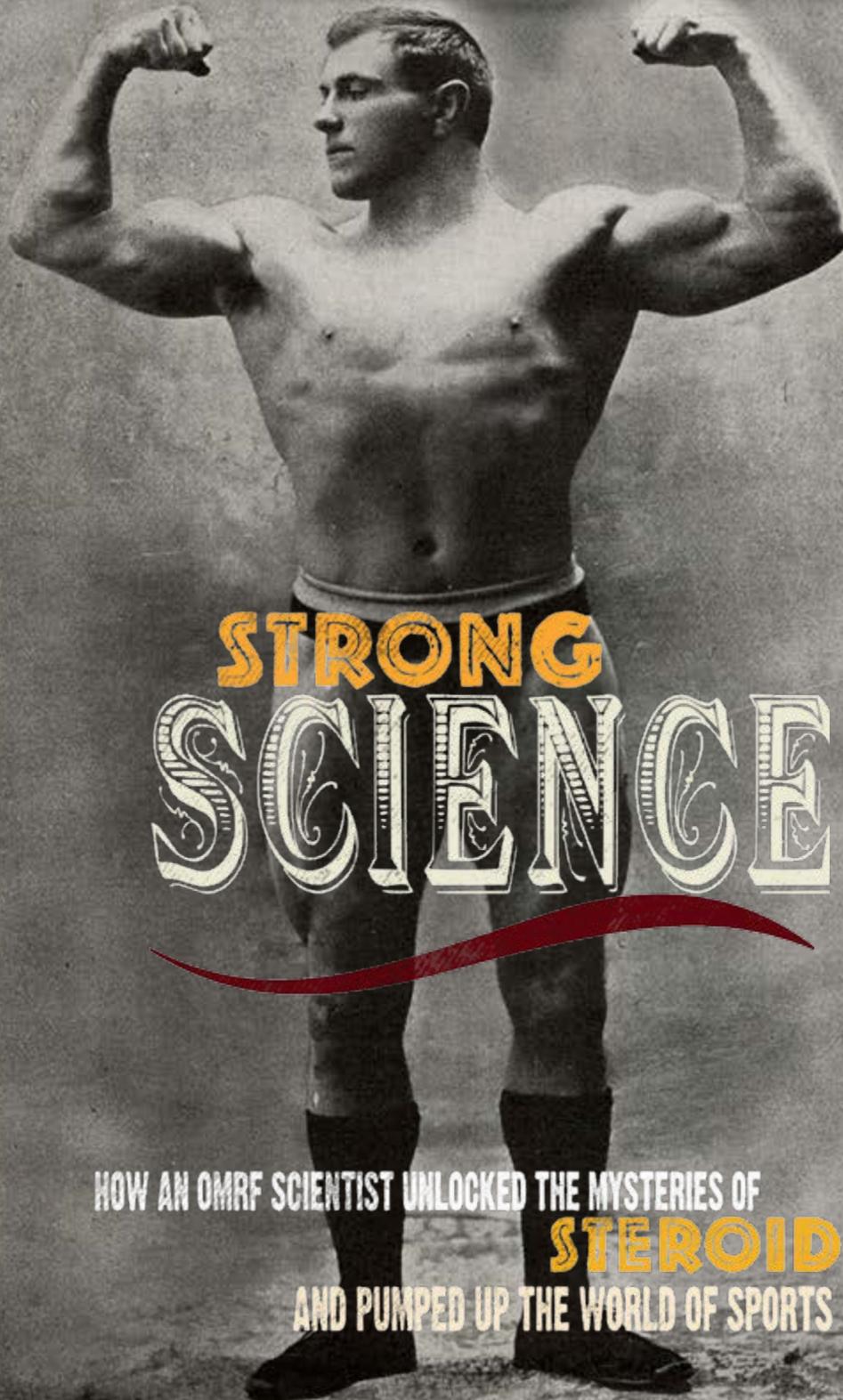


FINDINGS

omrf.org • Summer/Fall 2015



STRONG SCIENCE

HOW AN OMRF SCIENTIST UNLOCKED THE MYSTERIES OF
STERIODS
AND PUMPED UP THE WORLD OF SPORTS

We give to OMRF because medical research affects our children and children all over the world.
Katie & Will Merrick



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Chartered in 1946, OMRF is an independent, nonprofit biomedical research institute dedicated to understanding and developing more effective treatments for human disease. Its scientists focus on such critical research areas as cancer, diseases of aging, lupus and cardiovascular disease.



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It Takes Two

For Scott and Kendra Plafker, medical research is a team sport

Scott and Kendra Plafker have been married for 17 years. But this spring marked a milestone that precious few couples ever celebrate: Their first scientific paper co-authored solely by the pair.

“We’ve had plenty of papers with both our names on them, but it was special to be able to publish something on our own, just the two of us,” says Dr. Scott Plafker, a researcher in OMRF’s Aging and Metabolism Research Program.

With his wife, Kendra, he studies age-related macular degeneration, the leading cause of vision loss among elderly Americans. The couple is searching for ways to prevent and improve the treatment of the debilitating eye disease.

For many wives and husbands, working together might prove a recipe for disaster. But for the Plafkers, they’ve built a successful partnership in the laboratory by defining what each spouse is responsible for.

He sets the overall direction of the research, designing experiments and writing the grants that fund the projects. Meanwhile, she manages the day-to-day operations of a six-person lab that conducts the experiments.

“The goal is to have somewhat defined roles that complement one another so we can be as efficient as possible,” says Kendra. “We’ve done it long enough now that we have figured out how to strike the right balance. It just took time.”



RESEARCH RESPIRE

Outside the lab, Kendra uses yoga to stay fit and centered, while Scott prefers distance running. He’s completed five marathons, including the 2015 Boston Marathon, where this shot was taken after he finished in a time of 3 hours and 3 minutes.

The pair met in the early 1990s, when she was a lab technician and he was a graduate student at Johns Hopkins University in Baltimore. They married in 1997 and relocated to the University of Virginia and, ultimately, to Oklahoma in 2003, when he accepted a position to run his own laboratory, and she became his lab manager.

That transition, says Kendra, proved challenging. “We had worked side-by-side in the lab for years but on totally different projects. Once we moved to Oklahoma, everything was the same: the same projects, the same work schedule. That was a little weird to not have our own niches.”

Over time, though, the two figured out how to find balance by dividing up responsibilities. It’s similar to how they handle things on the home front, where Kendra cooks and manages finances, leaving laundry and cleaning detail to Scott.

“I’d definitely say Kendra is more in charge of big-picture things at home, and I’m more detail-oriented,” says Scott. “Our roles are completely reversed from how they are at work.”

In the lab, their successful collaboration has most recently led to the Plafker-and-Plafker-authored paper in the journal *Molecular Biology of the Cell*. The research study focuses on one of the main molecules they’ve been studying at OMRF.

That molecule, known as NRF2, is a powerful protein that’s in every cell in the body but is unable to operate or move until it’s released by a chemical activator. Understanding how it migrates into the nucleus of the cell and binds to DNA, says Scott,

could help scientists gain a deeper understanding of a variety of illnesses, including macular degeneration.

“To use a military reference, the protein NRF2 is like a general that is responsible for keeping the cells in our body safe from stress,” he says. “NRF2 orchestrates the troops—the many distinct types of anti-stress proteins in a cell—to work in a coordinated manner so they can effectively neutralize stress.”

Their manuscript has uncovered a new mechanism that regulates NRF2 to work more efficiently and better protect cells. Decreases in the NRF2 defense system have been linked to age-related macular degeneration and to other neurodegenerative conditions, including Alzheimer’s, Parkinson’s and Huntington’s diseases.

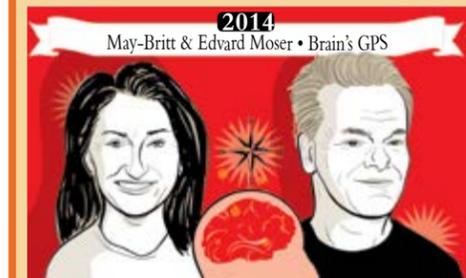
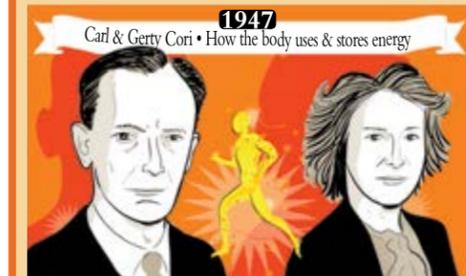
While working together might drive some couples to seek “alone time” off the job, the Plafkers enjoy many joint pastimes, including playing Scrabble, binge-watching shows on Netflix and traveling across Europe. They usually commute to and from work as a couple and can be found almost every day eating lunch together in the OMRF cafeteria.

Spending so much time with each other might not work for all couples, but, says Kendra, “It’s the only way we’ve ever known.” In fact, when Scott changed labs for a brief time, they realized just how much they cherished and missed their hyper-interactive partnership.

“Only seeing each other on the way in to work, at lunch and on the drive home,” she says, “that was weird and lonely.”

Two Heads Are Better Than One

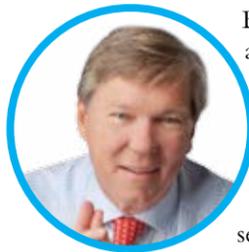
When it comes to scientific couples, the Plafkers have lots of company. For many wives and husbands in research, working together might prove a recipe for disaster, but quite a few of them choose to work together. In fact, four couples have won Nobel Prizes for their work together:



Enter Sandman

*Dear Dr. Prescott,
When I have difficulty falling asleep, I am torn about using over-the-counter sleep medications. Are there any long-term health effects associated with the use of sleep aids? In particular, I was wondering whether the use of these drugs might increase the risk of dementia?*

Mary Schneeberger, Oklahoma City



Before we talk about sleep aids, let's think for a moment about sleep itself. Or, more precisely, about how little sense it seems to make from an

evolutionary perspective.

By day, our ancient ancestors stalked antelopes and gazelles in the grasslands. But when night fell, they'd curl up to get some shut-eye. Which is an extremely dangerous thing to do when nocturnal predators like leopards and lions are prowling the savannahs. So for this trait of sleeping (which probably converted a few of its less fortunate carriers into cat chow) to have survived, it must carry some pretty big biological benefits.

Research has shown that sleep plays a key role in forming and consolidating memories. Ditto for building new neuronal bridges and leveling old ones. Experiments in the past few years have also pointed to sleep's essential role in physiological maintenance—specifically, clearing waste from the brain.

Not surprisingly, sleep deprivation has been linked to a variety of health problems: anxiety, depression, diabetes and hypertension. There's also the higher rate of vehicular accidents that comes with persistent drowsiness, not to mention a decrease in productivity. When a neurologist and sleep consultant to numerous professional sports teams (including the Oklahoma City Thunder) studied Major League Baseball players, he found that 86 percent of those who reported the highest levels of drowsiness were no longer in the league two years later.

In a chronically overworked and underslept world, many turn to non-prescription sleeping aids such as Nytol or the antihistamine Benadryl. Researchers have yet to determine whether aided sleep produces the same level of physiological benefits as natural sleep. But research released earlier this year did find an increased risk of dementia among senior citizens who engaged in long-term use of sleep aids like these, which block the neurotransmitter acetylcholine. Other studies have also associated the use of multiple

anticholinergic drugs (like the anti-depression medication Paxil and pain medications such as Tylenol PM) with lower levels of cognitive function.

Still, the evidence linking these drugs to dementia, Alzheimer's or other forms of cognitive impairment remains weak, with no underlying explanation of what might be happening on a biological level. Moreover, the most recent study—the most rigorous by far—suggests that risk increases only when people use these drugs for three years or more.

So I wouldn't be overly concerned that the occasional, short-term use of an over-the-counter sleep aid will cause Alzheimer's.

That said, if you're having trouble sleeping, there are other effective strategies that carry fewer potential side effects. Avoid all alcohol and caffeine before bed. Leave screens out of the bedroom, as the blue light emitted by devices like smartphones and TVs suppresses the release of the sleep hormone melatonin. Ensure your room is completely dark, as any light can disturb sleep patterns.

Most importantly, don't panic if you find yourself tossing and turning. Try to visualize the step-by-step process involved in an everyday activity like a workout or cooking a meal. But unlike our prehistoric cousins, there's no need to worry that when you do fall asleep, you might actually become a meal.



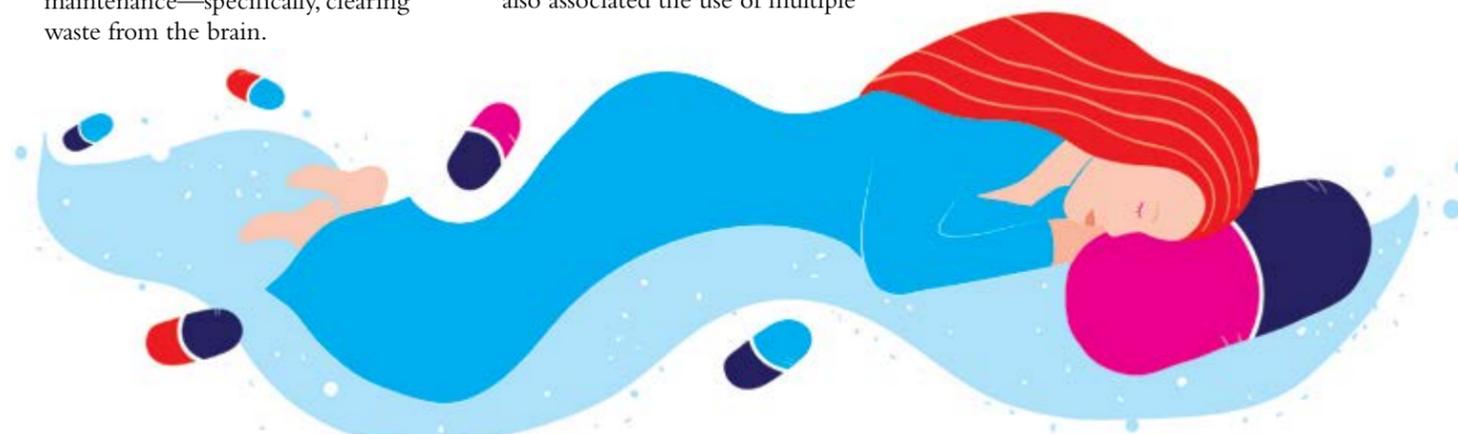
Dr. Tim Griffin

ARTHRITIS RESEARCHER

How do gifts from donors help your research?

“We had great ideas about how obesity was influencing arthritis at a cellular level, but we didn't have specific molecular targets. So we needed resources to gather data ... Another big thing was equipment. We needed a gas chromatography mass spectrometer. And funds to develop a specialized mouse wheel to measure the force the animals exert when they run. That took us more than two years to build, but now we have a unique resource ... It's scary to think about how much time and money it's taken to get to this point, but now we've discovered unique molecular targets that are ready to be explored.”

Dr. Tim Griffin has obtained a new five-year grant from the National Institutes of Health to study how aging and obesity contribute to arthritis.



On the up and up

An OMRF staffer has found his niche in the little-known sport of stair-climbing



Brad Pazoureck almost never takes an elevator.

A systems administrator who joined OMRF in 2001, he has good reason to avoid mechanized lifts: “Every flight of stairs I climb is training.”

He is the 28th-ranked tower runner among U.S. amateur men, according to Stairsport.com. The site ranks more than 34,000 Americans who, like Pazoureck, compete in competitive stair-climbing races.

A relative newcomer to the sport, Pazoureck completed his first race at Chicago’s Willis Tower (103 floors) in the fall of 2014. He ascended the building’s 2,109 stairs in just over 20 minutes, placing him in the top 100 of more than 3,000 participants.

“After that, I was hooked,” he says.

Since then, he’s competed in the Big D Climb at the Comerica Bank Tower in Dallas (1,276 steps) and the Stratosphere Climb in Las Vegas (1,455 steps). Closer to home, he finished third in Little Willie’s Triple Dog Dare (up and down three Oklahoma City office towers), and he won the local Fight for Air Climb.

Before taking up stair-climbing, Pazoureck, who lives in Yukon with his wife and two children, was a biker, skier and occasional participant in local runs. “But I was never a strong runner,” he says. “I was always middle-of-the-pack.”

To speed his recovery from a torn Achilles tendon three years ago, he began attending classes in OMRF’s onsite fitness center. Boot-camp exercises led him to realize that he had a talent for climbing stairs.

Pazoureck’s training typically involves twice-daily workouts that use a mix of running, gym work and classes to build fitness. He starts at the crack of dawn with his trainers at Fitness Together in Yukon. In addition, he tries to climb—and descend—at least 30 to 40 floors a day, usually in OMRF’s research tower. Often, to make the stair-climbing workouts more challenging, he’ll don a 35-pound weight vest.

“From the time he first walked into the fitness center to now,

Brad has increased his fitness level exponentially,” says Kelie Ashley, who manages OMRF’s fitness center and helps Pazoureck coordinate his training. “His dedication to training, his energy and his passion for this sport have been incredible to watch over time.”

According to Stairsport.com, stair-climbing competitions have grown more popular in recent years, with more than 100 events now taking place across the country. The events use staggered starts, with racers beginning every 5 to 10 seconds. Competitors employ their arms as well as their legs in the ascents, using handrails to help pull them up.

“It’s a total body workout,” says Pazoureck. “This may sound clichéd, but it’s the hardest sport you’ve never heard of.”

Despite the intense nature of stair-climbing, the sport’s community “is like one big family,” he says. “Everyone is there to do the best they can but also push each other to do as well as they can. It’s an amazingly friendly competition.”

In May, he participated in the first ever race up One World Trade Center, the newly constructed skyscraper that’s the tallest in the U.S. The race ascended 90 of the building’s 104 stories. Pazoureck made the climb in just over 16 minutes, covering an average of 5½ floors each minute. “It was an amazing experience,” he says.

Up next are a climb to the top of Seattle’s Space Needle in October, followed by a return to Chicago in November. There, he’s striving for another milestone: two races in the same day, including another trip up Willis Tower.

Regardless of whether he meets his goal of climbing the Windy City’s tallest building in less than 18 minutes—a significant improvement on his inaugural effort last year—Pazoureck knows he’s definitely discovered his athletic niche. “Now I’ve found a sport where I can excel, and it’s pushing me to improve every day,” he says. “It’s changed my life for the better.”

Rise Above

The sport of competitive stair-climbing traces its roots to the first Empire State Building Run-Up in 1978, where the speediest climbers ascended the iconic skyscraper’s 86 floors in about 10 minutes. Since that time, the sport has grown by leaps and bounds. According to towerrunning.com, if you want to participate in a competitive stair climb, you can now choose from 200 races in 36 countries.



STRONGMEN

-EXHIBITION-

FROM ALL OVER THE WORLD



INTERNATIONAL NEWS

MUSCLE MAN

THE STRANGE BUT TRUE
STORY OF HOW AN OMRF
SCIENTIST DISCOVERED
ANABOLIC STEROIDS

BY ADAM COHEN





he dark suit and a tie the hue of lime sherbet offered little in the way of disguise. Ditto for the salt-and-pepper beard and the rimless reading glasses perched on the bridge of his nose. No, one glimpse at the jacket stretched thin in a futile struggle to contain his grapefruit-sized biceps, and you could tell one thing about this man: He did not spend his days in an office.

Or, for that matter, testifying to a panel of legislators on Capitol Hill.

Yet here he was, Mark McGwire, all six-foot-five of him, folded into a chair and tucked in behind a microphone. The year was 2005, and the former Major League Baseball slugger was struggling to answer questions from members of a U.S. House committee about the use of anabolic steroids and other performance-enhancing drugs in America's pastime. Inquiries about how, exactly, a once-lanky rookie grew into a muscle-bound Hercules who, on 586 separate occasions, managed to drive a cork wrapped in yarn and covered in horsehide over outfield walls in places like Wrigley Field and Yankee Stadium.

"My lawyers have advised me that I cannot answer these questions without jeopardizing my friends, my family or myself," he told the committee, choking up and appearing close to tears.

Later, he refused a Congressman's request to give a clear answer about whether he'd used steroids.



"Are you taking the Fifth?" the Congressman demanded. "I'm not here to discuss the past," responded the slugger who'd once clubbed a record-breaking 70 home runs in a single season. "I'm here to be positive."

And so it went through the proceeding, with McGwire neither admitting nor denying what many suspected. But five years later, he would confess that he'd cheated. That like so many others who had played in baseball's so-called "Steroid Era," his prodigious power had come, at least in part, from a syringe.

Of course, baseball is hardly the only sport in which competitors have resorted to chemicals to gain an edge over their peers. Athletes in a variety of other sports (weight-lifting, body-building, wrestling, football, track and field, cycling, bobsledding, volleyball, basketball, swimming) have also been caught with their hands in the steroid jar.

Mark McGwire may be the most famous person to admit to using anabolic steroids, but he certainly didn't invent them. That happened long before he ever laced up his first pair of spikes.

As is so often the case in medicine, the tale of steroids stretches back many thousands of years. The story offers lessons in unintended consequences, about how beneficial research can come with an Achilles heel. And, oddly enough, it's a narrative that runs smack-dab through the laboratories of the Oklahoma Medical Research Foundation.

Dr. Charles Kochakian never imagined that his research would transform baseball players like former St. Louis Cardinals slugger Mark McGwire into steroid-pumped home run machines.

BEFORE THE PERIOD we call "history," which academics generally agree began with the Sumerians' invention of writing around 3500 B.C., ancient farmers developed methods for domesticating animals. As they experimented with how to transform feral beasts into obedient creatures they could use for food and to assist them in chores like farming and transportation, they hit upon a medical procedure that made the process significantly easier: castration.

The removal of testicles and penises made animals more docile, leading the Egyptians and Romans to believe that male reproductive organs held special powers. Later, the Greeks built upon this notion, using extracts from the testes in attempts to enhance athletic performance.

This idea endured for millennia. Then, in the 19th century, scientists found the first concrete evidence of a substance in the bloodstream produced by the testicles that, when eliminated, caused roosters' combs to shrink and the animals to lose both their interest in hens and aggressive behavior. A prominent physiologist and Harvard professor subsequently conducted a string of experiments where he injected himself with substances extracted from the testicles of guinea pigs and dogs. He reported not only that he enjoyed increased strength, mental ability and appetite, but also that the injections relieved his constipation and increased the arc of his urine stream. In no time, scientists and physicians began injecting patients with a wide variety of testicular extracts in attempts to find cures for ailments ranging from paralysis to migraine headaches.

The studies yielded mixed results. But they did suggest that the testes produced something that played a major role in stimulating the development of both muscle and male sexual characteristics. Researchers coined the term hormone for it, which in Greek means "to urge on."

After World War I, pharmaceutical companies ramped up efforts to isolate this hormone. In 1935, a team from the Dutch drug manufacturer Organon succeeded. It dubbed the hormone, which required 220 pounds of bull testicles to generate less than a thimbleful of the compound, testosterone. Later that same year, scientists from a pair of other companies showed that they could obtain testosterone without requiring staggering quantities of animal testicles; they'd found a way to synthesize it from cholesterol.

That discovery would earn a Nobel Prize. The researchers had invented an efficient method of creating a chemical that offered the tantalizing promise of both strength and fertility. This opened a new frontier in medical research, one that could be accessed through a substance—cholesterol—found in everyone's blood.

But though scientists possessed a method of producing testosterone, they now had to figure out what this mythical hormone could actually do.



As a boy growing up in northern Massachusetts, Charles Kochakian couldn't wait for winter to come. With the falling mercury came days filled with sledding and skiing, two of his favorite pursuits. It also offered the chance to skate on the Merrimack River, which sliced his hometown, Haverhill, in two.

The waterway, though, would not freeze with the snap of Jack Frost's fingers. Rather, around Thanksgiving, the ice would begin to form like Bermuda grass, advancing in tendrils that poked farther upriver each day. It was this annual winter occurrence that gave rise to one of Kochakian's first experiments.

On moonlit nights, he and his friends would strap on their skates and race atop the frozen waters to see how far they could get. But because rivers turn from liquid to solid from the top down, a hard, silvery face didn't necessarily guarantee a thick block of ice beneath.

The boys knew this well enough. Still, their curiosity and derring-do would inevitably get the better of them. They'd abandon the relative safety of long-frozen spots to explore new territory, the ice growing thinner with each push of the skate. The experiment would inevitably come to an end with the sharp crack of cleaving ice and, too often, at least one boy tumbling into the black, bone-chilling waters.

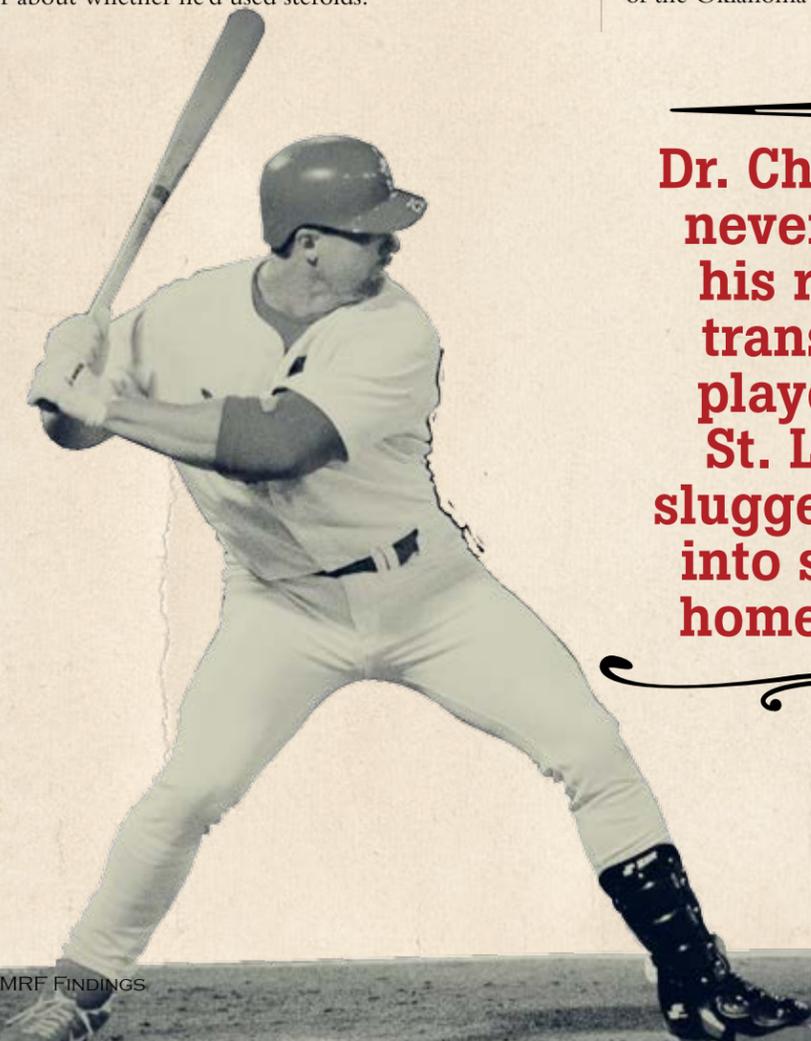
"At such times," wrote Kochakian, "we would build a fire on shore and dry out as best we could." Of course, "no mention was made of such an incident to our parents."

When not pitching himself headlong into the Merrimack, Kochakian proved an adept student. In the classroom, his curious nature also drew him to experiments of an altogether different sort: At Boston University, he earned his undergraduate degree in chemistry and, in 1931, a masters in organic chemistry.

Still, with the Depression in full swing, professional employment was nowhere to be found. For the next two years, he searched fruitlessly for jobs in chemistry while earning a meager income delivering newspapers and helping out at his hometown grocery store. Living with his parents, both of whom had emigrated from Armenia just after the turn of the century, he helped out around the house. He did his best to keep his scientific skills honed by conducting experiments in a makeshift lab he'd set up in a vacant bedroom.

In 1933, a professor at the University of Rochester responded to an ad Kochakian had placed seeking employment. Unfortunately, wrote the professor, the university could offer no position. Nevertheless, if Kochakian was interested, the university could waive his tuition and provide him with a small fellowship of \$500 for living expenses and food that would enable him to pursue a Ph.D. in biochemistry. The young chemist accepted.

Although he had taken but a single biology course in college, Kochakian proved so adept at the classwork that his advisor soon excused him from attendance. This freed him up to spend the balance of his graduate school career at work in the laboratory.





In the 1950s, **Dr. Charles Kochakian** (center) studied testosterone and other hormones as head of OMRF's biochemistry research group.

Kochakian's mentor had a particular interest in how the body transforms food into energy. Researchers had already shown that males' base metabolism rates were greater than those of females. But, the advisor asked his protégé, why is this the case? So Kochakian set to work in the lab to solve this metabolic mystery.

Preliminary data gathered from previous experiments suggested that the mythical male hormone (it would still be two years before scientists isolated and definitively identified testosterone) might be responsible for this differential. But who wanted to gather hundreds, or even thousands, of pounds of bull testicles to perform experiments?

Instead, Kochakian found a more readily accessible, but no less distasteful, source of male hormone: human urine.

He didn't know how much he'd need, so the eager graduate student erred on the side of excess. Using jugs that he placed in men's restrooms around the university campus, he managed to gather more than 1,000 gallons in the space of a half-year. Then, employing a multi-step process that involved both boiling the liquid and treating the distillate with various chemical agents, he was able to extract the hormone necessary to perform his experiments. "Needless to say," Kochakian wrote years later about the process, "the atmosphere in the laboratory and corridor was aromatic."

Kochakian regularly administered the hormone (which scientists would soon identify as androstenedione, a less potent cousin of testosterone) to a trio of dogs in the laboratory. His mentor had hypothesized that the hormonal "goosing" would amp up the animals' metabolism. But Kochakian found no such effect.

When repeated attempts yielded the same result, the graduate student worried that something had gone awry. So he decided to redo the experiment yet again. Only this time, to ensure that the hormones extracted from urine hadn't somehow confused the outcome, he'd gather his hormone from a different source.

With the help of a local slaughterhouse, he collected 100 or so bull testicles, then proceeded with the long and arduous process of extracting enough hormone to perform the experiments. Yet when he gave this new batch of hormone to the dogs, he got the same outcome.

Kochakian now felt confident that the hormone wasn't causing males to burn calories faster than females. This finding, though, wasn't the sort of ah-hah! moment he had hoped for.

Science takes its biggest steps forward by demonstrating a positive correlation—by establishing that x causes y. All Kochakian had shown was that x (male hormone) didn't cause y (revved up metabolic rates).

At best, the experiments were the scientific equivalent of solid but unspectacular police work. They'd eliminated a suspect. Perhaps that knowledge would help narrow the field of inquiry so that scientists might one day identify the "culprit" responsible for men's speedier metabolisms. In the meantime, though, that culprit was still out there.

As for Kochakian, he'd devoted two years of his life to trying to prove something he'd now demonstrated wasn't true. That wasn't the sort of research scientific journals would be eager to publish. And without a publication, his prospects for earning his doctorate looked bleak.

Desperate to rescue something meaningful from the experiments, he decided to pore back over his experimental data. Surely, he thought, there must be something of value in there.

As it turns out, there was. Buried in the results was a finding that would change Kochakian's life. It would also forever change the field of endocrinology.



When Kochakian scoured his lab notebooks, he discovered that each time he'd administered the urine extract to the dogs, their bodies produced a strongly positive nitrogen balance. This had happened almost immediately, and, Kochakian confirmed, it had also occurred when he'd given them the testicular extract.

Nitrogen serves as a fundamental component of amino acids, the molecular building blocks of protein. Usually, we get it through food sources such as meat, dairy, eggs and legumes. Our bodies constantly need to replenish our nitrogen stores, as we regularly deplete supplies through sweating, going to the bathroom, and the ongoing replacement of skin and hair.

A positive nitrogen balance means the body is taking in more nitrogen than it is losing. This state, Kochakian knew, was usually linked to periods of growth, times when the body is adding substantial amounts of muscle.

Here, Kochakian had simply induced the same condition by giving hormones to the dogs. When published in 1935, his studies were the first to prove the connection between male hormones and muscle-building.

This research would earn Kochakian his Ph.D. in biochemistry. It would also earn him a full-time academic appointment at the university.

Not long after Kochakian's watershed research, the pharmaceutical companies showed that the hormones he'd worked with (now dubbed testosterone and androstenedione) could be easily synthesized. So Kochakian repeated the experiments with the synthesized hormones, and he got the same results. That work cemented the idea that those compounds—members of a family of similarly structured compounds called steroids—promoted anabolism, the metabolic process of constructing larger molecules from smaller ones.

Anabolic steroids had been born. And the young researcher who'd figured out how they worked? Some would later call him "the father of anabolic steroids."



For the balance of his career, Kochakian would continue to study testosterone and other sex hormones. But he was never interested in building super men and women. Instead, his research centered on understanding how, exactly, they worked and how they might be harnessed to improve human health.

In 1951, Kochakian moved his laboratory from Rochester to the Oklahoma Medical Research Foundation, which

NOT THOSE KINDS OF STEROIDS

At some point in your life, a doctor may have prescribed steroids for you. Perhaps it was to treat a lung infection or asthma. Or maybe you took prednisone to help control the symptoms of rheumatoid arthritis, lupus or another autoimmune disease. You might even have used a topical steroid cream to help alleviate a skin condition like poison ivy or eczema.

These steroids, though, are different from the steroids that OMRF's Dr. Charles Kochakian discovered. Athletes have used those muscle-building compounds, known as anabolic steroids, for more than a half-century (see timeline, next page) to enhance their performances.

The term steroid simply means a family of molecules that share a common chemical ring structure. The body naturally produces many different steroids. Pharmaceutical companies can also synthesize these compounds in the laboratory for use as medications.

The most commonly prescribed steroids are corticosteroids. In the body, the adrenal glands produce these compounds, and they primarily function to reduce inflammation. Commercially produced corticosteroids include hydrocortisone and prednisone, and doctors prescribe them as pills, topical creams and, for asthma and other lung conditions, an inhaled form. When taken over a long period of time, oral corticosteroids can carry side effects such as weight gain and ulcers.

Anabolic steroids, meanwhile, are "male" hormones like testosterone that, in nature, are primarily produced by the testicles. (Women's ovaries and adrenal glands also produce these hormones in lesser amounts.) These substances cause the development of male sex characteristics and stimulate muscle and tissue growth. Doctors give dianabol, anadrol and other synthetic versions of these steroids to burn victims and people who suffer from chronic wasting conditions such as HIV and cancer.

Although U.S. law makes it a federal crime to obtain anabolic steroids without a prescription, an active black market exists in this country, especially among athletes and body builders. People who take unnecessary doses of anabolic steroids may display violent behavior, depression and mood swings and are at increased risk for numerous diseases, including cancer, stroke and heart attack.

STERIODS AND SPORTS

A BRIEF HISTORY

1936

Dr. Charles Kochakian discovers the anabolic (muscle-building) effects of steroids.



EARLY 1950s

West Coast bodybuilders start experimenting with anabolic steroids.

1952

Soviet weightlifters are believed to have begun using steroids at this point, and they capture 13 medals at the Helsinki Olympics.



1960

Dr. John Ziegler prescribes anabolic steroids to the entire U.S. weightlifting team in preparation for the Rome Olympics.



1961

Bill Pearl announces he's using steroids to train for the Mr. Universe bodybuilding competition, which he then wins.

1963

Alvin Roy, first strength coach in professional football, gives cereal bowls full of steroid pills to his San Diego Chargers players at training camp. The Chargers win the American Football League championship.

1974

The former **East Germany** initiates a systematic doping program that regularly administers steroids and male hormones to unknowing athletes as young as age 12.



1975

The **International Olympic Committee** adds steroids to its list of banned substances.

1988

Canadian sprinter **Ben Johnson** is stripped of his Olympic gold medal (and world record) after tests reveal a banned steroid in his system.



1991

A group of 20 former **East German** coaches confirms that the country's domination of international women's swimming for more than a dozen years was built upon an organized system of steroid use.



1991

Major League Baseball bans steroids.



1992

Former National Football League star **Lyle Alzado**, who'd used steroids for two decades, dies at age 44 of brain cancer. In a *Sports Illustrated* article published shortly before his death, he says he believes the disease was caused by his drug use.

1996

Ken Caminiti wins baseball's most valuable player award, only to admit later that he used steroids during the entire season. He dies in 2004 at the age of 41 from a heart attack, which the coroner rules was at least partially due to his drug use.



2004

The New York Times reports that an estimated 500 to 2,000 former **East German** athletes are experiencing significant health problems associated with steroids, including liver tumors, heart disease, testicular and breast cancer, gynecological problems, infertility, depression, miscarriages and children born with physical deformities.

2006

Floyd Landis wins the Tour de France, only to be disqualified for elevated testosterone levels. He subsequently acknowledged using steroids.

2007

Track star **Marion Jones** confesses that the three gold and two bronze medals she won at the 2000 Sydney Olympics were fueled by steroids. She is forced to return the medals and also to serve a prison term for previously having lied to federal investigators about her drug use.



2010

Mark McGwire admits that he used steroids for nearly a decade, including in 1998, when he set baseball's single-season home run record.

2012

The U.S. Anti-Doping Agency strips **Lance Armstrong** of his seven Tour de France titles for his use of steroids and other performance-enhancing drugs.



2013

Major League Baseball's investigation into an illegal steroid ring leads to the suspension of 13 players, including New York Yankees' star **Alex Rodriguez**.



"We have to go inside and look around. Because if we don't, we'll never know where a new idea might have led."

had opened its doors only the year before. OMRF's new director of research offered Kochakian the chance to lead a program in biochemistry and endocrinology.

At OMRF, Kochakian received a grant from the National Arthritis and Metabolic Institute to study whether testosterone could help control diabetes. He led a National Cancer Institute project examining how the hormone might be used to combat cancer. In yet another initiative, this one underwritten by the American Heart Association, he looked at how testosterone regulated the biochemistry of the heart.

Although we now typically refer to these compounds (and their synthetic twins) as anabolic steroids, they're actually more accurately described as anabolic-androgenic steroids, says OMRF President Dr. Stephen Prescott, a physician and medical researcher. "In addition to their muscle and tissue-building anabolic properties, the hormones are also androgens. That means they're responsible for giving men many of their male characteristics, things like deepening of the voice, body hair, fertility and maturation of the genitals."

Women also produce these androgens, though in much smaller amounts than men.

"In women, like in men, they're essential for kick-starting the process of puberty," says Prescott.

Although Kochakian's research failed to show that the hormones could treat diabetes or cancer, it did reveal their important role in growing heart muscle. "He also helped scientists understand how testosterone helps regulate other organs such as the kidneys and liver," says Prescott.

His work on the muscle-building properties of testosterone and other steroids helped illuminate their importance in the development of muscle and bones. "He discovered that administering testosterone could help control incontinence in older men by strengthening their bladder muscles," says Prescott.

While Kochakian was working at OMRF to understand how physicians might use steroids to help patients, West Coast bodybuilders had discovered that the compounds' anabolic properties could provide a significant competitive edge. At the 1952 Olympics, Russian weightlifters are believed to have won the first of what would prove to be many steroid-tinted Olympic medals.

These unintended consequences of his discovery, though, did not deter the OMRF researcher, who in 1953 added the title of coordinator of research to his duties at OMRF. "Dr. Kochakian had his program and knew what he was going to do," said Dr. Paul McCay, who joined OMRF as a metabolic researcher in 1954. "He wanted to understand the beneficial effects of male sex hormones."

But while Kochakian "was a hard worker who did a lot of good research" while at OMRF, says McCay, "he was a little bit aloof." He eschewed collaborations with foundation colleagues, preferring instead to work on his own projects.

Over time, this created tension within the foundation's scientific faculty and led OMRF to create a second, separate biochemistry research program.

In 1957, the University of Alabama at Birmingham offered Kochakian a position as a professor in its biochemistry department. Kochakian took the job, and he ended up spending the remainder of his career there.



Kochakian's biochemistry program at OMRF would represent the foundation's first and only foray into steroid research. When he left, that program ended.

OMRF's "other" biochemistry program, though, grew and thrived. Increasingly, it focused on metabolic processes and how they suffered damage as the body aged. McCay eventually led the program, which has since undergone several changes in name and research focus. More than 60 years after it began, the program—now known as the Aging and Metabolism Research Program—continues to search for new insights and therapies for diseases of aging.

While at OMRF, in addition to his lab work, Kochakian also started a summer research program for select high school and college students. That initiative would lay the groundwork for OMRF's Fleming Scholar Program, which since 1956 has provided more than 500 of Oklahoma's most promising science students with a one-of-a-kind summer laboratory experience. More than 100 of the program's graduates have gone on to careers in medicine and research.



Medical history is chock full of examples of unintended consequences. Sir Alexander Fleming never dreamed that failing to clean his Petri dishes would spawn the discovery of penicillin. When Pfizer scientists created the experimental drug known as UK92480 to alleviate chest pain, little did they know it would become Viagra, the best-selling treatment for erectile dysfunction.

Likewise, Charles Kochakian surely never imagined Mark McGwire, Lance Armstrong, Brian Bosworth nor Alex Rodriguez when he first observed the anabolic effects of male hormones. But his tale reminds us that the law of unintended consequences can cut both ways. Even seemingly beneficial medical research can have a weak spot.

Still, Kochakian's legacy does not end there. Today, physicians prescribe the hormones for burn victims and bedridden patients. They also use anabolic steroids to treat people suffering from muscle atrophy caused by HIV, anemia and certain types of breast cancer.

In the end, says Prescott, "A scientific discovery is neither good nor evil." It simply opens the door to knowledge.

"We might be inclined to shut the door for fear of what it might reveal," he says. "But that's the wrong approach. We have to go inside and look around. Because if we don't, we'll never know where a new idea might have led." ■

Genetics

By Shari Hawkins

Trillions of microbes

in our digestive tracts may

hold the key to controlling

everything from obesity to

autoimmune disease

At this moment, you probably think of yourself as an I.

As in, "I'm going to the grocery store to get some bread." Or, "I'm running a slight fever." Maybe even, "I'm so excited to read this new issue of Findings!"

But what if you're using the wrong pronoun? What if, despite your conscious perception, despite everything that you may have learned and felt and seen and heard up until this point in your life, you are actually a we?

You see, for every human cell in our bodies, there exist 10 other cells belonging to resident microorganisms. Put another way, Ross Perot, who won 18.8 percent of the popular vote in 1992, had a stronger claim to the presidency than we do to calling ourselves human.

It turns out that we're nothing more than an organic hotel. Sure, we're staffed by 10 trillion or so human cells. But the vast majority of the 100 trillion cells occupying our bodies belongs to the infinitesimal visitors lodging on our skin, in our mouths and deep within our digestive tracts.

Those lodgers are all the bacteria and other microscopic organisms that colonize our bodies. They fall into three basic categories: generally harmless freeloaders; symbiotic organisms, which derive some sort of benefit from us but also do something helpful in return; and, in very small numbers, pathogens, like bacteria or viruses.

"We've had this perception of microbes as germs, as pathogens, as disease-bearing organisms," said Lita Proctor, a scientist at the National Human Genome Research Institute and program director of the Human Microbiome Project, in a recent issue of the magazine *Genome*. "Much of the scientific

literature for decades and decades has been completely focused on pathogens, and that has also framed our point of view about microbes. But it has become clear that the vast majority of microbes we come in contact with on a daily basis are not pathogenic. They are either benign and couldn't care less that there is a human nearby or they actually provide a benefit."

Until recently, medical researchers basically ignored the vast majority of the microbial population that lives on and, in much greater numbers, inside us. But that, says OMRF's Dr. Patrick Gaffney, has changed.

"There's been a growing interest in and understanding of the microorganisms in our bodies," says Gaffney, a genetics researcher who has turned his attention to the genes of the tiny creatures who, on average, make up 2.5 pounds of our body weight. "We've realized they do important things to maintain our health, to produce important vitamins, for educating our immune systems, and to help us metabolize foods and maintain a healthy body weight."

In 2007, the National Institutes of Health launched the Human Microbiome Project, an effort to catalog the microorganisms living in and on human bodies. Using DNA sequencing technologies to analyze samples taken from hundreds of healthy people, researchers pieced together the first comprehensive picture of a normal human microbiome, a term scientists use to describe the collective genetic materials of all the microbes that live inside and on the human body. The next step, says Gaffney, "is to learn how changes in the microbiome correlate with physiology and disease."



INSIDE MAN At OMRF, Dr. Patrick Gaffney is using sophisticated DNA sequencing techniques to learn more about the human microbiome and its relationship to human health.

Already, research has shown that disorders in our internal ecosystem may predispose us to obesity and a range of chronic diseases. They may be responsible for a rise in allergies to nuts and other compounds. Evidence is mounting that intestinal microbes exacerbate or perhaps even cause some of the symptoms of autism.

Gaffney is among the growing ranks of scientists now digging deeper into the microbiome to understand how, exactly, it affects our health. Although he and his peers are careful not to promise that their work will lead to cures, the implications of what they've learned are staggering. And what we know today may represent only the tip of the iceberg.

Gaffney came to study the microbiome by a circuitous route. A physician by training, he began his research career during a fellowship at the University of Minnesota. Although the fellowship was supposed to be cancer-focused, he ended up focusing on the genetics of the immune system. He liked the work and the field so much that he stayed on at the university, first as a post-doctoral fellow and then as a faculty researcher, investigating autoimmune diseases. All of these illnesses share a common trait: The immune system confuses the body's own cells for pathogens and, as a result, it begins attacking itself.

Gaffney concentrated on lupus, an autoimmune disease that can strike any organ but commonly affects the joints, skin and kidneys. He focused on the genetic roots of this disease. Using an approach known as genome-wide association studies, his research team identified particular genes linked to lupus.

In 2007, that work brought him to OMRF, where he joined the foundation's Arthritis and Clinical Immunology Research Program and now holds the J.G. Puterbaugh Chair in Medical Research. Working with other OMRF scientists, his interest broadened to include the genetic origins of other autoimmune diseases like Sjögren's syndrome.

Not long before Gaffney came to OMRF, researchers finished the first scan of the entire human genome, the technical term for all the genes in our body. That colossal project took more than a decade to complete and cost upwards of \$1 billion. But rapid advances made the technology more efficient and affordable, making genetic scanners—and the vast array of information they yield—widely available.

In 2009, Gaffney established a “next-generation” DNA sequencing facility at OMRF. With this technology and increasing expertise at his fingertips, Gaffney began looking not just at the genomes of patients suffering from autoimmune diseases, but also at their microbiomes.

Research had begun to point to links between lupus and certain intestinal microbes. In particular, says Gaffney, “There's a possibility the trigger that sets off lupus might be hiding in the gut.” So he decided to take a look at the microbiomes of lupus patients to see what he could find.

Working with physicians in OMRF's Autoimmune Disease Clinic, he collected saliva and stool samples, where bacteria flourish, from 20 patient volunteers. He also gathered the same biological materials from 20 healthy individuals. Using sequencing technology, his team completed a genetic analysis of the two sets of samples, then looked for variations between the two groups.

The lupus patients exhibited a wide range of microbial species in their guts. But, says Gaffney, “Their colonies were less diverse than those of healthy individuals.”

Scientists can't yet say with confidence what a healthy microbiome looks like. Still, says Gaffney, “There's a generally emerging consensus that more diversity is better.”

Researchers believe that a wide variety of factors can contribute to a more uniform (and, presumably, less resilient) population of gut bacteria. In particular, they point to widespread use of antibiotics, diets heavy in processed food, exposure to environmental toxins, and generally “cleaner” environments that minimize contact with bacteria in everyday life. More uniform microbiomes have been linked to the risk of some cancers and gastrointestinal disorders.

Although Gaffney's study showed that the digestive tracts of lupus patients were more uniform than their healthy counterparts, that observation, says Gaffney, simply pointed to a larger chicken-or-egg question: “Did the lack of diversity cause lupus, or did the disease cause the lack of diversity?”

To find an answer, he has embarked on a larger follow-up study. That analysis will involve larger numbers of samples gathered from patients and matched controls, and it will look more probingly at the genetic profiles of the gut bacteria they find. “We're going to look at specific genes to try and separate cause from effect,” he says.

While Gaffney knows that the results of the new study won't lead to specific health recommendations—“Eat more yogurt with live cultures and cut your chances of developing lupus!”—he says that research projects like this are crucial if we're to gain a deeper understanding of what many are calling the “second human genome.”

The modernization of Western society has brought with it many positive changes: increased lifespans, improved quality of life, countless technologies that enrich our lives. But with these developments has, apparently, come a change for the worse. In our guts.

Led by Dr. Cecil Lewis, researchers at the University of Oklahoma analyzed microbiome samples taken from people who lived long ago, including a soldier frozen for nearly a century on a glacier and Otzi the Iceman, a 5,000-year-old specimen who is Europe's oldest known natural human mummy. The recent analysis showed that our guts were once far more diversified and used to look more like those of other non-human primates and rural people living in less-developed countries.

In particular, says Lewis, “The team concluded that the last 100 years has been a time of major change to the human gut microbiome in cosmopolitan areas.” Dietary changes and the widespread adoption of antibiotic and sanitary practices have largely benefited humans and our health. Still, he says, these alterations may also have come at a cost, “such as a recent increase in autoimmune-related risks.”

Indeed, bacteria play essential roles in the development of our immune systems, which are colonized at birth and later by microbes from our mothers and the environment. Once established, those microorganisms provide us with energy and vitamins that we can't make on our own. They



PERUVIAN PARTNERSHIP OMRF scientists helped anthropologists from the University of Oklahoma study the composition of the microbiome in a variety of cultures. OU researchers traveled to Peru to gather biological samples from the Matses tribe of Peru, pictured here examining their own microbes.

produce compounds that act as anti-inflammatories. Beneficial microbes help us fend off the pathogens. So it's not surprising that having less of them would lead to health problems.

Nevertheless, Lewis cautions against running out and buying the latest food labeled as “probiotic” or changing your diet radically in an effort to bolster your gut's bacterial population. “We see a lot of pseudo-science and fiction out there about influencing the microbiome. But scientists still don't understand the microbiome's biology or exactly how it works inside the body.”

As he compares the modern Western microbiome to those of other populations, Lewis has begun a scientific collaboration with Gaffney, who uses OMRF's next-generation sequencing facilities to analyze the samples Lewis gathers in the field. “This technology is sort of like the printing press for genomics,” says Lewis. “It's unlocking vital information that we didn't have even 10 years ago.”

In particular, with access to OMRF's sequencing expertise, Lewis found he could more easily analyze the bacteria present in ancient samples. This allowed him to form a more complete picture of ancient microbiomes. “It's like looking through a whole new lens. It exposes an extraordinary picture, one we never expected to see.”

Lewis does not limit his work to ancient civilizations, though. He and his team also traveled by canoe into the Amazon to study the diet and health of Peru's Matses community, who are among the last hunter-gatherers in the world. The Matses still hunt monkey, sloth and alligator, gather wild tubers in the forest, and fish in the rivers.

Although Gaffney says he will not be joining Lewis on a jungle trek anytime soon—“I'm not exactly the Indiana Jones type,” he laughs—he played a vital role in analyzing the samples that Lewis brought back from the Matses and also from the Tunapuco, a traditional community of potato farmers from the Andean highlands. That analysis showed that

the hunter-gatherers' and farmers' gut bacteria were far more diverse than those of residents of Norman, Oklahoma. The South American indigenous peoples carried bacteria usually absent in Western industrialized populations. Those microbes play a role in digesting carbohydrates. So, says Gaffney, “The next question is whether their absence in Western guts leaves us without an important player in the metabolism of food? And whether that could contribute to the increase in digestive disorders like colitis and Crohn's disease?”

In Gaffney's lab, the soft whir of machines at work fills the air. It's a hub of high-tech activity. Yet for all its mystique, next-generation DNA sequencing occurs inside equipment that looks like big, beige boxes. No multi-colored fluids pulsing through tubes. No whooshing or clanging sounds, no flashing lights. Just oversized rectangles with windows and slots where scientists insert bacterial samples for examination.

In spite of their seeming simplicity, though, those boxes produce mind-boggling amounts of scientific information. From a slide about the size of a Band-Aid, the sequencing process can yield seven to eight million bits of information and generate files upward of 500 megabytes in size. Sophisticated computer programs then scan the data for similarities and differences in the makeup of the bacteria. The resulting information helps scientists pinpoint patterns that signal the paths they should study.

All this new information, though, has generated as many questions as it has answers. Through the work of Gaffney, Lewis and others, we're learning more each day. In that process, we're gathering clues about the hordes of microbes that reside within and upon us. That work has given us some ideas—things like diversifying our diets and using antibiotics only when absolutely necessary—of how to begin taking better care of these invisible visitors.

After all, our lives may depend on them. ■

HE WAS A SCIENTIST'S SCIENTIST. HE GARNERED ACCOLADES FROM HIS PEERS WORLDWIDE. AND EVEN WHEN HE (MOSTLY) LEFT THE LAB TO BECOME OMRF'S EIGHTH PRESIDENT IN 1997, HE NEVER LOST HIS PASSION FOR RESEARCH AND THE PEOPLE WHO MAKE THE SCIENTIFIC ENGINE RUN.

J. DONALD CAPRA

JULY 20, 1937 - FEBRUARY 24, 2015

When Dr. J. Donald Capra died in February following a year-long battle with brain cancer, a bright light in the scientific world went out.

Capra was born in Barre, Vermont, in 1937 to Italian emigrant parents. He didn't speak English until he entered elementary school, but he proved to be a quick study in the classroom, ultimately graduating summa cum laude from the University of Vermont College of Medicine. Following his medical residency at St. Luke's Hospital in New York, he launched a career in research.

Before he became OMRF's president, Capra served on the faculty of the Mount Sinai School of Medicine and then, for more than two decades, at the University of Texas Southwestern Medical Center. In the laboratory, he made many important contributions to the field of immunology. In particular, his work on monoclonal antibodies provided important insights into the body's response to infectious disease, research that proved fundamental to our understanding of vaccines.

Capra guided OMRF for nine years, a time when the foundation enjoyed a significant period of expansion. Among his enduring legacies will be the National Institutes of Health's Centers of Biomedical Research Excellence program, which provides funds to help young scientists establish independent research programs. He also played a key role in creating the Oklahoma Biomedical Research Tax Credit.

"Don had wonderful vision as a leader," says Dr. Stephen Prescott, who became OMRF's president following Capra's retirement in 2006. "These initiatives he helped shape more than a decade ago still serve as wellsprings for OMRF's vitality and growth today."



Throughout his life, Capra kept others running to catch up with his tireless pace. Since age five, he needed only four hours of sleep each night, enabling him to turn each of his workdays into two or three for the average person. His emails flowed around the clock, chock full of new ideas, questions and even, on occasion, pestering.

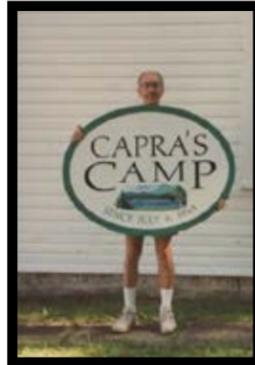
"Don expected a lot of himself, and he pushed, prodded and encouraged the rest of us to come along and pursue these exciting things that he could see before we did," says Dr. Judith James, Capra's first faculty hire at OMRF. "He always promoted the concept of team science, and he thrived while coaching those teams to incredible success."

During his career, Capra published 375 scientific papers and served as principal investigator of 72 National Institutes of Health grants. He also trained more than 125 graduate and doctoral students. Following his retirement from OMRF, he assumed the role of president emeritus and continued to mentor numerous young researchers.

Capra had an overwhelming passion for life and for knowledge. He loved music, sports, movies and tackling difficult questions. Every day, he read five newspapers and worked *The New York Times* crossword puzzle. An avid Dallas Cowboys fan, he attended more than 100 games. He claimed to have watched every *Star Trek* episode more than 20 times.

"He encouraged us to think, to do and to be more than we ever dreamed possible," says James. "Don's enthusiasm lives on in those he trained and those like me, who he encouraged. His legacy will continue to light a path for the rest of us to follow for years to come."

Capra is survived by Dr. Patricia Capra, his wife of 57 years, as well as two sons, three grandchildren and one great-grandchild.





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Team Spirit



Putnam City cheerleaders celebrate the 1975 launch of the district's annual cancer drive. In the ensuing decades, Putnam City has raised a total of \$3.2 million to support cancer research at OMRF. Hip, hip, hooray!