also received in-kind donations from manufacturers, he said. Recipients close the loop by sending photos of the items in use.

"It's sort of like Etsy for medical purposes, a small-scale grassroots effort," Zinchuk said.

But while the program has been an overall success, the ongoing destruction and violence are never far away. Last September, a Russian missile strike destroyed a mobile hospital and about $100,000 of medical items supplied by the group.

DU4U is also helping Ukrainians cope with the war's psychological impact. Group Co-president Irina Esterlis, PhD, associate professor of psychiatry, is helping mental health professionals in western Ukraine—a relatively safe region—treat refugees from Eastern Ukraine who are traumatized by the war. One of the most serious challenges is that Ukrainian psychiatrists and therapists aren't trained to treat post-traumatic stress, Esterlis said.

"A lot of psychologists in Ukraine have psychoanalytical or Gestalt training, which focuses on early-life experiences," said Esterlis, who was born in Ukraine. "Acute trauma that you experience in war or being raped or seeing your parents killed has nothing to do with how you were raised. A lot of them don't know how to treat people with acute trauma because they've never been in that situation."

Helping empower Ukrainian mental health professionals with new skills so that they can treat post-traumatic stress is therefore a top priority for the group, Esterlis said.

DU4U's third focus is women's health care. The group's other co-president, Alla Vash-Margita, MD, associate professor of obstetrics and gynecology, is helping her Ukrainian counterparts treat pregnant women and women who have been raped. The needs range from IV solutions given to women in labor to gynecologic instruments like hysteroscopes and laparoscopes, said Vash-Margita, an Ob/Gyn. The stress of war inevitably affects pregnant women in negative ways, said Vash-Margita, who is from Ukraine and graduated medical school there.

"From the maternity side, there's a great need because of the stress and poor living conditions," she said. "Women are lying in basements or traveling, with no connection with loved ones. Many women experience miscarriage or preterm labor. We've been asked to provide medication to prevent preterm labor and to prevent postpartum hemorrhage."

Treating rape victims is challenging because so many choose to keep the attack secret due to shame and stigma, and medical assistance often becomes available only at some time after the assault, Vash-Margita said.

The three faculty members agree that the need for help remains enormous. "It's not like you give 1,000 people services and now there's 100," Esterlis said. "That 1,000 keeps growing."

Zinchuk is so far the only one of the three faculty members to travel to Ukraine since the war began; he went last June to help set up a program to replace heart valves for vulnerable patients in the western part of the country. During the trip, he visited Borodyanka, a town near Bucha that also saw Russian atrocities, he said. What he witnessed left a deep impression.

"It's one thing to hear about it and to read about it, it's another to experience it," Zinchuk said. "What we saw there was horrendous. Destroyed buildings. Destroyed lives. The remains of people's lives like children's notebooks; toys, clothes in the building's rubble. A pharmacy that's destroyed. That's a meaningful experience for us, and it provides motivation."

DU4U could not do its work without partners. Dwight Hall at Yale, a center for public service and social justice, has been acting as their fiscal sponsor. "They [Dwight Hall] have been our lifeline, helping us receive donations until we can build up our enterprise," Zinchuk said. Similarly, William Rosenblatt, MD, professor of anesthesiology, and his REMEDY nonprofit organization have donated surgical supplies to DU4U.

Asked what DU4U needs, the YSM participants are blunt: money. After an initial outpouring, donations have slowed. The group, which recently obtained nonprofit status from the IRS, has conducted fundraisers in the past months, including a benefit concert by the New Haven Symphony, Zinchuk said.

"We're hoping to ramp up," he said. "I think the challenge is that in the last few months people are getting tired. Ukraine is not the top line of the news anymore. Similarly, the donations have petered out. We have to work harder to fund our mission."

—*Christopher Hoffman*

To donate to Doctors United for Ukraine, visit dwighthall.org/doctors-united-ukraine, which is hosted by Dwight Hall at Yale.

New hope for those with sickle cell disease

Complications from the inherited blood disorder known as sickle cell disease damage almost every part of the body. Patients are vulnerable to infections, and their life expectancy is cut short. Trips to the hospital are a fact of life for them, and many rely on opioid-based drugs to manage their pain.

But according to Niketa C. Shah, MD, associate professor of pediatrics at Yale School of Medicine, recent advances in treatment mean that people with the condition have a much brighter future. And three studies in which Shah is the principal investigator point to even better outcomes for sickle cell patients.

Shah's specialty is hematology and oncology. She is the director of the Pediatric Cellular Therapy Program and the Pediatric Bone Marrow Transplant Program at Yale.

Approximately 100,000 Americans have sickle cell disease, and most are African American. The condition is usually diagnosed at birth. Instead of being round, the red blood cells are shaped like sickles, which prevents proper blood circulation.

Transplanting normal bone marrow from a healthy donor to someone with sickle cell disease is among the most effective treatments. But as good as it is, doctors face challenges when performing a bone marrow transplant, which is not an option for most patients. So, Shah is studying ways to improve the procedure and make it accessible to more people.

"We are learning more and more about how to do bone marrow transplants. Things are looking very promising for patients," Shah said. In three ongoing studies, she assesses the effectiveness of new drug treatments that could help patients receive a bone marrow donation. In two of those studies, participants must be 21 or younger, and in the third they are between the ages of 2 and 10.

One started in 2021, and the other two have been underway since 2018. So far, Shah said the results are promising.

Ideally, donated bone marrow should come from a patient's sibling who is a perfect genetic match. In 90% of those cases, Shah said the patient is cured. But Shah said even this optimal scenario warrants further investigation, and one study will look at ways of making the procedure viable for children between 2 and 10 years old. Opening up transplants to children this young would be a step forward because they are less prone to rejecting the donation. Transplants traditionally are for patients suffering from severe complications. Shah is including children who are not as sick because even when that is the case, their condition can worsen as they get older.

But a bone marrow donation from a sibling who is also a good genetic match is possible for only about 20% of sickle cell disease patients. Because of this, Shah is studying drug treatments that can make this treatment viable for people even when the match is not perfect and even when the donor is someone outside the patient's family.

Even when the donation comes from a sibling who is a good match, patients can suffer from a condition known as graft-versus-host disease. The risk increases if the donation comes from someone outside the patient's family. Shah is studying new drug treatments that could make a patient less likely to reject a bone marrow transplant, even when the match is not perfect.

Shah says making bone marrow donations accessible to as many people as possible is important because less invasive treatments like blood transfusions often do not prevent serious health problems. For example, participants in one of Shah's studies, who are 21 or younger, are very sick even with transfusion therapy. To qualify, a patient must have suffered strokes, respiratory issues, joint problems, and missed a significant amount of school because of their health.

—*Ken Byron*

MARIA PONOMARIOVA ILLUSTRATION

The lingering symptoms of long COVID

Following the onset of the COVID-19 pandemic, as many as one in eight infected people, according to Akiko Iwasaki, PhD, Sterling Professor of Immunobiology, are developing long COVID, in which symptoms persist for weeks, months, or years post-infection. As an increasing number of people become debilitated by the post-viral syndrome, such researchers as Iwasaki and Harlan Krumholz, MD, Harold H. Hines, Jr. Professor of Medicine (Cardiology), are working to uncover the mysteries behind the unrelenting fatigue and numerous other symptoms that can lurk after developing COVID.

There is no universal definition of long COVID. The Centers for Disease Control and Prevention (CDC) defines long COVID—renamed by the CDC in late 2022 as "post COVID conditions," or PCC—as symptoms persisting a minimum of four weeks post-infection. The World Health Organization (WHO) describes it as unexplained symptoms beginning within three months from the onset of COVID that last at least two months. These symptoms may include unrelenting fatigue as well as a range of neuroimmune symptoms. Between 9% and 25% of COVID-19 survivors in the United States experienced at least one PCC, according to a CDC report issued in June 2022, and the already woefully under-resourced medical system is not set up to accommodate this new wave of patients.

At Yale School of Medicine, Iwasaki and Krumholz are striving to figure out how infectious diseases can trigger chronic illnesses. After the onset of COVID-19 in 2020, many providers and researchers believed the infections were acute. Now, said Iwasaki, the definitions of acute and chronic are becoming "a little bit blurred." Autopsy samples from individuals who had acquired COVID months before revealed evidence of the SARS-CoV-2 virus in different tissues, suggesting that effects of the virus had been ongoing. "This so-called acute infection may not be that acute," said Iwasaki.

They have several hypotheses for why long COVID may be causing lingering symptoms. First, there may be a level of virus remaining that causes inflammation beyond COVID's acute phase. Second, the acute infection may trigger autoreactive T and B cells that are creating an autoimmune response. Third, COVID-19 may create a dysbiosis (imbalance) within the gut microbiome that leads to PCCs or the reactivation of other infections. Or, the SARS-CoV-2 virus may be causing irreparable tissue damage leading to lingering symptoms, such as shortness of breath. It is likely a combination of all these things. "When we say 'long COVID,' there are probably four or five diseases, if not more, under that umbrella term," said Krumholz.

Long COVID is not the first post-acute infection syndrome. Such infections as Ebola, Epstein-Barr, West Nile virus, and Lyme disease are also known to cause lingering symptoms, including fatigue and post-exertional malaise.

Iwasaki believes that the growing research around long COVID could also shine light on the mechanisms behind other chronic illnesses. In her own research, she plans to compare the immune phenotypes of patients who acquired myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) from an unknown infection—in most cases, individuals don't know what infection triggered their disease—and those struggling after Lyme disease, to people with long COVID. "We want to understand what's common and what's different and how to illuminate the disease pathogenesis," she said.

As growing numbers of patients with PCCs continue to suffer, Krumholz sees the urgency for bringing patients into clinical trials in large numbers and running tests and evaluations rapidly. He and Iwasaki hope to formulate an approach that includes the enrollment of patients in the United States in trials, collection of blood and other samples in a convenient manner, the formulation of easily completed questionnaires, and more. "All of these things can easily be transferred and used for research into other conditions," he said.

The pandemic encouraged Krumholz, a cardiologist and physician-scientist, to pair up with Iwasaki, a basic science researcher in immunobiology. The two recently launched the Yale LISTEN Study, which, according to their website, strives to learn more about "long COVID, post-vaccine adverse events, and the corresponding immune responses." Although the researchers come from vastly different worlds, they have learned to build upon each other's expertise to confront the challenges of the pandemic. Because the symptoms of poorly understood chronic illnesses like long COVID are so widespread, they often fly under the radar of many physicians, who tend to be hyper-focused on their area of expertise. These new alliances may provide the more holistic view needed to better understand chronic illness.

"The wind is shifting already," said Iwasaki. "People realize that these diseases have been ignored and that it is time to act."

When asked if he feels that long COVID will illuminate treatment for other illnesses, Krumholz said, "There's not any doubt about it."

"I hope we'll be able to relieve the suffering for people with long COVID, but our work is also going to provide insights that we can quickly transfer to other poorly defined illnesses," he continues. "Through our combination of deep clinical science and expertise with laboratory science, we can begin to make progress where we've been stymied in the past."

— *Isabella Backman*

round up

a collection of recent scientific findings

OPPOSITE PAGE: PILLI ILLUSTRATION; THIS PAGE: ARCTIC IMAGES

HOTSPOT GEOCHEMISTRY

A new theory originating from a study led by Amy Ferrick, a graduate student in Yale's Department of Earth and Planetary Sciences, could answer longstanding questions about the nature of magma hotspots, which help create some of the most beautiful places on Earth, including islands such as Iceland and Hawaii. One clue: their chemical composition, which suggests that the hot spots are "isotopic highways" and may offer insights into how the mantle and crust formed.

BRAIN MECHANISMS

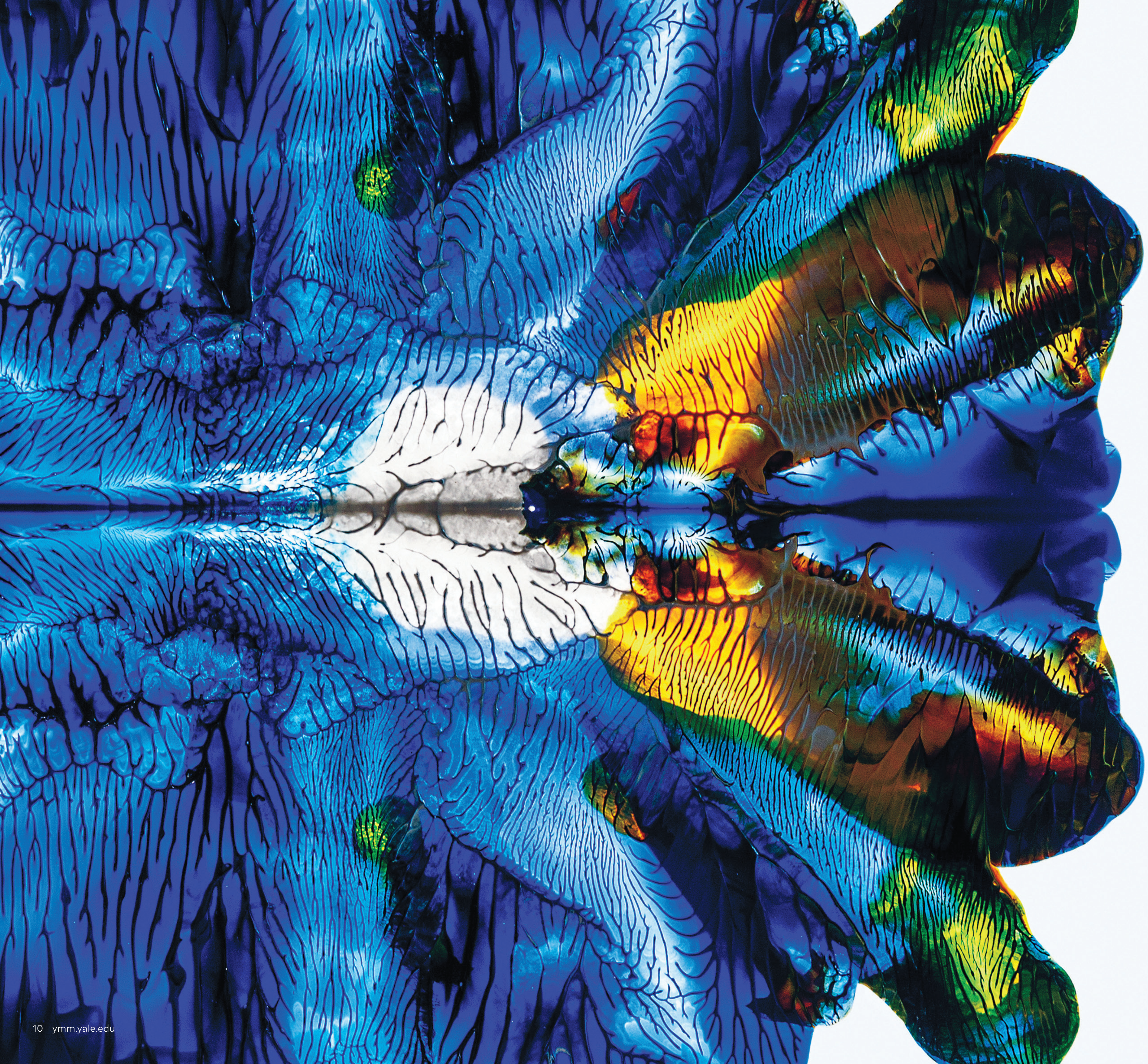
Tourette syndrome is a disorder characterized by uncontrollable motor or vocal tics that manifests in childhood, usually between the ages of 5 and 10, and can interfere with school performance, relationships, and quality of life. Using stem cells from patients to build 3D models that mirror portions of their brain development in a culture dish, a Yale team led by Flora Vaccarino, MD, Harris Professor in the Yale Child Study Center and professor of neuroscience, has illuminated the mechanisms underlying the condition as well as potential treatments for it.

PHYSICIAN TURNOVER

With burnout on the rise at many health care facilities, a recent study published in *PLOS ONE* used machine learning to predict with 79% accuracy which physicians would leave their jobs within the 2018–2021 study period. The study pulled data from electronic health records, rather than job satisfaction surveys, which tend to have low response rates. Length of tenure, age, the complexity of the physician's cases, and demand for services, were among the factors that impacted risk of physician turnover during the study period. "The findings highlight there's not a one-size-fits-all solution," said Andrew Loza, MD, PhD, co-senior author of the study and a lecturer and clinical informatics fellow at YSM.

BOARD INAUGURATION

Experts gathered in New Haven last December for the first meeting of YSM's Scientific Advisory Board, which draws from leading scientific institutions across the United States. Sessions focused on existing strengths, developing strengths, and cross-cutting themes. Topics included neuroscience; biomedical informatics and data science; and faculty development and partnerships with engineering.



A POWERFUL LEGACY

In 1921, when Yale School of Medicine (YSM) founded the Department of Pediatrics, a growing body of medical and scientific knowledge had begun to indicate that children required treatment and care that differed from that accorded to adults. YSM's new department established itself as a national leader in the field.

Over the years, the work that pediatricians have done with children, the research pediatricians have led into conditions and diseases, and medicine's understanding of how those conditions change over time and connect with adult disorders have transformed what is possible for many people.

YSM's pediatricians have been at the center of many of those transformations, and this issue should serve as a testimony to the efforts of faculty and staff over the years to advance pediatric medicine.

Adrian Bonenberger
Editor, *Yale Medicine Magazine*

Retrospective

OVER THE LAST CENTURY, THE DEPARTMENT OF PEDIATRICS HAS BEEN AT THE FOREFRONT OF MAJOR CLINICAL AND RESEARCH ADVANCES.

BY JOHN CURTIS

ON JULY 1, 1921, Edwards A. Park, MD, started his first day as chair of the medical school’s newly created Department of Pediatrics. He earned a salary of $7,000 per year and had a departmental budget of $25,000. He also had a pledge from the medical school of $225,000 to build a new pediatrics pavilion. Faculty numbered 11 physicians, four of whom were women.

A century later, the department has a faculty of 220 and a budget of more than $115 million. It has 13 subspecialty sections, and its faculty has been at the forefront of major clinical and research advances in pediatrics. In the 1940s, Edith Banfield Jackson, MD, pioneered the notion of "rooming-in," keeping newborns with their mothers rather than in a separate ward. In 1960, Louis Gluck, MD, created the world’s first neonatal intensive care unit at Yale. Since the department’s earliest days, Yale pediatricians have advanced the integration of psychiatry into the care of children. Dorothy Horstmann, MD, made a discovery about the transmission of polio that paved the way for vaccines. More recently, Yale faculty developed an “artificial pancreas” that allows adolescents to monitor their diabetes.

“The department has grown tremendously,” said Clifford Bogue, MD, chair of pediatrics and the Waldemar von Zedtwitz Professor of Pediatrics. “What that growth has allowed is greater sub-specialization and the development of tertiary and quaternary programs. When you only have three people in a section, you just cover the bases. When you have 15 or 20, you can have program X, program Y, program Z.”

ANCIENT TIMES

Specifics of the care of children date to the writings of Hippocrates, Galen, and Avicenna. But until the early 20th century, what we now call pediatrics fell under the rubric of women’s health or obstetrics. In 1853, Abraham Jacobi, MD, a German émigré in New York, began advocating for children’s departments in New York hospitals. He believed that pediatricians should take a more holistic view of health that included infant feeding, child hygiene, and disease prevention. Sir William Osler, MD, also advanced the notion that children should be treated separately. “Osler was the first to say that there are practitioners who are experts in diseases of children, and he gave it the name *pediatrics*,” said Margaret Hostetter, MD, who was chair of the Department of Pediatrics from 2002 until 2010.

The late 19th and early 20th centuries were a time of increasing industrialization, urbanization, and immigration. The progressive movement sought social changes, one of which was an end to child labor. In 1889, Jane Addams and Ellen Gates Starr founded Chicago’s Hull House, a settlement house for European immigrants that included the country’s first child guidance clinic. “The idea was to provide care broadly for children of immigrant families,” said Linda Mayes, MD, chair of Yale Child Study Center.

In New Haven in the late 19th century, children admitted to New Haven Hospital still went to the women’s wards. The Lady Visitors, the hospital’s ladies’ auxiliary, noted in their annual report in 1886 a need for separate women’s and children’s wards. “Patients with nervous complaints should not be subjected to the noise, which is often torture to them. Nor should the poor children — be deprived of the small amount of pleasure and fun that is possible for them.” In 1913, a separate, 12-bed children’s ward was established, as physicians increasingly understood that children, who are constantly growing and changing, had different medical needs.

“That is what is fascinating about pediatrics,” Hostetter said. “Everything is developing — the immune system is developing, the brain is developing, language skills, gross and fine motor skills. The pediatrician has to be able to see not only that everything is moving along appropriately, but also see when there is a diversion off the beaten track.”

MARGARET HOSTETTER, MD //

> “Osler was the first to say that there are practitioners who are experts in diseases of children, and he gave it the name *pediatrics*.”

THE FLEXNER REPORT AND PEDIATRICS AT YALE

The Department of Pediatrics owes its creation, in part, to the Flexner Report of 1910. The Carnegie Foundation for the Advancement of Teaching had commissioned education reformer Abraham Flexner to evaluate the country’s medical schools, many of them diploma mills. Flexner’s review placed medical schools into three categories — those that should be shut down, those that were exemplary, and those that were flawed but salvageable. In New England, only Yale and Harvard rose to that latter category.

The consequences of the Flexner Report persist a century later. The closing of medical schools disproportionately affected those that educated Black students, women, and the socioeconomically disadvantaged. For the last 10 to 20 years, medical schools, including Yale, have moved on from Flexner’s model of medical education by integrating science and clinical teaching. But at Yale in 1910, Flexner’s report led to significant reforms. First, Herbert Eugene Smith, MD, who at 25 years in his post was the school’s longest-serving dean, was replaced by George Blumer, MD. In 1913, the school entered into a formal affiliation with New Haven Hospital. Until then, collaborations had been informal, relying on existing relationships between medical school faculty and their hospital colleagues. Among Flexner’s recommendations was the creation of clinical and research departments whose full-time chairs would also serve as chief physicians in their respective hospital services. Initially, departments were created in four specialties — medicine, pathology, surgery, and pediatrics. Because of a lack of facilities, the new pediatrics department would not be launched for eight more years. ***/yale medicine magazine***

John Curtis is a frequent contibutor to Yale Medicine Magazine.

Department of Pediatrics Leadership

1921–PRESENT

1921

EDWARDS PARK

In 1920, when Milton C. Winternitz, MD, became dean of the School of Medicine, he began courting Edwards Park, MD, who was ensconced at Johns Hopkins, as chair of pediatrics. For Park, one of the appeals of Yale was the high prevalence of rickets in New Haven—Park was an expert in the disease, a vitamin D deficiency that causes bone deformities. One of his first steps as the new chair was to launch a study of rickets.

Martha Eliot, MD, who joined Park to work on the rickets study in 1923, was one of four women on the Yale faculty. Her research showed that rickets could be prevented by taking vitamin D, a treatment that all but eliminated the disease in America. She went on to become chief of the U.S. Children's Bureau, and together with colleagues, she drafted language in the 1935 Social Security Act related to maternal and child health. In 1947, she was the only woman to sign the constitution creating the World Health Organization.

Another member of the faculty, Ethel Dunham, MD, was the first woman house officer at New Haven Hospital. Park asked her to join the faculty in 1921 and placed her in charge of the pediatrics outpatient clinic at the New Haven Dispensary and the newborn infants' nursery.

1926

GROVER POWERS

In 1926, Park returned to Hopkins; and Grover F. Powers, MD, who'd come to Yale from Hopkins with Park, became chair. He held that post for 25 years, making him Yale's longest-serving pediatrics chair to date.

During Powers' term, a promised pavilion and other renovations came to pass. In the early 1930s, the Laboratory of Medicine and Pediatrics, the Clinic Building, and the Raleigh Fitkin Memorial Pavilion for Children were built to provide ambulatory sites and offices for faculty and staff. The Fitkin Building rose thanks to a gift from Abram E. Fitkin, an investment banker and philanthropist who'd lost his son to a childhood disease. "This was really the beginning of the establishment of ambulatory sites for subspecialty pediatrics, inpatient units, and faculty offices and laboratories," said Clifford Bogue, MD, the current chair of pediatrics and the Waldemar Von Zedtwitz Professor of Pediatrics.

Edith Banfield Jackson, MD, was among what Bogue called "the star-studded staff" that Powers recruited. A child psychologist who had trained with Freud, Jackson grasped the significance of the mother-child bond. She fought for what would become "rooming-in," allowing newborns to stay with their mothers instead of being placed in separate wards. Her ideas conflicted with existing protocols, but in 1949, New Haven Hospital became the first in the country to allow rooming-in. "This [practice] revolutionized postpartum care, and became an antecedent of modern birthing units," Bogue said.

Another stellar faculty member was Ruth Whittemore, MD, who established the first rheumatic fever and cardiac clinic in New England at Yale.

1952

MILTON SENN

With Powers' retirement in 1951, Milton Senn, MD, became the third chair of pediatrics. He'd arrived at Yale four years earlier as director of the Child Study Center and would continue as head of both departments. The Child Study Center had been launched by Arnold Gesell, MD, PhD, in 1911 as a "psycho-clinic" at the New Haven Dispensary—a facility on Crown Street founded in 1871 to provide free medical care to the city's working class and needy.

It was felt by some that Senn's heart remained in the Child Study Center—while he continued to lead the center, he created a post of physician-in-chief to run the pediatrics department. Senn believed that mental health should be part of pediatric care, and in his annual reports he referred to the two departments jointly as the Department of Child Health.

Among Senn's innovations were extending visiting hours for families of hospitalized children and starting a longitudinal care program, in which residents would follow a child from birth over an extended period of time. Faculty recruitment continued, and one hire was Dorothy Horstmann, MD, an internist whose findings about the transmission of poliovirus infection paved the way for a vaccine. Horstmann became the first woman at the medical school to earn tenure and the first to receive an endowed chair—named for John Rodman Paul, and existing in the School of Public Health.

Hospital construction also moved along with a new building, the Memorial Unit, which included a newborn nursery with 95 bassinets.

The integration of mental health and pediatrics, and the relationship between the Department of Pediatrics and the Child Study Center, continue to this day. "They are the closest departments in the School of Medicine," said Linda Mayes, MD, chair of Yale Child Study Center and the Arnold Gesell Professor of Child Psychiatry, Pediatrics, and Psychology. "It makes the most sense for the Child Study Center and Pediatrics to be collaborating heavily, because you really can't split physical health and mental health."

One new initiative, said Bogue, embeds center psychologists into the ambulatory pediatric practice for immediate consultations. "It's tremendous in helping address mental health issues that our patients have. They don't have to go to a separate place or make a separate appointment. Our faculty love it. They see the impact that caring for the mental health needs of our patients has on their physical health."

1963

CHARLES DAVENPORT COOK

The tenure of Charles Davenport Cook, MD, recruited from Harvard and Boston Children's Hospital, was marked by a new initiative that provided joint training of residents in medicine and pediatrics; the founding of what is now the Cornell Scott-Hill Health Center; and one of the earliest programs to identify child abuse or neglect. And Cook began creating the department's first subspecialty sections, appointing Jerome Grunt, MD, to the new section of pediatric endocrinology in 1964. Myron Genel, MD, professor emeritus of pediatrics, arrived to replace Grunt in September of 1971. "Both Jerry Grunt and myself were one-man pediatric endocrinology divisions at first, and I relied on the adult endocrine service and its postdoctoral fellows for several years until Howard Pearson became chair of pediatrics," he recalled. The position's "main responsibility" was as program director of the NIH-supported Children's Clinical Research Center.

Cook's goal was to increase faculty expertise in specific areas, Genel said. There were experts in nephrology, hematology, gastroenterology, infectious diseases, ambulatory care, and cystic fibrosis. But, Genel said, "These weren't sections. There were just individuals responsible for the various disciplines. It was a relatively small, compact department with perhaps 25 members, each of whom had responsibilities for their specific sub-areas."

Because the medical school was still relatively small, Genel said, he found collaborators in internal medicine, who were located on a floor below in the Dana Building. "A lot of the postdoctoral fellows in internal medicine rotated on our service. We co-authored a number of papers with them before I was able to support pediatric endocrine fellows," he said.

Warren Andiman, MD, professor emeritus of pediatric infectious diseases, arrived in 1973 as a postdoc and was assigned to work with Horstmann on a trial of a rubella vaccine. The training paid off years later when Andiman took a leadership role in the care of persons infected with HIV/AIDS and received funding to study the disease and the virus more thoroughly. In the 1990s, he led a study that popularized the discovery that HIV-positive mothers could be prevented from infecting newborns through treatment with AZT and helped make the practice commonplace in Connecticut.

Andiman recalled the department in the 1970s as "almost like a nuclear family of specialists who knew each other really well. We were on a first-name, slapping-on-the-back kind of relationship. Every Friday at four o'clock, we had an end-of-week conference. A few of the most interesting cases were presented by an attending to the whole department."

1974

HOWARD PEARSON

When Howard Pearson, MD, an expert on pediatric blood diseases, became chair in 1974, his priority was to expand the subspecialty sections. "His feeling was that one-person divisions could not possibly be productive when you had clinical responsibilities and teaching responsibilities," said Genel. "One thing that would always suffer would be research."

Eugene Shapiro, MD, vice chair for research and professor of pediatrics (general pediatrics) and of epidemiology (microbial diseases), arrived in the early 1980s for a fellowship and credited Pearson with fostering a good relationship with community pediatricians. "One of the first things that struck me was how good the quality of general pediatric care was in the community and, secondly, how good the relationship was between the community practitioners and the academics," he said.

Shapiro also recalled seeing, though he did not know it at the time, the hospital's first AIDS patient. "We couldn't figure out why an apparently normal infant would die of *Pneumocystis* pneumonia. Several years later, the little girl's mother was found to be HIV+." Shapiro supported Andiman's research into HIV transmission, providing biostatistical analysis of the reams of data collected by Andiman and his team of nurses and social workers.

In addition to building up the subspecialty sections, Pearson established the first endowed professorship in pediatrics; entered into an affiliation with the Hospital of St. Raphael to improve the care of children and provide another learning environment for residents; created a pediatric ICU; and initiated a newborn screening program for sickle cell disease. During his tenure, the South Pavilion was built, which allowed the department to concentrate pediatric services in one area.

The endowed chair, named for John F. Enders, was awarded to I. George Miller, MD, whom Andiman described alongside Horstmann as a "luminary" in the history of the medical school and Department of Pediatrics.

After stepping down as chair, Pearson joined with actor/philanthropist Paul Newman in founding the Hole in the Wall Gang Camp for children with cancer, sickle cell anemia, HIV/AIDS, and blood diseases. He served as the camp's medical director for 14 years.

1986

JOSEPH WARSHAW

Joseph Warshaw, MD, continued the expansion of subspecialty sections, and the department saw significant growth in research. He'd arrived at Yale in 1973 as director of perinatal medicine but left in 1982 to chair pediatrics at the University of Texas Southwestern Medical Center. During Warshaw's tenure as chair, he also became the school's deputy dean for clinical affairs. "He was a wonderful figure not only at Yale but also nationally and internationally," said Margaret Hostetter, MD, who later became chair of pediatrics at Yale. Under Warshaw, she said, the department became a pediatrics powerhouse, thanks to his recruitments. He also helped plan the Children's Hospital and the Yale Child Health Research Center. In 2000, Warshaw left Yale to become dean of the medical school at the University of Vermont.

2002

MARGARET HOSTETTER

In 2002, Margaret Hostetter, MD, became the first woman to lead the pediatrics department. Because of her expertise in infectious diseases, Warshaw had recruited her as chief of the immunology section and director of the Yale Child Health Research Center in 1998. Like Pearson and Warshaw, she saw a need to expand the subspecialty sections, and the faculty grew from 60 physicians to 90.

"There were two or three divisions that were running on fumes," she recalled. "They had terrific people who were asked to do everything—do research, take care of patients, hire faculty. It's a tall order."

Hostetter worked with Marna Borgstrom, MPH, then president and CEO of Yale New Haven Hospital, and Carolyn Slayman, PhD, the med school's deputy dean for scientific affairs, to expand the department's roster of physician-scientists. "When Marna Borgstrom took over the leadership of YNHH, it was clear to me that her interest was in expanding the clinical impact of Yale. The interest of the medical school was in research," Hostetter said. "So the partnership was ideal."

Another looming reality was the perennial lack of space on the medical campus—pediatrics had just 14 examination rooms. "We had to find other clinical space," she said. A satellite branch opened on Long Wharf in New Haven, but that created other complications. "The challenge was distance. It's difficult to perform at 333 Cedar if you're supposed to be down at Long Wharf."

2012

GEORGE LISTER

George Lister, MD, the Jean McLean Wallace Professor of Pediatrics and professor of cellular and molecular physiology, had served as chief of critical care for 25 years before moving to the University of Texas Southwestern. He returned to Yale in 2012. During his tenure, he expanded the Department of Pediatrics' clinical footprint and strengthened its educational mission. He has served as president of the Society for Pediatric Research and the American Pediatric Society, and chair of the board of directors of the American Board of Pediatrics.

2017

CLIFFORD BOGUE

Clifford Bogue, MD, became chair in 2017 after two years as interim chair. A physician-scientist, he came to Yale in 1989 for a fellowship in critical care medicine. Although his duties as chair leave no time for research, he still spends four weeks each year as a hospitalist. "It's a great opportunity for me to see how things are functioning and get better insights into how I can help support our staff, our trainees, and our faculty," he said.

Reflecting on changes in the practice of pediatrics, Bogue noted advances that have benefited all specialties. "We now have much more capacity and knowledge to diagnose genetic disorders. The next big leap is how we translate that into therapies. We have a number of investigators looking at the genetic components of congenital heart disease and rare diseases, trying to understand the genetic mutations and the molecular and biological pathways so we can design therapies."

Among the efforts in gene editing at Yale is one to enable physicians to treat the genetic mutations underlying cystic fibrosis. The multidisciplinary team published their findings in *Nature Communications* in 2015. "Right now, we can do this in cell cultures and animal models, but the goal is to keep refining this to be able to provide it as a therapeutic," said senior author Marie Egan, MD, vice chair for research, professor of pediatrics (respiratory) and of cellular and molecular physiology. "This is step one in a long process."

Even with faculty numbering 220, Bogue sees still more growth in the department's future. One of the limits has been space. In 2011, when he served as interim chair after Hostetter stepped down, he and Cynthia Sparer, executive director of Yale New Haven Children's Hospital and president of ambulatory care for Yale New Haven Health System, began looking for satellite locations. "We knew that we were not going to grow and be the top-notch children's hospital we wanted to be without going around the state and having sites for patients closer to home," Bogue said. The department now has satellite spaces in Greenwich, Norwalk, Old Saybrook, and Trumbull, and a second site in New Haven. Another site is slated to open in New London in May.

With faculty spread out, maintaining collegiality has come up for discussion at Bogue's meetings with his vice chairs. "Cohesion in a section becomes so much more important," he said, noting that the COVID pandemic has made it harder to keep people connected. "We're still trying to figure out how you maintain those connections—how you get people together for those random collisions where you have a conversation, and you learn something new about somebody, and maybe something comes of it." Efforts are in place, however, to provide some cohesion. "We have weekly research-in-progress meetings. The sections themselves have their own research meetings and one at the departmental level. Word gets around," Bogue said.

The department, Bogue said, is also committed to diversity. Since its creation in 1921, it has fostered a reputation for nurturing women on the faculty. Currently, 70% of the faculty's assistant professors are women, as are 56% of associate professors, and 33% of full professors. About a quarter of the faculty, Bogue said, are nonwhite or Latino. "It's important that we have a faculty that represents the diversity of the patients we serve. They bring a diversity of experiences and perspectives that makes us a better department."

In 2018, Marietta Vazquez, MD, was named vice chair for diversity. Initiatives include student fellowships for medical students from underrepresented groups and research programs for med students at historically Black colleges and universities. "It's really important for our patients to see doctors who look like them, so they feel much more comfortable," Bogue said.

For Bogue, the department's greatest strength is its people. "We have high-quality faculty, people that are inquisitive, that are interested in making an impact," he said. "Most of the faculty aren't here just to see patients. They want to make a difference. It's an incredibly collegial and supportive group. It's harder as it gets bigger, but it's a place where people are truly respected and enjoy each other and work well together. That makes it a special place."

Outliving disease

ADVANCES IN MEDICINE ALLOW PEOPLE TO
LIVE WITH CONGENITAL DISEASES
THAT MIGHT HAVE BEEN FATAL IN THE PAST.

BY KEN BYRON

CHRISTOPHER JOSSICK had his first open-heart surgery when he was five weeks old. Born more than a month prematurely, Jossick weighed approximately four and a half pounds, and his heart was about the size of a walnut.

Jossick, now 27 and living in Newtown, Connecticut, needed the surgery because of a rare congenital heart defect called truncus arteriosus. There are about 250 cases of this defect diagnosed in the United States each year. The aorta, a large artery that carries oxygen-rich blood to the body, and the pulmonary artery, which carries oxygen-poor blood to the lungs, do not separate completely in babies born with truncus arteriosus. Instead, the baby has a single artery leaving the heart containing both oxygen-poor and oxygen-rich blood. An abnormally high amount of blood is sent to the lungs, which makes it difficult for the baby to breathe. People born with truncus arteriosus rarely survive to adulthood without surgery within the first few months of life.

When William Hellenbrand, MD, professor emeritus of pediatrics (cardiology), started practicing medicine 50 years ago, the prognosis for someone like Jossick would not have been as good as it is now.

“Chris would have had bleak prospects; it would have been a difficult outcome,” said Hellenbrand. He joined the Yale School of Medicine faculty in 1976 and was one of Jossick’s first doctors.

In the early 1970s, the mortality rate for babies born with some complex congenital heart defects was as high as 90%. Today, that rate has dropped to about 5%. Hellenbrand said that dramatic advances in surgical techniques and the use of catheters to perform minimally-invasive procedures that once required open-heart surgery now mean that people who once would have died in infancy or shortly after birth can live to adulthood.

Because of advancements in catheterization, doctors can replace a defective heart valve without open-heart surgery, said Britton Keeshan, MD, MPH, an assistant professor of clinical pediatrics whose specialty is cardiac catheterization for children and adults. He said that some congenital heart conditions once meant that people born with them might have as many as eight surgeries during their lives. Now, they may need only one or two. “We have converted some surgeries into catheterization procedures, which has huge downstream consequences for children and adults who are just trying to live their lives,” Keeshan said.

A device called a Melody™ valve, inserted through a catheter to replace a defective pulmonary valve in the heart, has revolutionized the treatment of congenital heart defects since its introduction in the early 2000s. The Melody™ valve consists of a segment of bovine jugular vein mounted inside a platinum-iridium stent. Jossick said that he had three open-heart surgeries in childhood. He was an early recipient of a Melody™ valve and hopes that the new device means that he won’t need surgery again.

One person in 100 is born with a congenital heart defect, the most common birth defect, said Robert Elder, MD, associate professor of pediatrics (cardiology) and of internal medicine (cardiology). Elder is director of the Yale Adult Congenital Heart Program and one of Jossick’s doctors.

Last September, Jossick and Elder participated in the Walk for 1 in 100 in West Hartford, one of a series of events to raise money and awareness for the American Congenital Heart Association. Jossick raised more than $2,000, and organizers said that he was one of its top fundraisers.

Joining them for the event was Adrienne Webb, who is also one of Elder’s patients and was born with a group of four heart defects called tetralogy of Fallot. Like Jossick, the defects Webb was born with resulted in insufficient oxygen in her blood, also known as a cyanotic heart defect. As a result, she had her first open-heart surgery when she was 7 to repair a hole between the two lower chambers of her heart. At age 18, Webb had another open-heart surgery, this time to replace her pulmonary valve. In 2011, the valve was replaced with the Melody™ valve.

Webb is now 59 and leads an active life. She is a project manager at Yale Law School; she enjoys hiking in Vermont and New Hampshire and horseback riding twice a week. But Webb’s experience is also a cautionary tale, Elder said. Even when surgery as a small child is successful, people with congenital heart defects will often need procedures and treatment for the rest of their lives. In 2019, Webb was diagnosed with endocarditis, an infection of the heart’s chambers and valves.

The condition was a real setback for Webb. “I was not in a good place, it was like the fire department pulled up, and the house was fully engulfed in flames,” she said. In Webb’s case, the infection attacked the pulmonary valve doctors had put in her heart in 2011. Because of this complication, she needed open-heart surgery to replace the valve for the third time and was in the hospital for a month, followed by a cardiac rehabilitation program. “I slowly worked my way back, but now I’m doing all of my normal activities,” Webb said.

BRITTON KEESHAN, MD, MPH //

“We have converted some surgeries into catheterization procedures, which has huge downstream consequences for children and adults who are just trying to live their lives.”

As with any other chronic health problem, heart patients have a role to play to ensure that they get the most benefit from advances in medical technology. For example, seeing a specialist who treats congenital heart defects in adults is crucial, even if you feel fine. Doing so, Elder said, can uncover a problem before it gets out of hand. “Dr. Elder is exactly right. It’s important for people like us to stay in care because we have lifelong, complex issues,” Webb said. ***/yale medicine magazine***

Ken Byron is a frequent contibutor to Yale Medicine Magazine.

A new way to see

ORDERING AN MRI FOR A PREMATURE BABY USED TO BE A MORE COMPLICATED DECISION.

BY CHRISTOPHER HOFFMAN

THE MRI MACHINE AT THE CHILDREN'S HOSPITAL was eight floors down from the Neonatal Intensive Care Unit, a long and problematic journey for a preemie. Everything from the temperature change—the NICU thermostat is set in the 70s, warmer than the rest of the hospital—to bringing along life-sustaining equipment like ventilators and IV lines presented a challenge.

A baby's need for an MRI had to be carefully weighed against the risks, said Matthew Bizzarro, MD, professor of pediatrics (neonatal-perinatal medicine) and chief of neonatology at the Yale New Haven Children's Hospital NICU. "We are dealing with a very fragile creature who doesn't handle transportation well," Bizzarro said. "Putting them in an elevator and moving them several floors increases risk."

When the hospital decided to build a bigger and improved NICU, Bizzarro and other Yale neonatologists saw an opportunity. Why not put an MRI in the new unit, eliminating the potentially perilous trip to and from the imaging suite? Adding to the case for an in-house MRI was a new machine developed in Israel specifically for babies and preemies. The MRI junior is about half the size of a regular machine, Bizzarro said. Another plus: Its magnetic field is smaller, allowing equipment containing metal, as well as doctors and nurses, to remain in the room during the procedure. That feature eliminated the need for Rube Goldberg-like measures to keep babies connected to medical equipment during imaging. It also meant that smaller, less stable babies could now get an MRI, Bizzarro said.

Yale New Haven needed little convincing, and the new device arrived in the expanded and upgraded NICU in 2020, going into service early the next year. "I really didn't have to talk them into it," Bizzarro said. The hospital is one of just two or three in the United States with the device. The machine has made an MRI for a preemie or baby much easier and less risky.

"Taking a baby down to the MRI took a good 15 minutes," said Yeisid Gozzo, MD, director of the Yale New Haven Children's NICU. "Now we can do it in a third of that time. It allows us to get more information more quickly."

The new device has not entirely eliminated the need for anxious trips to the larger MRI. Because it is smaller and has less powerful magnets, the NICU MRI doesn't provide as much detail. That said, most of the time the MRI junior does the job, Bizzarro said.

Given an MRI's confined space, the noise it makes, and the need for patients to hold still, you would think babies would do poorly in the machine. The opposite is true, Gozzo said. Babies appear to tolerate the procedure better than many adults. "What we have found is that the vast majority of the time, if we just feed and swaddle them, they just go to sleep," she said. "They do pretty well in the scanner. The noise doesn't seem to bother them."

Yale doctors are using the device to check for brain bleeds, hydrocephalus, structural malformations, white matter injuries, damage caused by oxygen deprivation, and other maladies associated with preterm birth. The most common usage of the MRI junior is taking a snapshot of a preemie's brain at discharge, setting a baseline for care. "All in all, it's been a benefit to the NICU to have the scanner in there," said Steve Peterec, MD, the unit's associate director. "We can see if interventions work or not."

One of the biggest benefits of the pediatric MRI is its ability to track brain development over time. The series of images allows doctors to diagnose and treat problems earlier. Bizzarro cited cerebral palsy, a major concern for preterm babies, as an example.

"We can't make the diagnosis in the NICU," he said. "But what we can do is identify things on an MRI that wouldn't be seen in an ultrasound, which would key us into an increased likelihood for that patient to develop cerebral palsy down the road. That could mean earlier intervention within the hospital and after discharge."

Bizzarro said there has been a learning curve as doctors figure out the best uses of the machine. The device is especially promising as a research tool, enabling physicians to develop better treatments and interventions, he said. "I think there's a lot of untapped potential as we get more and more used to the device," Bizzarro said. "As we get more familiar with it and as the technology advances, it opens up a lot more options, particularly for research."

YEISID GOZZO, MD //

> "Taking a baby down to the MRI took a good 15 minutes; now we can do it in a third of that time. It allows us to get more information more quickly."

The MRI junior is a highlight of Yale's upgraded NICU. The new unit, which opened in 2018, is large enough to accommodate 68 babies compared to 50 in the old one. Babies who were once kept 10 to a room are now in singles or doubles. Rooms have space for mothers, if the baby's condition allows it, enabling them to bond with and breastfeed their newborns. The unit also has its own operating suite so that babies needing surgery no longer need to be moved to another part of the hospital, Peterec said.

While the MRI's use can vary—in some months, doctors order only a few scans; other months it's in heavy use—the machine has proven a major plus for the NICU, Gozzo said. In addition to being easier on the babies, the on-site machine allows doctors to get vital information fast, she added. "It's an additional resource," she said. "It's a pretty big deal when you want to take a baby in an incubator with all these pumps and on a ventilator down all these floors (to the MRI). It has made [imaging] a lot safer for the baby."

In the last decade, the average number of babies in Yale's NICU at any given time has gone from the 40s to about 60, Peterec said. The reasons for the increase are not entirely clear, as the incidence of prematurity has decreased in recent years from 13% to 10%. One explanation may be that more babies are born at earlier stages of prematurity, between 28 and 32 weeks' gestation. "Babies are spending a longer time in the unit," Peterec said. */yale medicine magazine*

Christopher Hoffman is a frequent contributor to Yale Medicine Magazine.

Beyond the clinic

ON-SITE ATTORNEYS HELP ADDRESS THE SOCIAL DETERMINANTS OF HEALTH.

BY JEANNA LUCCI CANAPARI

KEEPING CHILDREN HEALTHY is an effort that extends well beyond the walls of any health clinic, and helping the most vulnerable children—those who come from underserved communities—requires a strong, coordinated effort involving doctors, nurses, social workers, teachers, parents and guardians—and now, lawyers. And at the sharp end of that crucial collaboration is the Medical-Legal Partnership.

The Medical-Legal Partnership (MLP) places attorneys on site at health care clinics and hospitals to address the social determinants of health. These factors include access to housing and utilities; education and employment; immigration and insurance status; and personal and family safety. According to a National Academy of Medicine white paper, 80% to 90% of a person's health is shaped by the social determinants of health, which are known to contribute to poorer health outcomes and increased costs. And these factors disproportionately affect children from low-income and minority communities.

The Medical-Legal Partnership Project at Yale is an interdisciplinary collaboration between the Center for Children's Advocacy (CCA) and Yale New Haven Health (YNHH). The Medical-Legal Partnership Project serves the Yale New Haven Children's Hospital, both inpatient and outpatient, but focuses on patients from underserved groups, as well as those in the Connecticut Husky Medicaid program. While the Medical-Legal Partnership Project focuses on pediatric patients, other partnerships at Yale and on the national level address other concerns, including care for veterans, palliative care, and oncology.

Ada Fenick, MD, associate professor of pediatrics, has served as the medical director of the Medical-Legal Partnership Project since its founding in 2013. She worked alongside Alice Rosenthal, the founding attorney of the Medical-Legal Partnership Project, for nine years until Rosenthal's retirement last fall, when attorney Sarah Mervine joined the Medical-Legal Partnership Project. Fenick and Rosenthal describe MLPs as being like a "three-legged stool," with three important activities that underpin the work of an MLP.

PATIENT CARE AND LEGAL REPRESENTATION

The first leg of the stool is direct patient care and, when necessary, ensuring the care of individuals through legal representation. "We are an interdisciplinary team, and when we work together, we can work to the height of our licenses," says Rosenthal. Rosenthal is not a health care lawyer by training, but focuses on child advocacy and public interest poverty law. At the Medical-Legal Partnership Project, she provides legal aid in the three areas of greatest need: education, housing, and benefits. She addresses a subset of the social determinants of health known as health-harming legal needs.

To address these needs, a family may require a lawyer to step in and deal with negligent landlords to handle necessary mold or rodent mitigation, two housing conditions that worsen asthma and cause avoidable hospitalizations. Another family might need to speak up at school to gain Wi-Fi access so that a child's smart diabetes pump can work during class. Someone else may need a lawyer to ensure that a child receives disability benefits. In some cases, Rosenthal can provide advice and alert patients to their rights in a particular area. In other cases, the lawyers can represent patients in court. "Other people might give up a little earlier," says Fenick. "When a parent can say, 'I am going to call my lawyer,' things happen."

Many of the early medical-legal partnerships were based in pediatric settings. The first was founded in 1993 in Boston in response to the high number of children with asthma returning repeatedly to the hospital with symptoms that did not respond to treatment. The second began in Connecticut in 2000 with the Center for Children's Advocacy, a Hartford-based organization that entered into a partnership with Yale in 2013. Today, according to the National Center for Medical-Legal Partnership, 37 children's hospitals in the U.S. employ MLPs. From June 2013 through July 2021, the Yale pediatric MLP, which is fully funded by YNHH, received 2,548 referrals.

Physicians can now also use the electronic medical record to make referrals to the MLP. Additionally, physicians conduct screenings with patients that cover social determinants of health in order to flag medical issues, such as the need for mold mitigation before winter asthma flares.

"It's hard to have a screening program when you have no opportunity to assist or refer them to help," says Maryellen Flaherty-Hewitt, MD, associate professor of clinical pediatrics and medical director of pediatric primary care. "It's difficult for families to share [that] they are struggling, particularly if they feel that there is no help available," she says. "It's not that we are collecting data or being nosy about their lives; we actually have resources to share with them and put in place so they can get the help they need."

PHYSICIAN EDUCATION AND TRAINING

Flaherty-Hewitt cares for patients at the children's hospital's ambulatory care practice located at 150 Sargent Drive in New Haven—a new location that opened in 2020 in partnership with affiliated community health centers Fair Haven and Cornell Scott. As home to the Yale pediatric residency continuity clinic, the practice is central to the second leg of the MLP mission: education and training. There, the MLP is a crucial part of the care new physicians are learning to provide. "Residents can have that as part of their toolbox to help their patients from the beginning of their training," says Flaherty-Hewitt.

Much of the education takes place beyond 150 Sargent Drive; talks and didactics reach health care providers affiliated with YSM and YNHH at many locations. Education is also provided to social workers and other community-facing employees, as well as groups within the community.

"We don't have to know every law," says Fenick. "But our job is to spot the problem, and knowing the law helps you understand that there is a problem."

ADVOCACY

The third leg of the stool is wider advocacy, and the necessary work to change laws that have negative effects on large groups of patients. As one example, Fenick says, a group of residents traveled to Hartford last year to testify in favor of eliminating the religious exemption from the state education laws requiring children attending public and private schools and day cares in Connecticut to comply with immunization requirements to attend school.

In addition to the ambulatory care MLP, Yale is also the home of the first MLP in the country focused on behavioral health. The Yale Child Study Center entered into a partnership with the CCA in 2020 and works with a CCA attorney to provide legal interventions for children suffering from family trauma and health-harming environmental stressors that have severe effects on children's lives and disproportionately harm children of color.

"I like to think of the MLP as changing the way we provide care and how we teach care to learners," says Rosenthal. "When learners and providers think of the social drivers of health, they will know that a solution is at hand that can have an impact on how they address the health of the child, and how they can act preventatively." ***/yale medicine magazine***

Jeanna Lucci Canapari is a frequent contibutor to Yale Medicine Magazine.

Racing to solve rare diseases

INSTITUTIONAL SUPPORT ENCOURAGES RESEARCHERS AND CLINICIANS TO DIAGNOSE AND TREAT RARE DISEASES.

BY BRIAN HUDGINS

TWO CLINICIANS AT YALE CHILD STUDY CENTER, Fred Volkmar, MD, and Alexander Westphal, MD, PhD, provided Abha Gupta, MD, PhD, support during a preliminary study of 15 families affected by childhood disintegrative disorder, which revealed neurobiological differences between it and other forms of autism.

During postdoctoral training, Gupta’s general autism research had not included meeting any individuals or families affected by childhood disintegrative disorder. The collaboration with Volkmar and Westphal gave Gupta, associate professor of pediatrics, a firm footing to push her research forward. Her initial encounters with patients had a lasting impact.

Childhood disintegrative disorder (CDD), or severe regressive autism, typically affects one or two in 100,000 children. It is characterized by a relatively late loss of acquired skills in social, language, and motor functioning. “These children have experienced normal development, and it sometimes seems like the regression is overnight,” Gupta said. “When development stabilizes, they are often severely impaired.”

Gupta and her colleagues could find no clear signal of the cause of CDD regression. “About three-fourths of the kids have a striking period before the regression when they are very agitated or upset,” Gupta said. “The disturbing thing about CDD is wondering if younger kids feel that stress, and they cannot articulate it.”

Gupta’s immediate goal is to recruit 50 families to obtain funding for whole genome sequencing and imaging studies. Gupta has received patient referrals from Jennifer Bain, MD, at Columbia University. Sally Ozonoff, MD, at UC Davis, has analyzed family home videos to document the timing and nature of CDD regression.

Funding for such projects, however, has become more difficult to secure during the last few years since CDD was removed from DSM-5 and placed into the broader category of autism spectrum disorder.

CHANGE OF HEART

Collaboration, mentorship, and institutional opportunity in the Department of Pediatrics at Yale School of Medicine (YSM) are crucial to rare disease research. By definition, a rare disease does not affect many people, and it can be difficult to justify directing scarce or precious resources away from efforts to treat a more widespread condition.

At YSM, however, abundant institutional capabilities exist to support research. The Department of Pediatrics and Yale Child Study Center boast a long-standing tradition of inquiry into obscure childhood ailments that can have catastrophic consequences later in life. Knowledge and relationships that go back decades help shape research today.

The late Ruth Whittemore, MD, a pediatric cardiologist, authored papers as early as 1987 addressing genetic factors of congenital heart disease. With that foundational research in hand, Martina Brueckner, MD, professor of pediatrics (cardiology), has witnessed a striking recent change in available data on the causes of congenital heart disease.

“The field of what causes congenital heart disease has substantially changed during the last 12 to 15 years,” Brueckner said. “When I was training, we were told it was multifactorial. If a child was born with a heart defect, parents would be blaming themselves.”

Current research suggests that most of those cases of heart disease are either influenced by genetic factors or are entirely caused by genetic mutations. Richard Lifton, MD, who served as chair of the Department of Genetics at Yale from 1998 to 2016, helped to develop genomic approaches to the diagnosis of rare diseases. “Some of the first papers using exome sequencing to make genetic diagnoses came out of Yale,” Brueckner said. “The Yale Center for Genome Analysis has been incredibly generous about sequencing all of our congenital heart disease samples. After the Human Genome Project, we were first able to do a large-scale genomic analysis of congenital heart disease patients around 2010.”

When the National Institutes of Health started pumping funding into congenital heart disease research a dozen years ago, Lifton and Brueckner turned out to be in the right place at the right time. That enabled Yale and a handful of other institutions throughout the United States to develop a large genomic and phenotypic database of patients through their NIH-funded group, the Pediatric Cardiac Genomics Consortium. The consortium has recruited 15,000 congenital heart disease patients. The Yale Center for Genome Analysis has been able to do exome sequencing on a large number of patients. “Hopefully by the end of 2023, we will have sequence data on 14,000 of the 15,000 patients,” Brueckner said. “Now that you have so many patients and real data, we have learned that a lot of congenital heart disease does have clear-cut genetic causes.”

WIDENING THE SCOPE

Being able to return test results more quickly to rare disease patients has provided a boost for Mustafa Khokha, MD, professor of critical care pediatrics and of genetics, and his peers. Khokha is also the director of the Pediatric Genomics Discovery Program, which seeks to discover the genes that cause childhood diseases. “Sometimes it could take years to see results because these patients are rare,” Khokha said. “Returning that result to patients — nothing is more motivating than that.”

As the cost of whole genome sequencing has gradually dipped to about $200, opportunities to examine small patient populations have increased.

“That [low cost] is important — it is the number one boost to innovation,” Khokha said. “If we see a patient who we think might have a genetic disorder, there is very little hesitation from us to sequence the patient because there isn’t a cost barrier.”

Birth defects are a leading cause of infant mortality, accounting for 20% of infant deaths in the United States, according to the Centers for Disease Control and Prevention. “Even though these disorders are very rare molecularly — overall, they are the biggest problem in pediatrics,” Khokha said.

Whether the diagnosis is CDD, congenital heart disease, or a host of other rare diseases, medical scientists at YSM are applying existing rare disease research on a broader scale. “Rare diseases do not just impact one patient,” Khokha said. “They have a tremendous impact on general biology.” ***/yale medicine magazine***

Brian Hudgins is a first-time contributor to Yale Medicine Magazine.

Learning from children

FOR OVER A CENTURY, RESEARCHERS HAVE
STUDIED CHILDREN'S WELL-BEING.

BY JENNY BLAIR, MD

CHILDREN ARE NOT ONLY CARED FOR, scolded, rewarded, and punished. They are also theorized about—and those theories change with time. Adults have concluded, variously, that children are in constant spiritual danger, or that they are inherently close to God, or that they are blank slates.

Around the turn of the 20th century, some Western health professionals decided to gather data on children by studying how they grow. One of the first to do so, psychologist and pediatrician Arnold Gesell, MD, PhD, spent his most influential years at Yale, founding in 1911 what later became Yale Child Study Center.

Gesell's then-novel interest in children's development, and the insistence of his successor Milton Senn, MD, on a cross-disciplinary approach, established traditions of curiosity and collaboration at Yale that have long influenced the world of child mental health.

Today's Yale Child Study Center is a leader in the study of such topics as varied as pediatric trauma, psychopharmacology, autism, mind-body connections, and how early childhood experiences and environmental influences affect health throughout the lifespan. One of its unifying principles is that children's mental and physical well-being aren't separate. That insight informs the close ties between the center and the Department of Pediatrics, according to Yale Child Study Center Chair Linda Mayes, MD.

“[Pediatrics Chair Clifford Bogue, MD] and I are keen to continue to work closely together and to bring the departments together,” said Mayes, who is Yale Child Study Center's Arnold Gesell Professor of Child Psychiatry, Pediatrics, and Psychology. “We really have a hope for an agenda about child health. Not child physical health, not child mental health—child health.”

WHERE CHILD MENTAL HEALTH BEGINS

As an assistant professor in Yale University's Department of Education, Gesell founded a children's clinic in 1911. At the time, he was one of very few scholars of child development to study babies, and he used new tools like photography to investigate developmental milestones. In 1934, his groundbreaking *Atlas of Infant Behavior* provided these milestones for parents' reference.

Gesell spoke out against scolding and physical punishment and advocated for child welfare reform. Though not all his views have aged well—he favored eugenics, even while supporting environmental interventions like preschool programs—his approach offered an alternative to authoritarian parenting guides and guilt-inducing psychoanalytic theories.

Upon Gesell's 1948 retirement, Senn assumed leadership of the children's clinic, which became the Child Study Center, and later was named chair of the Department of Pediatrics. Senn not only helped entwine the two departments, he also widened the center's focus to include social workers and educators, initiating the interdisciplinary emphasis that continues today.

SUPPORTING TRAUMATIZED CHILDREN

In fall 2021, the American Academy of Pediatrics declared a state of national emergency in child and adolescent mental health. COVID-19 and its widespread death and disruption had poured fuel on an existing crisis, with rates of depression, anxiety, and suicidal behavior climbing in young people years before the pandemic.

Many such mental health problems arise after trauma and early-life adversity, according to Mayes; without intervention, affected children may face lifelong poor health.

“We as humans have a pretty adaptive biology. But you can bend a tree so that it breaks,” Mayes added.

Still, there are ways to help bolster that tree. Yale Child Study Center has a long history of caring for pediatric trauma survivors. The late Donald J. Cohen, MD, Yale Child Study Center's 1980s- and '90s-era director and one of his generation's leading child psychiatrists, developed an extensive international network of collaborators to improve the care of traumatized children around the world. Steven Marans, MSW, PhD, Harris Professor in the Child Study Center and professor of psychiatry, renowned for training police to work sensitively with traumatized children, co-directs the Yale Center for Traumatic Stress and Recovery, which develops new trauma interventions and provides direct services to children who have witnessed or experienced violence.

Many of those kids come Marans' way via emergency physician Kirsten Bechtel, MD, professor of pediatrics (emergency medicine) and of emergency medicine. Bechtel, an expert in caring for traumatized and abused children, works alongside Yale Child Study Center fellows to care for troubled and suicidal children who come to the Emergency Department. She is partnering with Yale Child Study Center faculty to develop ways to prevent abusive head trauma—including a 90-second video to help new parents cope with frustration—as well as on legislation to limit children's access to firearms.

“We're trying to find where we naturally have overlap, and then garner our forces to work together,” Bechtel said. “We're lucky—we have lots of resources at Yale, and we're lucky that we have folks who are studying behavioral health.”

FACING UNCERTAIN FUTURES

Arguably, climate change is the greatest crisis younger generations face, and anxiety related to its potential effects is a growing topic of psychiatric research. Associate research scientist Laelia Benoit, MD, PhD, studies how children and adolescents in France, Brazil, and the United States perceive and feel about climate change.

They are alarmed but not paralyzed, she's found, and they're keen to take action. Furthermore, they respond positively to messages of hope and collective climate action, such as inspiring stories of change on social media.

“We are focusing on making sure that the new narratives are something that helps you feel empowered, have fewer mental health issues, and take concrete action at your local level, using media that young people actually use, like TikTok or Instagram,” Benoit said.

Amid societal inequity, some of today's children will go on to lead much healthier lives than others. The divergence starts young. How exactly early-childhood experiences affect lifelong health fascinates associate research scientist Amanda Dettmer, PhD, who studies those questions using nonhuman primates.

There are striking similarities between human and monkey infants. Both experience difficult health if they are born into worse social situations or if their attachments to caregivers are disrupted. But, Dettmer said, “What's been really hard to determine in humans is why.”

Using a vast data set and biobank from her previous work with monkeys at the National Institutes of Health, Dettmer is working to tease out the biological processes that tie early experiences to lifetime health. So far, it has become clear that infant monkeys with disrupted attachment tend to be hyper-responsive to stress, while the immune systems tend to falter in infant monkeys who are lower ranking in the troop. Dettmer expects a more detailed picture to emerge in time.

Because monkeys reach adulthood in just a few years, Dettmer has data ready to analyze across the lifespan. All of it is relevant, and all of it begins in infancy and childhood.

“One of my grants is from the National Institute on Aging,” Dettmer noted—hardly the norm in a pediatric department. “It's just a reflection of the way the science is moving, which is much more collaborative—and understanding that studying lifelong health is really important.” ***/yale medicine magazine***

Jenny Blair, MD is a frequent contibutor to Yale Medicine Magazine.

A century of innovation

Many of the people and significant achievements that have marked the history of the Department of Pediatrics were brought to life in a wide-ranging exhibit of captivating black-and-white photos and unusual artifacts hosted by the Yale Medical Historical Library. The exhibit, on display last summer, told the story of how a once-tiny department grew into a global leader in the pediatric community.

“We wanted to show how the department has grown, as well as what our faculty have accomplished and the huge breakthroughs in research that happened here,” said Jennifer DeSantis, chief of staff for the Department of Pediatrics. “It also shows that we are not just colleagues, but one big family.”

From the beginning, the department was making history. Four of the original 11 faculty members were women, which was revolutionary at that time. These women included Ethel Dunham, MD, best known for her expertise in the care of premature infants, and her life partner Martha May Eliot, MD, whose work led to the disappearance of rickets—a condition that caused brittle bones in children—in the United States.

As the department grew, it attracted more groundbreaking leaders. In 1949, Edith Banfield Jackson, MD, launched Yale’s Rooming-In Program, an innovation for its time that allowed mothers and babies to be cared for in the same room following birth.

“We really wanted to feature people,” said Kaiulani (Kai) Shulman, the main curator of the exhibit. “Throughout each of the cases, there was at least one significant department member highlighted.”

Not only did Yale bring together some of the country’s most brilliant minds in pediatrics, it also became a powerhouse for innovations that would transform the field. In 1960, Louis Gluck, MD, created the first neonatal intensive care unit (NICU), which held nine incubators. In the late 1970s, William Tamborlane, MD, and the late Robert Sherwin, MD, transformed the treatment of type 1 diabetes by inventing insulin pump therapy.

The exhibit also highlighted Yale Pediatrics’s Primary Care Center, which was opened by former pediatric chair Howard Pearson, MD, in 1975. It expanded in 2016 to include its Howard Avenue location, a neighborhood clinic at Yale New Haven Hospital’s Saint Raphael Campus, and Chapel Pediatrics in Hamden, allowing the center to serve more patients. In 2020, the department consolidated all its operations to a new location at 150 Sargent Drive.

“Today, Yale Pediatrics Primary Care Center strives to provide the population with an integrated and embedded behavioral health program in a federally qualified pediatrics health care setting,” the exhibit read. “General Pediatrics at Yale strives to provide care for every aspect of the child from birth until young adulthood and focuses on the family as a unit.”

“The Primary Care Center case was my favorite to create,” said Shulman, who fondly remembers hauling her bag full of collected items for the exhibit on the New Haven bus. “So many department members were instrumental in making this case happen—we collected a copy of *Clifford the Big Red Dog*, a Denver Developmental Screening Test kit, and even an old reflex hammer. The combination of all these artifacts, generously donated by faculty, created the most vibrant and exciting case.”

DeSantis’ favorite part of the exhibit was the last case, which included a collage of the faces of the pediatrics department today. “We really highlighted our trainees, who are growing into the best pediatricians they can be, and are becoming a part of our family,” she said. The case also included a #BlackLivesMatter painting symbolizing the department’s commitment to fostering an inclusive environment, and a softball trophy representing the tradition of having a pediatric softball team.

“On this 100th anniversary of Yale Pediatrics, we have so much to be proud of!” read a quote in the final case by Clifford Bogue, MD, the Waldemar Von Zedtwitz Professor of Pediatrics and chair of pediatrics. “Our department has been innovating in health care for children, training the best and brightest, and making impactful discoveries to further improve the lives of children and their families.”

The exhibit also served as a reminder of the resources that make such achievements possible. “Especially at Yale, we often get desensitized to how amazing this place is and how we have access to such incredible resources,” said Shulman.

— *Isabella Backman*

OPPOSITE PAGE, TOP The members of the 1921-22 pediatric staff at Yale New Haven Hospital.

OPPOSITE PAGE, BOTTOM Louis Gluck, MD, created the first neonatal intensive care unit in 1960.

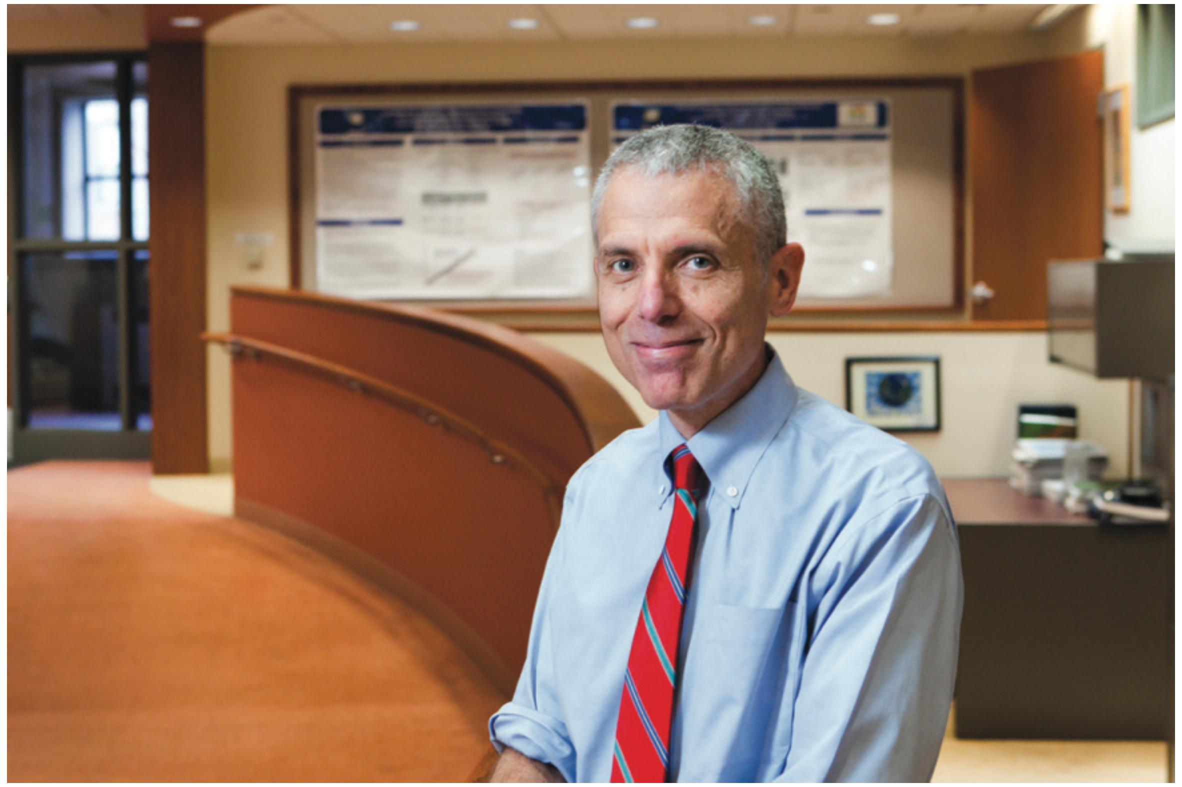
TOP Milton Senn, MD, who assumed leadership of the Child Study Center in 1948, is shown here with Assistant Professor Eveline Omwake, director of the Center’s Laboratory Nursing School.

ABOVE The Rooming-In Program was launched by Edith Banfield Jackson, MD, in 1949.

HISTORIC IMAGES COURTESY OF THE HARVEY CUSHING/JOHN HAY WHITNEY MEDICAL LIBRARY

Uncovering the genetics of learning disabilities

IN CLASSROOMS ACROSS THE UNITED STATES, five to 10 million children struggle with dyslexia. While offering intervention strategies in grades 1 through 3 can drastically improve the trajectory of a student's education, the window for effective intervention is narrow. That makes early and accurate screening key. Now, researchers are discovering clues in our genes that could speed early assessment of the risk of dyslexia.



Interventions for dyslexia and other learning disabilities work best when done early. Yale researcher Jeffrey Gruen, at right, is studying the genetics of these disabilities to identify at-risk kids before they fall behind.

ROBERT A. LISAK PHOTO

For several decades, Jeffrey Gruen, MD, professor of pediatrics (neonatology) and of genetics, has been studying the genetics of learning disabilities like dyslexia. Now, he's director of the new Yale Program for Learning Disability Research, which brings together faculty and students across the university to tackle this common problem. Through a cutting-edge clinical trial called the New Haven Lexinome Project (NHLP), the program also seeks to uncover the underlying neuroscience of disabilities.

Jeffrey Gruen, MD //

> “Our mission is to harness the broad expertise of faculty and students from across the university to study learning disabilities in these core areas.”

“Most people recognize that learning disabilities run in families, but they often don't make the connection that it's genetic,” said Gruen. “And so in the last 20 years, we've been identifying those genes and the genetic variants that seem to be associated with prominent learning disabilities.”

Fifteen percent of students around the world suffer from a learning disability, including delayed onset of speech [specific language impairment], verbal trait disorder, dyscalculia [math disability], and attention deficit disorders. One of the most common learning disorders is dyslexia, or difficulty in learning to read. A widely held misconception about disorders like dyslexia, said Gruen, is that they are associated with lower intelligence.

“There are smart people around the world who have high IQs and are incredibly functional, but have a really hard time with reading,” he said. “There have been surveys of Fortune 500 CEOs, for example— they report a much higher prevalence of dyslexia than the general population.”

Left untreated, dyslexia can hinder students' education, cause low self-esteem, and pose obstacles to meeting their potential as they grow older. Intervention at any age can provide great benefit to struggling students, but treatments are most effective when implemented early. About 75% of first- through third-graders, for example, could be reading at their grade level two years after the completion of a quality intervention program. However, about half of students with dyslexia aren't identified until high school or later. For this group, response to intervention drops to 25%.

Our current education system has what Gruen calls a “wait-to-fail model.” Around the end of first grade, students with dyslexia begin to fall behind their peers as they face a more challenging curriculum. These students don't begin to receive treatment until they are already struggling; and even with intensive and early intervention, the learning gap never fully closes.

“Children with dyslexia are smart. They can hide their struggle, and you won't necessarily see it until they are challenged with a complex curriculum,” said Gruen. “And with the wait-to-fail model, they never catch up. This [gap] affects them obviously in their academic careers, but also in life.”

In September 2021, in collaboration with colleagues including Eugene Shapiro, MD, professor of pediatrics (general pediatrics) and of epidemiology (microbial diseases), and Clifford Bogue, MD, the Waldemar Von Zedtwitz Professor of Pediatrics and chair of the department, Gruen launched the Yale Program for Learning Disability Research.

This multidisciplinary program spans the fields of neuropsychology, biostatistics, education, neuroimaging, and genetics. It has several goals, including uncovering the neuroscience underlying learning disabilities; educating school staff and pediatricians on the role of genetics; and advocating for policies that support early intervention. “Our mission is to harness the broad expertise of faculty and students from across the university to study learning disabilities in these core areas,” said Gruen.

The centerpiece of the program, he said, is the NHLP. From 2013 to 2021, Gruen’s team conducted a longitudinal study of 492 typically developing elementary schoolers across 32 New Haven public schools. The students were enrolled in first grade and followed through fifth grade. The researchers conducted whole-genome sequence analysis; assessments three times per school year on reading, language, and executive function; and for some students, serial functional MRIs. Through generating a dataset based on the seven-year clinical trial, Gruen hopes to better understand how genetic variations affect intervention outcomes.

“Think of the New Haven Lexinome Project as the data pipeline for the Yale Program for Learning Disability Research,” said Gruen. “Our current group of graduate students and postdocs are working now to analyze it.”

Most states currently offer universal evidence-based screening for dyslexia, said Gruen, though none offered genetic screening as of 2022. Through research, he hopes to promote genetic screening as a way to assess dyslexia risk early. This approach could enable parents to screen their children as early as infancy, and allow at-risk children to receive evidence-based intervention before they fall behind in school.

“It’s really important that we translate our discoveries about genetics in the lab into something that’s actionable and useful for schools,” said Gruen. “We hope to get states and regions to include genetic screening in their learning disability screening so that kids can be identified early, when intervention really works the best.”

— *Isabella Backman*

A pillar of pediatric research

When Eugene Shapiro, MD, professor of pediatrics (general pediatrics) and of epidemiology (microbial diseases), graduated from Yale College in 1970 (Branford College), the trajectory of his life looked very different from what it later became. A genial and quick-witted storyteller, Shapiro (“Gene” to his friends) had majored in English. He wrote his senior thesis on D.H. Lawrence; he was going to study, teach, or write.

He did something else instead—he started to take premed classes, hoping to attend medical school. He applied to and was accepted by the University of California, San Francisco (UCSF), and completed his MD there in 1976. While there, he met his wife, who became an accomplished Ob/Gyn clinician. They matched together to Pittsburgh, and did their residencies together. Shapiro and his wife had their first child during their residencies—and she may very well have been the first woman to give birth during an Ob/Gyn residency, he added. It was during Shapiro’s years in Pittsburgh that he developed an interest in pediatric infectious diseases.

“My first mentor at Pittsburgh was Ellen Wald, MD. She’s currently chair of the Department of Pediatrics at the University of Wisconsin, Madison. I was able to observe her methods and diligence, and that taught me a lot about how to carry out successful research projects,” said Shapiro.

The couple’s next stop was New Haven, where Shapiro secured a fellowship at Yale School of Medicine through the Robert Wood Johnson Clinical Scholars Program (now the National Clinician Scholars Program). This interest, together with a desire to alleviate children’s suffering, has guided his professional career ever since.

“The RWJCS fellowship helped me refine a lot of what I’d seen in Pittsburgh,” said Shapiro. “It was where I received my first grant; I applied while still a fellow for a National Institutes of Health (NIH) grant to look at the effectiveness of pneumococcal polysaccharide vaccine. I joined the Yale School of Medicine (YSM) faculty in July, and had the grant funded in September.”

The body of work for which Shapiro is probably best known by the public, however, began accidentally. During a general pediatric clinic, a parent called in because her child had been bitten by a tick. In the process of deciding what to do, Shapiro and the residents he was supervising discovered that there had been relatively little published on the subject at that time.

“The original research on Lyme disease was carried out by Allen Steere, MD, here at YSM,” said Shapiro. “But there were a lot of questions that still needed answers. We came up with a randomized clinical trial of antibiotic prophylaxis for tick bites. That’s how I first became involved with Lyme disease.”

Quoted in dozens of articles and featured on broadcast media on the subject in the late 1990s and early- to mid-2000s, Shapiro saw both the positive and negative sides of publicity. He was invited to share his thoughts and expertise with the World Health Organization, the NIH, the Food and Drug Administration, and other groups. Unfortunately, he experienced some backlash from the same groups that have become prominent in the last few years—“anti-vaxxer” and science-skeptic movements facilitated by social media and misinformation.

“People get worried when they’re sick. Doctors and scientists don’t always have the answer, or an answer people want to hear. During moments of grief, people can be incapable of hearing certain answers—such as ‘we don’t have an answer for your specific problem,’” Shapiro said.

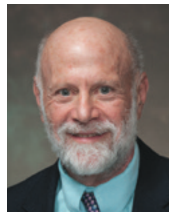
Shapiro is proud of his success at establishing big-picture research projects during his decades at Yale, including helping begin the prestigious Clinical and Translational Science Award program (CTSA), and his early involvement with Yale’s Investigative Medicine Program, of which he is deputy director. He is co-director for education with the Yale Center for Clinical Investigation (YCCI), which houses the CTSA and plays an important role in advancing young scientists’ careers. YCCI has also worked to recruit a diverse group of subjects for clinical trials to ensure that the trials’ findings are as representative as possible.

“Over the years I’ve mentored, trained, or taught hundreds of students, fellows, and junior faculty,” Shapiro said when asked about his impact as a faculty member. “From research projects to grant-writing programs to residencies, I’ve been incredibly fortunate to connect with so many physicians and PhD scientists.”

The culture of collaboration and cooperation that’s part of YSM’s institutional DNA has, according to Shapiro, played a key role in his success, both in terms of research and by connecting him with so many investigators. “A lot of the people I helped train or mentor as fellows or residents are young faculty themselves now, or more senior,” Shapiro said. “That’s one of my greatest pleasures: to see those people with whom I worked come into their own as scientific leaders.”

Although medicine may seem distant from Shapiro’s undergraduate degree, many of his professional achievements have revolved around successfully crafting narratives, from grant-writing to institution-building. It turns out that having a background in literature isn’t as detached from science and medicine as one might think.

— *Adrian Bonenberger*



For over 40 years, pediatric infectious diseases specialist Eugene “Gene” Shapiro has helped make YSM’s Department of Pediatrics one of the best in the country.

Q&A WITH
Marietta Vazquez
CONDUCTED BY
Isabella Backman

Marietta Vazquez with supplies destined for Puerto Rico.

ANTHONY DECARLO PHOTO

Looking forward

MARIETTA VAZQUEZ, MD, professor of pediatrics (general pediatrics) and associate dean for medical student diversity, is a trailblazer for diversity, equity, and inclusion (DEI) efforts both in her department and across the medical school. Born in Puerto Rico, her identity has shaped who she is today as a clinician and researcher. *Yale Medicine Magazine* spoke with Vazquez about her journey to medicine, as well as her present and future initiatives.

Can you recall any experiences that influenced you to go into medicine? My most impactful personal experience was being a patient when I was 14 years old. I was a classical ballet dancer, but I was born with club feet, and I had surgery to correct the foot defect. That surgery went wrong and led to me not being able to walk for two years as a teenager. They told me that I would lose my foot, and I would never be able to walk again. It was very traumatic. I went through 10 surgeries over the years. I thought it would've discouraged me from medicine, because I had seen the worst part—when things go wrong. But the process of working with this plastic reconstructive surgeon who built me a new foot that I still walk around with today was one of my most inspiring experiences.

A second experience that really solidified my interest in pediatric infectious diseases happened when I was a medical student in Puerto Rico in the early 1990s. The AIDS epidemic was very much an epidemic of families at this time because of high rates of IV drug use. And within weeks of when I first started taking care of children as a medical student, my very first patient died from HIV. It was very sad, but at the same time, it stirred my interest in figuring out what was going on. Why did that happen? And what could have been done to help the situation?

You first came to Yale from Puerto Rico as an undergraduate and returned for residency after receiving your MD from the University of Puerto Rico. What drew you to Yale? There were two things. One was [Yale's] emphasis on inquisitiveness and the critical thinking aspect of things. It seemed to me from conversations with residents that this was a program where they would train residents who kept asking, "Why? Why am I doing this the way I'm doing this?" I wanted to be in a place where I wouldn't just be told what to do, but would be pushed and encouraged to try to figure things out on my own.

Number two was the community. Coming from an island, I work best in an environment in which I'm close with the people that I'm working with. It was important to me not only to find a place where I would get good training, but also where I would not just be one little ant in a big conglomerate. At Yale, I felt like I could get to know people and people could get to know me. And fast forward almost 30 years later, this [still] holds true. I stayed because I love the Yale and New Haven communities, on top of being challenged daily and learning all the time.

You were the first Latina vice chair of DEI in the Department of Pediatrics and the first Latina associate dean at YSM. Are there any initiatives you have taken in these leadership positions that you are especially proud of? In terms of [being] the vice chair of pediatrics, I'm most proud of how my department has grown and what we've accomplished together. We're not where we want to be yet, but we have changed the culture for the better. Four years ago, we made a commitment to fundamental diversity training. We understood that to be able to have difficult conversations, we needed to understand the basic language of diversity. It was very difficult because we were the first and still only department in the School of Medicine where this foundational training in DEI, antiracism, and social justice is mandatory. It's an expectation of not only faculty, but all trainees and staff.

In my role as associate dean, which I've not held for that long, I've devoted a lot of time to just listening and trying to understand what the important issues are and being the go-to person for medical students when things are tough. We've developed a medical student Diversity Council; worked diligently to better organize and expand student affinity groups; and are developing structure so that the voices of all medical students are heard.

These are not just my products, but the product of a lot of people who work alongside me, as well as those who came before me—including many women and underrepresented minorities in medicine at Yale who forged the path.

What are your future goals? I have many! I work with a phenomenal team in the office of Diversity, Inclusion, Community Engagement, and Equity (DICE), and we would like to continue to expand our pathway programs and bring in more students from underrepresented backgrounds. Our goal is to not only provide opportunities to those students, but to show them that Yale is a great place for them to come and train. We also want to strengthen and grow the student Diversity Council and expand the student opportunities for community involvement. I always tell students that the minute you are admitted to Yale School of Medicine, you're not just part of the Yale community, but also the New Haven community.

A lot of what they're going to learn will take place in our classrooms and at the hospital, but much of it also takes place in the community. I hope to expand the opportunities for medical students to really become engaged in the New Haven community and see it as part of their education.

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

Jumping into the deep end

MARIE EGAN OF YSM'S Department of Pediatrics has had a long and successful career helping patients and advancing research. Her advice to new doctors? Don't dip your toe in the water: jump in.

One of the Department of Pediatrics' key leaders, and a nationally renowned expert in the field of pediatrics, Marie Egan, MD, occupies many illustrious roles. She's Yale Professor of Pediatrics and Cellular and Molecular Physiology, director of Yale's Cystic Fibrosis Center, and vice chair for research in Yale's Department of Pediatrics. She's also an interim division chief for Yale's Pediatric Pulmonary, Allergy, Immunology, and Sleep Medicine Division. Additionally, Egan sits on a number of national committees for the Cystic Fibrosis Foundation and several other committees focused on reviewing grants and professional development.

What brought you into pediatrics? As an undergrad at the University of Pennsylvania, I planned to be a scientist. I loved schoolwork, but it was hard for me to focus just on the academic side of things—I wanted more human contact. I decided to volunteer at the Children's Hospital of Philadelphia. They were short on play therapists, so I started running a playroom for sick children. I was 18, and I think the children saw me as a big kid. I started to notice they were free and open when talking to each other. Adults and white coats weren't encouraged to come into the playrooms.

I kept seeing the same children, and learned they had cystic fibrosis (CF). They knew how sick they were. They talked about who had died, who was still living, and who had been hospitalized. But the moment adults or parents came in, their tone would totally change. They were talking like little kids again, I think for their parents' sake. It kind of blew my mind. I don't think anyone should have to be that brave at that age. I knew I wanted to be involved in science and molecular biology, but I realized at that point I could take things to the next level and be a doctor, to try and help allow kids to be kids.

What adversity have you faced? It's one thing to be bright and innovative. In the world of science, you need to understand that the first time you do something it might work out brilliantly, but it's the next 15 times you do it that will verify your success, which can take a very long time and yield results that aren't what you hoped for.

Which accomplishments bring you pride? From a career standpoint, I'm proud of the fact that so many patients tell me I've made a difference in their lives, and of the brilliant people I've mentored. From a research standpoint, I have several accomplishments that may be important, including high-impact papers I've published in well-regarded journals.

Also, when I first started doing work on CF as a disease, some people thought it was derivative, that it made one's work less pure than working on a physiologic process. But over the last 20 years, I've gotten a lot more people interested in studying CF, and they're making a huge impact on how we understand and treat the disease and improve patient care.

What projects are you currently working on? I am working on a project with the chair of therapeutic radiology, Peter Glazer, MD, PhD, and Mark Saltzman, MD, PhD, with the Department of Biomedical Engineering and Chemical Engineering, focusing on a gene editing approach for CF. There are certain changes in the CFTR gene that cause genetic mutations that lead to CF. Editing those out could basically cure someone. Right now, we can do this in cell cultures and animal models, but the goal is to keep refining this to be able to provide it as a therapeutic.

Any advice for those entering medicine? Every day, I love coming to work. I get to be creative, to really think, and I'm never bored. I also think it's an incredible honor and privilege to help people navigate chronic illness and disease.

I do think people should know this type of journey is not one where you can put a toe in the water; you really have to jump in. Don't think you'll get rich or famous, don't think it'll be easier with time, but know it will be incredibly rewarding.

Living for others

Zoe Nakos Canellakis, PhD, a senior research scientist at Yale School of Medicine in the Department of Pharmacology, was born September 7, 1927, in Lowell, Massachusetts, and died on October 22, 2022, at the age of 95 in Canaan, Connecticut. She received her undergraduate degree in economics at Vassar College in 1947, graduating Phi Beta Kappa; a Master of Science in biochemistry at the University of California, Berkeley; and a PhD in physiological chemistry from the University of Wisconsin in 1954 for her work on tyrosine aminotransferase. After a postdoctoral fellowship at Yale University, she joined the faculty in 1955. In her early career, at a time when molecular biology and the biochemistry underpinning genetics were just beginning, Canellakis discovered many basic features of the regulation of another important enzyme, ribonucleotide reductase, which helped advance our understanding of the biosynthesis of precursors for DNA replication.

Zoe Nakos Canellakis, PhD //

> "It is wasteful to train scientists who either leave science or fail to develop their full potential in science.

Canellakis was promoted to senior research associate in 1967 in the Department of Pharmacology. Despite a demanding role as assistant dean of the Graduate School from 1972–77, she continued to pursue research and provided fundamental insights into the biologic role of polyamine biosynthetic enzymes in cell growth, differentiation, and embryology. In 1982, she was named a senior research scientist of Internal Medicine and Pharmacology. Following a successful career as a scientist and leader as the assistant dean and as a fellow of Berkeley College from 1975 (advising countless undergraduates in their academic schedules and research theses), she retired in 1993 as Yale Emeritus faculty and a Koerner Fellow.

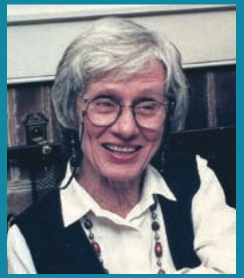
Throughout her career as a pioneer and champion of women in science, she mentored many women, helping them to achieve successful careers. As chair of the Committee on Equal Opportunities for Women of the American Society of Biological Chemists and Carnegie Conference on Women keynote speaker, she organized panels that focused on helping scientists, especially women, advance along their chosen career paths. In a 1985 editorial, she wrote, "The need to ensure full participation of able and talented women in the active scientific community is clear. It is wasteful to train scientists who either leave science or fail to develop their full potential in science. Everyone gains by including able women in the profession."

She had insatiable curiosity and was admired for her ability to quickly assemble a meal for two or 20 from her freezer, as well as her penchant for organizing her kitchen like a laboratory with all reagents alphabetically organized by their chemical names.

Canellakis will be remembered for her warm and generous mentorship and friendship, as well as her ability to connect people from her wide network of friends and colleagues. She changed the trajectory of many of her mentees' lives. When one of them asked what they could do to thank her, she simply said, "do it for someone else."

Yuka Manabe, MD, professor of medicine at The Johns Hopkins School of Medicine.

Manabe, Yale College, BS '87, worked in Canellakis' lab and was a lifelong friend.



A celebration of life will be held for Canellakis at Yelping Hill in West Cornwall, Connecticut on Aug. 5, 2023.

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yale medicine magazine

YALE UNIVERSITY, 50 DIVISION STREET, 2 SCIENCE PARK, NEW HAVEN, CT 06511
ymm.yale.edu ISSUE 170