Research institutions can do basic science, but they cannot translate it. Community hospitals can provide exceptional care, but they cannot do research. UC San Diego Health does both — and does them well.
AS A YOUNG MAN, Howard Feldman majored in English literature, which taught him much about human nature. But behind the traits and vagaries of human behavior lay something even more fascinating to the Canadian: the human brain. And behind that, something still more so: the mystery of its malfunctions.

The Tau of Howard Feldman

New director brings both experience and fresh ideas to the search for an Alzheimer’s cure

Photography by David Ahntholz

“A→B→C”

“Basic research drives the process. We do things that cannot be done or aren’t done elsewhere. We ask and answer questions; clinical trials and application are the last step. You need knowledge first to get from A to B to C.”

— HOWARD FELDMAN, MD
Director, Alzheimer’s Disease Cooperative Study

UC San Diego has long been at the forefront of Alzheimer’s disease research, thanks to the partnership of our community. To become a part of our team through your giving, please call 858-822-4062.
And so Feldman changed career paths. He became a physician, ultimately specializing in neurology with an emphasis upon the cognitive disorders of dementia.

Now, at the age of 58 and owner of a long and much-admired career ([The Lancet](https://www.thelancet.com), among the world’s oldest and best-known medical journals, once dubbed him the “master of dementia”), Feldman is director of a comparably renowned enterprise: the Alzheimer’s Disease Cooperative Study (ADCS) at UC San Diego.

The ADCS was founded by the late Leon Thal, MD, a pioneering neuroscientist in Alzheimer’s research, to promote the discovery, development and testing of new drugs for the treatment of AD. It is part of a larger effort at UC San Diego that includes the Shiley-Marcos Alzheimer’s Disease Research Center, the Memory Disorders Clinic and the Memory, Aging and Resilience Clinic, a novel center providing comprehensive cognitive, emotional and physical health evaluations of older adults.

Feldman comes from the University of British Columbia, where he was professor of neurology, executive associate dean of research and, like Thal, an international leader in geriatric cognitive disorders. At UC San Diego School of Medicine, he will also serve as dean for Alzheimer’s and Related Neurodegenerative Research.

Quiet, politic, with an easy smile, Feldman is known for his expertise in large-scale clinical trials. He helped lead the Canadian Study of Health and Aging, for example, which followed 10,000 elderly Canadians for a decade, chronicling their changing health status. At ADCS, however, Feldman has a different plan. After decades of massive effort, monumental studies and national trials (more than 200 drugs have been tested), there remains no singularly effective treatment for AD, which affects more than five million Americans and is the sixth leading cause of death in the United States.

Feldman isn’t particularly critical of past work, but says AD scientists can learn from cancer research to better parse the problem and then develop smart, innovative tools and trials that advance the science steadily, if not spectacularly.

Too many past trials, he said, have been all-or-nothing exercises. If a touted experimental drug didn’t pan out, the trial collapsed. “The key is that no trial should end in failure,” said Feldman. “Every trial should not just test a therapy. It should have other goals in place to cycle back knowledge for everyone’s benefit. You don’t just test the medicine, you learn about what else is happening so that the next trial or test is better.”

To Feldman’s mind, that likely means smaller, more nimble trials with sharpened targets, more quickly and sustainably done. The ADCS serves a fundamental role, he said. “Basic research drives the process. We do things that cannot be done or aren’t done elsewhere. We ask and answer questions; clinical trials and application are the last step. You need knowledge first to get from A to B to C.”

Not surprisingly, Feldman doesn’t predict imminent success, either with current therapies being tested or with new ideas still percolating in labs. “Alzheimer’s is too complex. The more we know, the more questions we have and the more uncertainty. The trick is to not let the uncertainty prevail. You have to keep in mind where you’re trying to go. You set goals. You might not reach them all or on schedule, but you need to know what you’re trying to achieve.”

And where you will do the trying. For Feldman, at the apex of his career, that’s at ADCS.
Many diseases do not give up their secrets easily. They lurk, undetected, for years or reveal their response to treatment only reluctantly and with cost. Sometimes, this means resorting to dramatic, even health-threatening procedures such as needle biopsies or exploratory surgery.

IN RECENT YEARS, however, clinicians and researchers at UC San Diego School of Medicine and elsewhere have begun developing new tests that detect the onset of disease, monitor its progression and measure its retreat with minimal effect on the patient.

So-called “liquid biopsies” represent a new diagnostic tool based on the idea that critical genetic information about the state of disease can be found in blood or other fluids, such as urine. All clinicians require is a sample. The current focus is primarily in cancer, but researchers are also actively searching for blood-based biomarkers that might indicate the furtive presence of neurodegenerative conditions, such as Alzheimer’s disease, or fetal abnormalities.

“Liquid biopsy allows us to follow genomic changes over time,” said Razelle Kurzrock, MD, director of the Center for Personalized Cancer Therapy at Moores Cancer Center at UC San Diego Health. “We can detect a tumor’s resistance to therapy months before it shows up in scans. Why wait until the tumor grows when we can tell from blood that it’s growing?”

Liquid biopsies are relatively simple to obtain when needed. Tissue sampling of the lungs or prenatal testing can be problematic, perhaps impossible, and require time in an operating room with heightened risk of possible infection. In contrast, a single vial of blood taken during routine lab draws might contain circulating cancer cells or fragments of mutated DNA shed from a tumor.

“As the technology advances, we hope to be able to use liquid biopsies to diagnose cancer,” said Hatim Husain, MD, assistant professor of hematology-oncology. “Right now, we are using the information we gain thoughtfully to monitor disease and to help guide treatment based on the tumor’s genetic profile. We are excited about early monitoring strategies to see how we can utilize such technologies to select therapies based on markers of response within the first week of treatment.”

Blood-based tests have been available commercially for five years in prenatal screening. The tests look for abnormalities in fragments of DNA that flow in a pregnant woman’s blood. A fetus with three copies of chromosome 21, for example, has Down syndrome.

“Blood is such a rich resource. If we put effort into this research, we’ll find something. It’s necessary. Neuramimaging, such as an MRI, isn’t sensitive enough. Fluid biomarkers in cerebrospinal fluid and blood may allow us to detect the onset much earlier because they allow for the monitoring of pathological changes at the biochemical level before actual pathology in the brain is visible.”

— ROBERT RISSMAN, PhD

To join us through your generosity as we redefine the way we care for patients battling cancer and other illnesses, please call 858-822-4662.

Liquid biopsy for cancer detection and monitoring is a bit further developed, but there are still significant challenges, such as determining whether all tumor types shed DNA into the blood and pinpointing exactly where that circulating DNA originates.

“Although we are still learning a lot, it is a breakthrough technology,” said Kurzrock. “At this time, we obtain information on more genes from tissue than we do in blood. One of the limitations is that tumor DNA in the blood is miniscule. It’s miraculous we can even detect it, but the technology is changing rapidly. We will refine liquid biopsy and make it even better for patients.”

Kurzrock and Husain are using liquid biopsy technology in the Profile Related Evidence Determining Individualized Cancer Therapy (PREDICT) clinical trial — a project focusing on the outcome of patients who have genomic testing performed on their tumors and are treated with targeted therapy. They developed a liquid biopsy program to understand how to best exploit this technology in the clinic.

“What we need are very large studies across institutions, better access to drugs that can be used with the genetic data obtained and better clinical trial designs that put this technology to use to stratify patients prospectively, not retrospectively,” said Husain.

Do that, he said, and progress will go with the flow.

“Blood is such a rich resource. If we put effort into this research, we’ll find something.”

— ROBERT RISSMAN, PhD

Credit: Thomas Deerinck, National Center for Microscopy and Imaging Research, UC San Diego.
Imaging the human heart is both art and science

The heart speaks, a rhythmic “lub-dub” that can tell doctors much about its health and function. But often that is not enough. The hardness of the heart, like most organs, lies in its relative invisibility. It does not reside upon your sleeve, but sits nestled between lungs, tucked within a pericardium under bone, muscle and other tissues of the chest.

Modern imaging technologies at UC San Diego Health, including the Sulpizio Cardiovascular Center, are increasingly opening the heart to view, study and improve diagnoses.

Echocardiograms were the first of modern imaging technologies. Originally one-dimensional ultrasound images in the 1950s, they were followed by nuclear imaging in which special cameras image the uptake of radioactive substances by cardiac muscle.

The latest echocardiography techniques prove even more dramatic and revealing. At UC San Diego Health, these echocardiography techniques provide two- and three-dimensional, real-time visuals of a patient’s pumping heart and the structure and function of the valves that control blood flow.

Coronary computed tomography (CT) angiography offers exquisite detail of coronary arteries for non-invasive diagnosis of coronary artery disease and anomalies.

Magnetic resonance imaging (MRI) not only gauges morphology and function of the heart, it also discerns muscle scarred by past infarctions, infection or other processes.

The newest technologies hybridize powers between advanced imaging and computation to provide insight into flow and function. For example, computational fluid dynamics with echocardiography, CT and 4D Flow MRI to tap into the relationships between the pumping heart and flowing blood.

These technologies, in combination with advances in optical and scanning research microscopy capable of revealing the unseen minutiae of the heart, render pictures that truly are heartfelt.
Inflammation brings heat to healing, but unchecked it can burn

Inflammation is a contradiction in germs. It is a primary line of defense against viruses, bacteria and other infectious pathogens, but it can also lay the seeds for a spectrum of disorders, from multiple sclerosis and asthma to heart disease, some kinds of cancer and neurodegeneration.

AT UC SAN DIEGO SCHOOL OF MEDICINE and UC San Diego Health, researchers and physicians are leading efforts to resolve this dichotomy to better understand and harness the healing and protective powers of inflammation while, simultaneously, constraining its contrary capacity to harm.

Inflammation is one of the immune system’s elemental tools to fight infection and promote healing. Cut your finger, for example, and the injury immediately triggers blood cells, called platelets, to join together, form a clot and release small proteins called cytokines, which cause the injury to swell and redden, to become inflamed. Other cells soon arrive, including white blood cells — macrophages, T cells, B cells — to clear away the damage, kill any invasive microbes at the site and conduct repairs. Once healed, the cells disperse, inflammation disappears and all is well again.

Trouble arises when inflammation occurs when and where it’s not needed or when it persists longer than necessary, becoming a chronic condition that ultimately hurts more than it helps.

“Inflammation is very important for healing and tissue regeneration,” said Michael Karin, PhD, Distinguished Professor of Pharmacology and Pathology and Ben and Wanda Hildyard Chair for Mitochondrial and Metabolic Diseases. On the other hand, he said, “I believe that 80 to 90 percent of diseases are related to inflammation.”

“I believe that 80–90% of diseases are related to inflammation.”
— Michael Karin, PhD

"I believe that 80–90% of diseases are related to inflammation.”
— Michael Karin, PhD
Inflammation is essential for healing, but if you have chronic inflammation, it produces cytokines that stimulate healing all the time. That means a lot of cell division, which increases the chance for a mutation.

— Michael Karin, PhD

Cancer, a Wound That Never Heals

Karin has pioneered the study of inflammation’s role in cancer, though his ideas were initially met with skepticism. “It’s well known that the immune system keeps us free of cancer,” said Karin, “but I was saying that immune system inflammation also causes certain cancers. It was a bit controversial.”

In the 1980s, researchers had begun to notice that patients with inflammatory bowel disease were at much higher risk for developing colorectal cancer. They noted a connection between hepatitis, which inflames the liver, and liver cancer; and a link between gastritis (inflammation of the stomach) and stomach cancer. “This suggested that more inflammation meant more cancer,” said Karin.

Digging in, Karin began to explain how cancer hijacks the inflammatory process. “Inflammation is essential for healing, but if you have chronic inflammation, it produces cytokines that stimulate healing all the time. That means a lot of cell division, which increases the chance for a mutation.”

If that happens, the malignancy continues to proliferate out of control because it’s fueled by the body’s ongoing attempts at repair. “That’s why cancer has been likened to a wound that never heals.”

Karin said the cancer link has only been shown thus far in autoimmune diseases of the gastrointestinal area, particularly hepatitis, pancreatitis and colitis. “The chronic inflammation of colitis causes erosion of the intestinal mucosa, which then constantly try to regenerate. There’s a lot of cell division going on.”

He is currently exploring several molecules that might stop tumor proliferation in the liver, pancreas and other gastrointestinal sites.

Heart Disease

Inflammation is a powerful player in heart disease, where it both fuels and destabilizes cholesterol plaque buildup, which impedes blood flow or worse, results in a plaque that ruptures, forming a clot that causes a heart attack or stroke.

Christopher Glass, MD, PhD, professor of medicine and cellular and molecular medicine, studies a key immune system soldier in this process — the macrophage. Macrophages are white blood cells that gobble up viruses, bacteria and other unwanted cells. They also serve as sentinels, recruiting other immune cells to injury and infection sites.

Glass believes that macrophages perceive arterial plaque buildup as an injury and rush in with other immune cells to heal the “wound.” They move into the artery wall, consuming cholesterol. “They take up some of the fat proteins, but get bogged down in that process — the macrophage turns into foam cells that fuel inflammation,” said Glass. “We don’t really understand why this happens, but my theory is that macrophages get signals from other arterial cells that inhibit their protective functions.”

The cell type’s importance is further reflected in mouse studies that found that the absence of macrophages means the absence of atherosclerosis, said Glass. He and colleagues have made progress in finding ways to control their negative effects, but challenges remain. “You don’t want to risk blocking macrophages to the point that the body cannot fend off infections. It’s a balancing act.”

Which, in the end, perfectly describes inflammation.
Recruited in 2015 from Johns Hopkins School of Medicine, the Wahlin laboratory is one of only a handful in the world that have produced stem cell-based 3D models for studying human eye development in a petri dish.

The focal point is the ability to grow “mini-retinas,” which are not merely cultured layers of retinal cells, but organized 3D tissues containing photoreceptor cells (the rods and cones that transform light into biological signals), ganglion cells (that convey signals to the brain) and supporting glial cells.

Wahlin and colleagues can watch these mini-retinas develop in real time.

Understanding retinal differentiation is a first step toward being able to grow transplantable-grade retinal cells, which might then be used to treat two of the most common causes of vision loss and blindness in the world: macular degeneration and glaucoma.

New gene-editing techniques have further enhanced the clinical potential of “disease-in-a-dish” models of retinal degeneration. For example, it is now possible to mutate genes associated with retinal degeneration and observe how these mutations affect cell differentiation, loss and survival. The experiments can be worked in the other direction: researchers can try to fix faulty genes and track the effects on retinal development.

This type of experiment is particularly valuable for understanding inherited childhood eye diseases, such as Leber’s congenital amaurosis.

If ultimately proven effective, the research opens the door to using viral gene therapy to repair a person’s DNA.

“We can potentially keep thousands of children from going blind each year,” Wahlin said.

Researchers are also exploring the idea of administering pharmaceutical products that might prevent degeneration or trigger the eyes’ latent ability for renewal and repair. The retina-in-a-dish model provides the advantage of being able to grow hundreds of tiny retinas for systematic testing of pharmaceutical compounds.

Toward this effort, the Wahlin lab has been screening a library of small molecules to identify pathways that activate and inhibit retinal development. “If we can block degeneration in early stages of disease or activate glial cells in later stages to regenerate into photoreceptor cells, we can begin testing potential new therapies for reversing retinal degeneration,” he said.

Robert N. Weinreb, MD, Distinguished Professor of Ophthalmology and director of Shiley Eye Institute, said the Atkinson lab represents a powerful convergence of science to address a huge unmet need to cure blindness.

“Stem cell therapy and gene editing techniques offer tremendous promise to restore vision to individuals worldwide who have retinal degenerations, glaucoma and other blinding eye diseases.”

Newts and frogs are famously celebrated for their ability to regrow lost or damaged body parts, but birds and mammals — to a much more limited degree — also possess the powers of regeneration.

Perhaps nowhere is this ability more eye-popping than, well, the ability to repair vision. Nature clearly has a template. Researchers at UC San Diego School of Medicine are looking for ways to apply it to treat and cure eye disease.

Karl J. Wahlin, PhD, an assistant professor of ophthalmology and director of the Richard C. Atkinson Laboratory for Regenerative Ophthalmology at Shiley Eye Institute, is leading efforts to understand the fundamental biology controlling human eye development and the eyes’ innate self-repair kit.
For 50 years, these three words have described UC San Diego Health’s unprecedented, unsurpassed commitment to patient care.
For 25 years, the Shiley Eye Institute has offered a bigger, bolder vision.

The Donald P. and Darlene V. Shiley Eye Institute is a site to behold. Situated on the east campus, it’s San Diego’s first and only academic comprehensive treatment and research vision center. In fact, it’s several centers in one, each with a particular focus. This year, Shiley celebrates its 25th anniversary. Here’s a look back through the years:

1983 – Department of Ophthalmology at UC San Diego School of Medicine established, with Stuart I. Brown as first chair
1984 – Ophthalmology clinic opens on campus
1990 – First Diagnostic Innovations in Glaucoma Study (DIGS) begins; ongoing DIGS becomes largest observational cohort study of glaucoma patients in world
1991 – Shiley Eye Center opens, spurred by $1M gift from Donald and Darlene Shiley
1994 – Anne F. and Abraham Ratner Children’s Eye Center opens, with David Granet as director
1996 – Circle of Sight, a vision lecture series, debuts
1997 – Thyroid Eye Clinic opens, under direction of Don O. Kikkawa with Granet and Bobby Korn
2001 – Shiley EyeMobile for Children, first state-of-the-art vision clinic on wheels, hits the road. Each year, the EyeMobile offers thousands of vision screenings, exams and free pairs of glasses to needy children.
2003 – Groundbreaking African Descent and Glaucoma Evaluation Study (ADAGES) begins, investigating links between glaucoma and persons of African descent
2004 – Hamilton Glaucoma Center opens, with Robert N. Weinreb as director; Joan & Irwin Jacobs Retina Center opens, with William R. Freeman as director
2005 – Felipe Medeiros and colleagues develop first validated risk calculator to predict glaucoma
2011 – Weinreb appointed chair of Department of Ophthalmology
2012 – Ophthalmic BioBank launched, with Radha Ayyagari and Linda Zangwill as co-directors
2013 – ADAGES III genetics study launched
2013 – Natalie Afshari implants an artificial cornea, a first at Shiley
2014 – Napoleone Ferrara awarded Antonio Champalimaud Vision Award and Gairdner Award for discovery of vascular endothelial growth factor, a key molecule in promoting wet macular degeneration; discovery leads to new vision-saving therapies for macular degeneration, diabetic retinopathy and other blinding diseases
2015 – Shiley Eye Center becomes Shiley Eye Institute
2015 – Richard C. Atkinson Laboratory for Regenerative Ophthalmology announced, with Karl Warfin as director
2015 – Dorota Skowronska-Krawczyk and colleagues report first link between genetic mutation and cause of optic nerve damage in glaucoma
2016 – Kang Zhang and colleagues report stem cells regenerate lens, restore vision in children after cataract surgery

From far left, clockwise: Napoleone Ferrara, MD; Shiley Eye Institute; Shiley EyeMobile for Children; Hamilton Glaucoma Center and Jacobs Retina Center; Ratner Children’s Eye Center; Linda Zangwill, PhD (right) and Radha Ayyagari, PhD; and a glaucomatous optic nerve.
“We can use external light as a remote control to trigger nanoparticle breakdown.”

ADAH ALMUTAIRI, PhD

Nanomedicine

N. a method of engineering tiny particles and machines and using them to prevent, diagnose and treat human diseases.

“GETTING PATIENTS TO TAKE THEIR MEDICATION AS PRESCRIBED IS THE BIGGEST CHALLENGE IN HEALTH CARE TODAY — ONE THAT COSTS THE INDUSTRY AROUND $300 BILLION EACH YEAR,” said Adah Almutairi, PhD, associate professor in the Skaggs School of Pharmacy and Pharmaceutical Sciences and director of the Center for Excellence in Nanomedicine at UC San Diego. Almutairi wants to take the patient out of the equation altogether. “Taking your medication should be as easy as setting up autopay for your bills — do it once and forget about it.”

To make this possible, Almutairi and team are developing injectable nanoparticles that carry drugs or diagnostics, but release them over time as the nanoparticle degrades. The breakdown of these nanoparticles — balls of tangled polymers — can be controlled from either inside or outside the body.

“We can use external light as a remote control to trigger nanoparticle breakdown. Or, we can make nanoparticles that degrade when they encounter particular molecules in the body, such as molecules that cells produce during inflammation.”

These triggers provides a chemical reaction that snaps polymer strands, opening holes and allowing the nanoparticle’s cargo to seep out.

In one of many applications for this technology, Almutairi’s team is collaborating with Kang Zhang, MD, PhD, professor of ophthalmology and chief of Ophthalmic Genetics at Shiley Eye Institute at UC San Diego Health, to use her inflammation-triggered nanoparticles to treat age-related macular degeneration — the leading cause of vision loss in people over 60.

Almutairi and Zhang have developed nanoparticles that remain in the eye of a mouse for up to one year after injection. Every time the nanoparticles are exposed to inflammation, a hallmark of disease flare-up, they release the macular degeneration drug VEGF Trap-Eye. VEGF Trap-Eye inhibits blood vessel growth, which keeps vision-damaging inflammation at bay.

“We haven’t tested it in humans yet, but so far this system works just as well as the drug, only without daily injections,” Almutairi said.

Many people don’t take their medications as often as they should

Remote-controlled nanoparticles carrying therapeutic payloads
Many bacteria release toxins that poke holes in human cells. Toxins released by E. coli and Salmonella, for example, two bacterial species that commonly cause food poisoning, puncture cells lining the digestive tract. That’s typically what causes diarrhea and other symptoms.

Liangfang Zhang, PhD, professor at Moores Cancer Center at UC San Diego Health and UC San Diego Jacobs School of Engineering, and his team are developing nanosponges to neutralize bacterial toxins. These nanosponges are cores of PLGA, a biodegradable polymer commonly used in many FDA-approved therapeutic devices, wrapped with human red blood cell fragments.

Thanks to their human disguise, the nanosponges attract pore-forming toxins, which incorporate into the membrane surfaces the same way they would in cells. The polymer core prevents the nanosponge membrane from collapsing, and the toxins are trapped. “Our nanosponge platform can disarm pathogens of their toxic factors and render them less harmful and more susceptible to our immune defense,” Zhang says. “This same approach could also provide a therapeutic intervention for a number of animal venoms that are difficult to treat.”

Red blood cells aren’t the only human disguise Zhang and his team are giving nanoparticles. In a separate project, they are coating PLGA cores with membranes from human platelets, blood cells responsible for clotting. Platelet cloaks help drug-delivering nanoparticles hide from the host immune system. Platelets also naturally stick to injured blood vessels and pathogenic bacteria in the bloodstream.

“We are now taking steps to carry this work forward, by scaling up the manufacture of the red blood cell nanosponges and platelet membrane-coated nanoparticles and planning for preclinical toxicology study of the nanoparticle formulations,” Zhang says. “We are also verifying the efficacy of nanosponges against many bacterial toxins and animal venoms that pose major health threats, and examining the effect of human blood types on the nanosponge performance. Ultimately, we aim to translate these nanotechnologies into new therapeutics.”

Platelet cloaks help drug-delivering nanoparticles hide from the host immune system.

“Nanosponges immortalized by human red blood cell fragments can attract and trap bacterial toxins.”

“Some therapies have trouble getting where they need to go.”

“Micromotors powering micromachines are about one-fifth the width of a human hair.”

One reason many medicines — chemotherapy, for example — cause unwanted side effects is because they circulate throughout the entire body after a person gets an injection or swallows a pill, and the drug can’t accurately distinguish between healthy and diseased cells.

To help target drugs to the cells and tissues where they will do the most good and least harm, Joseph Wang, PhD, Distinguished Professor, Chair of Nanoengineering and SAIC Endowed Chair in the UC San Diego Jacobs School of Engineering, and his team are pioneering micromotors that power micromachines. (Micromachines are about one-fifth the width of a human hair; nanomachines are even smaller.)

In one example, Wang collaborated with Liangfang Zhang to engineer micromachines powered by stomach acid. The micromachines can load and release a test payload of gold nanoparticles in the stomach of a mouse.

“We hope to use micromotors and nanomotors for targeted drug delivery of diagnostics and therapies.”

“Micromotors powered micromachines can load and release gold nanoparticles in one-fifth the width of a human hair.”

When the zinc bodies of the micromotors hit the mice’s stomach acid, the chemical reaction produces tiny bubbles that thrust the motors forward. In the experiment, the mice ingested a solution containing hundreds of these micromotors. The motors activated as soon as they hit the stomach acid and sped toward the stomach lining at a speed of 60 micrometers per second. They can self-propel for up to 10 minutes, the researchers found.

“In the future, it may be possible to add navigation capabilities and other functions to the motors, to increase their targeting potential,” Wang says. “Ultimately, we hope to use micromotors and nanomotors for targeted drug delivery of diagnostics and therapies, as well as tumor biopsies.”
Teaching the Art of Doctoring

Knowledge, skill, experience and judgment are all vital, of course, but equally precious and perhaps more readily recognized is a physician’s proverbial “bedside manner.”

“The Student-Run Free Clinic is an amazing opportunity to practice displaying our compassion in a professional setting,” said Kristin Cadenhead, MD, a professor of psychiatry. “It’s incredibly important,” said Kristin Cadenhead, MD, a professor of psychiatry. “No matter how smart you are, if you are not communicating and connecting with your patients, you are not going to be very effective.”

For many doctors, it’s an innate talent, but Cadenhead says it can also be taught, though the subject itself is constantly evolving.

Six years ago, UC San Diego School of Medicine began to purposefully weave the art of doctoring into its four-year curriculum. It began with expending the traditional curriculum structure: no more first two years devoted to medical education, last two to clinical care.

“We now view the first two years as preclinical ones, where the emphasis is on the building blocks that will support students when they are doing clinical care in earnest in the third year,” said Charlie Goldberg, MD, a professor of clinical medicine.

Take “standardized patient” exercises, for example, where first- and second-year students practice interview skills with actors portraying patients with a scripted condition and socioeconomic background. “In one scenario,” said Roopali Gupta, MD, an assistant clinical professor of medicine, “student-doctors meet a female-to-male transgender man and are asked to elicit a focused history in a way that respects his preferred pronoun and gender identity.”

“Part of being a compassionate physician is maintaining a non-judgmental attitude,” said Elizabeth Doyle, a first-year medical student. “We are taught to ask whether the person has a preferred pronoun or name. We get feedback from our peers and professor on whether we validated the person’s emotions, and named or labelled the emotions that were elicited by the patient.”

The actor-patient also provides feedback to the doctor-in-training, which can prove most valuable. “They tell us whether they felt listened to, respected, understood and why,” said Doyle. “I have found their feedback particularly helpful in reinforcing the school’s message that patients are not passive targets of the care we give them. They are some of our most important teachers.”

In another scenario, a dying patient asks his physician to pray with him. What should a doctor do? “There is not a right answer,” said Cadenhead. “We have students debate the question. The goal is to prepare them for what they will experience in the real world and help them make choices that are right for them and their patients.”

“I’m not sure you can teach compassion, but we are being given the opportunity to practice displaying our compassion in a professional setting,” said Doyle, the first-year student. “Having these sensitive topics brought up again and again during our training also normalizes the expectation of compassionate and caring behavior.”

Physician, heal thyself

“We now view the first two years as preclinical ones, where the emphasis is on the building blocks that will support students when they are doing clinical care in earnest in the third year,” said Charlie Goldberg, MD, a professor of clinical medicine.

Take “standardized patient” exercises, for example, where first- and second-year students practice interview skills with actors portraying patients with a scripted condition and socioeconomic background. “In one scenario,” said Roopali Gupta, MD, an assistant clinical professor of medicine, “student-doctors meet a female-to-male transgender man and are asked to elicit a focused history in a way that respects his preferred pronoun and gender identity.”

“Part of being a compassionate physician is maintaining a non-judgmental attitude,” said Elizabeth Doyle, a first-year medical student. “We are taught to ask whether the person has a preferred pronoun or name. We get feedback from our peers and professor on whether we validated the person’s emotions, and named or labelled the emotions that were elicited by the patient.”

The actor-patient also provides feedback to the doctor-in-training, which can prove most valuable. “They tell us whether they felt listened to, respected, understood and why,” said Doyle. “I have found their feedback particularly helpful in reinforcing the school’s message that patients are not passive targets of the care we give them. They are some of our most important teachers.”

The UC San Diego Student-Run Free Clinic, which provides no-cost care (medical, dental, pharmaceutical and legal) to underserved populations in San Diego, offers another venue for learning the art of doctoring and more.

“Currently about 90 percent of our medical students volunteer with the free clinic,” said Michelle Johnson, MD, an associate clinical professor in family medicine and co-medical director of the free clinic. “We thought about making participation mandatory, but we want our patients to see that desire and spirit of service from their caregivers and to cultivate the higher ideals of medicine in our students.”

“The Student-Run Free Clinic is an amazing source of pride,” said David Brenner, MD, vice chancellor for UC San Diego Health Sciences and dean of the School of Medicine. “When students talk about what they’ve done that has really changed their careers in medical school, the first thing they mention is the Student-Run Free Clinic.”

“The UC San Diego Student-Run Free Clinic,” which provides no-cost care (medical, dental, pharmaceutical and legal) to underserved populations in San Diego, offers another venue for learning the art of doctoring and more.

“Currently about 90 percent of our medical students volunteer with the free clinic,” said Michelle Johnson, MD, an associate clinical professor in family medicine and co-medical director of the free clinic. “We thought about making participation mandatory, but we want our patients to see that desire and spirit of service from their caregivers and to cultivate the higher ideals of medicine in our students.”

“The Student-Run Free Clinic is an amazing source of pride,” said David Brenner, MD, vice chancellor for UC San Diego Health Sciences and dean of the School of Medicine. “When students talk about what they’ve done that has really changed their careers in medical school, the first thing they mention is the Student-Run Free Clinic.”

“We now view the first two years as preclinical ones, where the emphasis is on the building blocks that will support students when they are doing clinical care in earnest in the third year,” said Charlie Goldberg, MD, a professor of clinical medicine.

Take “standardized patient” exercises, for example, where first- and second-year students practice interview skills with actors portraying patients with a scripted condition and socioeconomic background. “In one scenario,” said Roopali Gupta, MD, an assistant clinical professor of medicine, “student-doctors meet a female-to-male transgender man and are asked to elicit a focused history in a way that respects his preferred pronoun and gender identity.”

“Part of being a compassionate physician is maintaining a non-judgmental attitude,” said Elizabeth Doyle, a first-year medical student. “We are taught to ask whether the person has a preferred pronoun or name. We get feedback from our peers and professor on whether we validated the person’s emotions, and named or labelled the emotions that were elicited by the patient.”

The actor-patient also provides feedback to the doctor-in-training, which can prove most valuable. “They tell us whether they felt listened to, respected, understood and why,” said Doyle. “I have found their feedback particularly helpful in reinforcing the school’s message that patients are not passive targets of the care we give them. They are some of our most important teachers.”

UC SAN DIEGO HEALTH DISCOVERIES MAGAZINE
Neglected tropical diseases are infectious maladies that disproportionately affect people living in poverty in tropical or subtropical regions of the world, such as Chagas disease, amebiasis, leishmaniasis and schistosomiasis. These and other conditions affect more than one billion people in 149 countries.

"WE CALL THESE DISEASES ‘NEGLECTED’ because of the lack of resources and attention dedicated to studying, preventing and treating them — especially considering the millions of people they afflict," said James McKerrow, MD, PhD, professor and dean of the Skaggs School of Pharmacy and Pharmaceutical Sciences at UC San Diego. It’s the duty of a public university, said McKerrow, to take up the cause of finding new treatments when others do not.

WHEN MCKERROW took the helm of the Skaggs School of Pharmacy in 2014, a major goal was launching a new high-throughput robotic drug discovery facility for testing potential drugs on the microbes that cause neglected tropical diseases. Now a reality, the facility is being used by many research groups in the pharmacy school, School of Medicine and other institutions to screen hundreds of thousands of chemical compounds for those few that might inhibit or kill dangerous pathogens.

Some of these chemical compounds are completely new drug precursors; others are existing drugs that have already undergone safety studies in humans, potentially saving time and money if they prove effective in treating additional diseases. For example, McKerrow and his team are working with Janssen Research & Development, LLC, one of the Janssen Pharmaceutical Companies of Johnson & Johnson, to test an existing drug for its efficacy in treating Chagas disease. Chagas is endemic in Latin America, where it’s the leading cause of heart failure, and is an emerging infection in other regions of the world, including California.

The Janssen R&D drug works by inhibiting a human protein called Cathespin S. Previous studies showed that inhibitors of a parasite-specific relative of Cathespin S can treat Chagas disease in infected animals, but these inhibitors later failed safety tests," McKerrow said. The Janssen R&D drug is already proven safe in humans, so McKerrow and his team are now confirming the drug’s antiparasitic activity in lab studies and infected animals before testing it in humans with Chagas disease.

"While leptospirosis is curable with penicillin, we can’t treat people if we don’t know they are infected," said Vinetz, who is also a physician certified by the American Society of Tropical Medicine and Hygiene in tropical medicine and traveler’s health. "Unlike the malaria parasite and other pathogens, it’s extremely difficult to isolate leptospira bacteria or detect a person’s antibodies against them."

To overcome this challenge, Vinetz and collaborators recently sequenced the leptospira genome, a landmark study he says has launched the next generation of research on the bacterium. They are now using this genomic information to test new diagnostic techniques on blood and tissue samples they have been collecting from suspected leptospirosis patients in Sri Lanka.

"Now that malaria transmission has largely been disrupted in Sri Lanka, leptospirosis is a priority," Vinetz said. “Once we get a handle on diagnosing the disease, we’ll be better equipped to prevent and treat it. Ultimately, we hope to help break the cycle of poverty and disease in this region of the world."
REFRAME
OF MIND

New mood disorders center offers depressed
and anxious patients a brighter future

SEVENTEEN-YEAR-OLD WILLIAM GOODMAN spends his time
taking online courses, working part-time in construction and
socializing with his friends. It sounds like a regular schedule for
a teenager, but for William, these activities are “big miracles”
after battling severe depression and anxiety for more than
two years. At one point, the high school honor student and
varsity athlete was not able to eat, talk or interact with anyone
outside the four walls of his bedroom.

“The depression was unrelenting, and I didn’t want to continue
living this way,” said William.

William’s mother, Nancy, watched her highly energetic
and intelligent son slowly deteriorate to the point where
he couldn’t function. “It was like watching a dark cloud
permanently form over William’s head and torment him,”
she said.

William’s parents researched ways to help him. Several
doctor visits, hospitalizations and rounds of antidepressant
medications, including selective serotonin reuptake inhibitors
(SSRIs), did not help their desperate teenager and left him
feeling hopeless.

“I was exhausted from the disappointment,” said William.
“I was ready to try anything to feel better.”

That’s when the family learned about the Center for Advanced
Treatment of Mood and Anxiety Disorders at UC San Diego
School of Medicine. The center is the first of its kind to
specialize in using evidence-based and non-traditional
treatments for patients with psychiatric disorders who have
not responded to conventional therapies.
Ketamine can produce a dramatic improvement within 24 hours, often curbing suicidal thoughts with no signs of addiction.

"Standard antidepressant medications eliminate depression in less than half of the patients who take them," said David Feifel, MD, PhD, the center’s director and professor of psychiatry at UC San Diego School of Medicine. “We wanted to create a place where we could use the most innovative and advanced technologies to treat patients who have no other options.”

One in six Americans will experience clinical depression in their lifetime.

“Clinical depression is not just a bout of feeling blue, which everyone experiences. It’s a brain malfunction in which circuits of the brain that make it possible to experience pleasure shut down. Some patients find simple tasks, like brushing their teeth, overwhelming and others can’t even get out of bed,” said Feifel. “The brain is the most complex organ in the body, and psychological disorders can be difficult to treat.”

Feifel and his team are on the forefront of treatment, using therapies like transcranial magnetic stimulation (TMS).

“As the number of patients suffering from treatment-resistant depression rises, psychiatry experts need to research and rapidly implement new therapies if we want to save lives,” said Feifel.

IN 2009, UC SAN DIEGO was the first in San Diego to offer TMS as a treatment method for clinical depression and other neuropsychiatric conditions. The noninvasive procedure involves a device that generates magnetic pulses to stimulate neurons in the region of the brain involved in mood and depression. Over time, the magnetic currents reestablish normal activity in brain circuits involved in regulating mood.

“TMS directly targets the abnormal firing pattern of the brain cells. It is a paradigm shift in the treatment of depression, which for the past 50 years has been dominated by pharmacological interventions,” said Feifel.

A main focus of the center is to explore ways of combining or repurposing emerging treatments to defeat the most unmanageable cases of clinical depression. Feifel and his team have found that one of the most promising combination approaches is the use of TMS with ketamine.

Ketamine is a compound commonly used as an anesthetic. It also has hallucinogenic properties, which has made it a popular party drug called “Special K.” The compound works like a flash mob in the brain, temporarily taking over a certain chemical receptor. Although not FDA approved to treat depression, researchers like Feifel have found that infusions or injections of ketamine can produce a dramatic improvement within 24 hours, often curbing suicidal thoughts with no signs of addiction.

I in 6 Americans will experience clinical depression in their lifetime.

“Some of the novel treatments that are regularly used for clinical depression at the center have also been shown to produce benefits for other psychological disorders, such as obsessive-compulsive disorder, post-traumatic stress disorder and addiction. Feifel’s team, for example, are now exploring the drug oxycotin as a potential therapy for anxiety, depression and schizophrenia.”

“‘The brain is the most complex organ in the body, and psychological disorders can be difficult to treat.’”

— David Feifel, MD, PhD

"A limitation of ketamine alone is the benefit from each treatment only lasts anywhere from several weeks to a few days. However, ketamine and TMS combined complement each other’s properties and work more effectively for treatment-resistant patients,” said Feifel.

William traveled from Arizona to San Diego weekly to receive a combination of TMS and ketamine at the center.

“It was an exhausting journey but worth every mile,” said William. “After several weeks of treatment, I started to feel more like the person I used to be.”

Other techniques, like electroconvulsive therapy (ECT), known as shock therapy, have also been shown to be effective. The procedure is done under general anesthesia and uses small electric currents that are passed through the brain, intentionally triggering a brief seizure. ECT seems to cause changes in brain chemistry that reverse symptoms of certain mental illnesses. It is an older technique with a lot of side effects, such as memory loss, not often used by the center.

For William, the center has meant light at the end of a long tunnel.

“I am now able to carry on a conversation with my parents and enjoy time outside of the house with my friends,” said William. “These are huge accomplishments that I was starting to think weren’t possible.”

Being at the leading edge of treating mood and anxiety disorders is possible thanks to the compassionate giving of people like you. To make a gift in support of this transformational work, please call 858-822-4562.
New center is energizing diabetes and metabolic disease research

Thermogenesis naturally occurs in brown and beige fat cells. Researchers believe it might be exploited to increase energy expenditure.

A CENTURY AGO, patients diagnosed with diabetes were given, at most, two years to live. In 1921, a surgeon named Frederick Banting made a discovery that changed diabetes treatment and saved the life of a 14-year-old boy who was near death. The boy became the first of millions of people who have since received the hormone insulin — the master regulator of energy (glucose) storage — as a way to manage diabetes as a chronic disease.

Metabolic diseases, including diabetes, can occur as an autoimmune disorder or when energy intake from food consumption and energy expenditure from physical activity or the body’s metabolism become unbalanced. The body adjusts to this imbalance by changing how it secretes and responds to hormones like insulin. These disorders are a public health threat tied to the expanding problem of obesity. In the United States, two-thirds of the population are overweight or obese. Despite constant reminders that diet and exercise are ways to combat growing waistlines, worldwide obesity rates have doubled and people are on average 30 pounds heavier than they were in 1960.

“As much as we have learned, we still do not have all of the answers we need to treat metabolic diseases or control obesity,” said Alan R. Saltiel, PhD, who studies insulin’s role in regulating cellular sugar levels, including how cells send and receive signals. “In the U.S., one-tenth of the population is stricken with diabetes. It’s the seventh-leading cause of death and will rise if uncontrolled.”

Finding safe and effective therapies that regulate energy intake and expenditure is not simple. A balance between energy use and storage — homeostasis — involves many internal and continuous conversations throughout the body, including the brain, liver, gut, fat and muscles.

Saltiel is looking deeper into dysfunctional metabolic processes to identify pathways that might guide the development of new therapies. He is particularly interested in the connection between obesity and diabetes. Insulin resistance can occur as an inflammatory response to obesity in fat and liver cells. The initial response is normal, but when the body doesn’t regulate its weight, the problem becomes chronic, leading to insulin resistance. Saltiel’s research is now focused on understanding one way to combat this problem — thermogenesis, or the generation of heat within the human body. He is interested in how fat cells generate heat, and how these cells are controlled and respond to hormones like insulin and epinephrine (adrenaline).

Thermogenesis occurs naturally in a type of fat cell called the brown or beige fat cell. Researchers believe these cells might be exploited to increase energy expenditure. Combined with diet, physical activity or therapy that regulates hunger, just modestly activating thermogenesis could help people lose weight, said Saltiel.

As director of the newly formed UC San Diego Institute for Diabetes and Metabolic Health, Saltiel is bringing researchers together to expand the university’s diverse programs to better understand, treat and prevent metabolic diseases. Even before arriving at UC San Diego in 2015, Saltiel was collaborating with Jerrold M. Olefsky, MD, professor of medicine and associate dean for scientific affairs, David Brenner, MD, vice chancellor of health sciences and dean of the UC San Diego School of Medicine, and Ronald Evans, PhD, Salk Institute for Biological Studies professor, to understand this process. They looked at more than 180,000 compounds before identifying an older asthma drug that inhibits a pathway blocking epinephrine, which increases the “browning” of fat cells. Boosting brown fat cells may produce weight loss and improve insulin sensitivity in ways that diet does not.

“Diabetes drugs and obesity therapies today are not good enough,” said Saltiel. “In most cases, diet and exercise alone aren’t working for the management of metabolic diseases. This is partly explained by evolution, which selects for traits enabling us to handle what our bodies think — that a famine is always just around the corner. As a result, there are powerful forces that drive us to consume food and then store the energy in the most efficient way we can — as fat.”

To join us in redefining diabetes and metabolic health, please call 858-822-4562.
Mark H. Tuszynski, MD, PhD, professor in the Department of Neurosciences and director of the Translational Neuroscience Institute at UC San Diego, received the Reeve-Irvine Medal for Spinal Cord Injury Research for his contributions to spinal cord repair research. The award is named, in part, after the late actor Christopher Reeve.

Three UC San Diego School of Medicine faculty were elected to the National Academy of Medicine: Napoleone Ferrara, MD, Distinguished Professor of Ophthalmology and Pathology and senior deputy director for basic science at Moores Cancer Center; Christopher K. Glass, MD, PhD, professor of medicine and cellular and molecular medicine; and Roberto Malinow, MD, PhD, Distinguished Professor of Neurosciences and Neurobiology and the Shiley Endowed Chair in Alzheimer’s Disease Research in Honor of Dr. Leon Thal. There are now 30 faculty who are members of NAM.

Patty Maysent was officially named CEO of UC San Diego Health. Maysent joined the university in 2012 and served as chief of staff and chief strategy officer to CEO Paul Viviano before his departure in 2015.

UC San Diego School of Medicine and Chiba University School of Medicine in Japan established a five-year, $2 million partnership to create a new collaborative research center to investigate the most promising aspects of immunology, especially the area of mucosal immunology, and to speed development of clinical applications.

The UC San Diego Center for Microbiome Innovation, led by Rob Knight, PhD, professor of pediatrics and computer science and engineering, was created in late 2015 to better understand microbiomes — collections of microbes that live on and around us — and harness them for human and environmental health. In May 2016, the center was named a key participant in the White House’s National Microbiome Initiative. Knight, Pieter Dorrestein, PhD, professor of pharmacy, pharmacology and pediatrics, and Embriette Hyde, PhD, assistant project scientist and manager of the American Gut Project, attended the launch event in Washington, D.C.

Local philanthropists Gary and Mary West provided $11.8 million to create a state-of-the-art senior emergency care unit within the Emergency Department at Jacobs Medical Center. The Gary and Mary West Senior Emergency Care Unit will enhance care for older adults and enable a multi-year medical research initiative in partnership with the West Health Institute to support their mission of making successful aging a reality for seniors in San Diego and the nation.

María Elena Martínez, PhD, professor of family medicine and public health, co-leader of the Reducing Cancer Disparities research program, and Sam M. Walton Endowed Chair for Cancer Research at Moores Cancer Center at UC San Diego Health, was named to a Blue Ribbon Panel to help inform scientific direction at the National Cancer Institute for Vice President Joe Biden’s National Cancer Moonshot Initiative.

Experts at the UC San Diego Autism Center of Excellence will be part of the largest autism study ever undertaken in the United States — an effort to collect information and DNA from 50,000 individuals, ages 3 to 100, with the neurodevelopmental disorder. The effort, sponsored by the Simons Foundation Autism Research Initiative, involves 21 leading research institutions across the country, each recruiting participants and collecting data.

The Altman Clinical and Translational Research Institute — a seven-story, 359,000-square-foot edifice on the east campus — opened its doors. Supported by a $10 million donation from Steve and Lisa Altman, the ACTRI is part of a national consortium created to energize bench-to-bedside efforts.

Roughly one-quarter of all Americans have nonalcoholic fatty liver disease (NAFLD), a chronic condition that can lead to cirrhosis, liver cancer and liver failure. Combining basic science, biomarkers, imaging and clinical efforts, the School of Medicine launched a new NAFLD Research Center, under the direction of Rohit Loomba, MD, to better understand the disease and develop treatments where none currently exist.
UC San Diego Health Sciences comprises one of the nation's top research-intensive schools of medicine; the Skaggs School of Pharmacy and Pharmaceutical Sciences; and UC San Diego Health, the region's only academic health system.

discoveries.ucsd.edu
On July 1, 1966, the University of California Board of Regents assumed a $350,000 annual lease for County Hospital — a three-year-old, 11-story structure rising just north of downtown San Diego, overlooking the still semi-bucolic pasturelands of Mission Valley.

It was renamed University Hospital and decreed the primary clinical teaching facility of the even newer UC San Diego School of Medicine, which the Regents had approved four years earlier but which wouldn’t actually hold classes for another ten nor graduate its first doctors until 1972.

Fifty years ago, the future of local health care was mostly inspired imagination — for the city, for the new university and for what would ultimately become UC San Diego Health, the region’s only academic medical system and, by most measures, one of the best in the world.

University Hospital, which the Regents purchased outright in 1981, is now UC San Diego Medical Center in Hillcrest, part of a larger system that currently includes Shiley Eye Institute, Moores Cancer Center, Sulpizio Cardiovascular Center, numerous community clinics and, this year, the Jacobs Medical Center — a gleaming new edifice of silver and glass rising on the university’s east campus in La Jolla.

The distance from UC San Diego Medical Center to Jacobs Medical Center is perhaps a dozen miles, but between them stretches a timeline of extraordinary achievement, marking UC San Diego Health as not just a preeminent center for medical research and teaching, but the place to go for care that is first, best and only.

On July 1, 1966, the University of California Board of Regents assumed a $350,000 annual lease for County Hospital — a three-year-old, 11-story structure rising just north of downtown San Diego, overlooking the still semi-bucolic pasturelands of Mission Valley.
...