*by
Tim Dean

Dartmouth Center's Leading Research Informs Policy, Improves Children's Health

The RIPPLE EFFECT

It's a sunny July morning in rural Lyme, New Hampshire, and Amy Gubbins is standing in her kitchen going over the results again, while her two young boys, Noah, age 4, and Zachary, age 2, play in the background.

"A few months ago, we took part in a children's study that Dartmouth is doing," she explains. "Noah wore a vest for three days with monitors that measured both the air quality that he was exposed to and his activity levels." While Gubbins was pleased to see that Noah met the recommended physical activity levels for good health, the air quality test findings have given her pause.

The results—from the New Hampshire Birth Cohort Study's 3-Year Assessment—include a personal letter from Margaret Karagas, PhD, principal investigator on the study, a fact sheet on wood stoves, and resources to learn more about improving air quality in the home. They show that Noah was exposed to high levels of indoor air pollution, including fine particulates, black carbon (soot), and secondhand smoke.

"The last measure confused us, since we don't smoke at all," says Gubbins, "but then we remembered that there were contractors here during that time putting in a new shower for us, and we noticed they were smokers.

"We were running the wood stove a lot because it was winter, and we know we have a 'tight' house," she continues, "but my husband Erik and I were still alarmed that the levels could be so high. We're following up to find out if our wood stove is EPA-approved, to see if we should have a retest done, and learn what else we can do."

For Gubbins and her family, participating in research has become a routine part of their medical care. "We've been involved in the birth cohort study since I was pregnant with Noah—they asked me at one of my first prenatal appointments at Dartmouth-Hitchcock if we'd be interested," she says, noting that they did the same with Zachary when he came along. "For us, it was absolutely a no-brainer. We both felt like it was an interesting and important study."

Amy Gubbins with sons (left to right) Noah and Zachary.
Photo by Rob Strong

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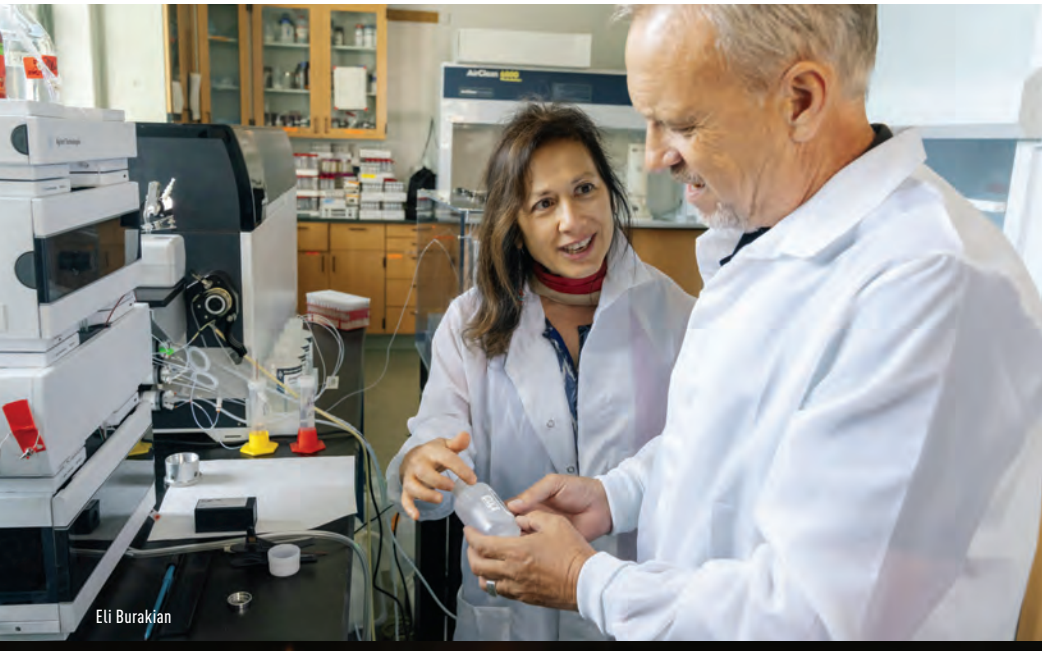
In addition to providing well water samples and a number of different biospecimens (from she and the boys) for the study, including placental tissue, urine, blood and stool samples, and nail clippings, she has filled out online questionnaires about Noah's and Zachary's diets and does regular phone interviews with study coordinators to report changes in their overall health status.

With funding from the National Institute of Environmental Health Sciences, the Birth Cohort Study was established to investigate the role of environmental factors on pregnancy and newborn outcomes. Now with more than 2,000 maternal-infant pairs and over 50 participating obstetricians, it is the largest longitudinal study of pregnancy and infant-child health of its kind in the U.S.

When Karagas and her colleagues started the cohort in 2009, as part of the Dartmouth Toxic Metals Superfund Research Program, their initial focus was on arsenic, a naturally occurring element widely distributed in the Earth's crust. They began by recruiting pregnant women on private water systems at their homes—as these sources supply about half the population in the state and are not regulated by the Environmental Protection Agency (EPA), they may contain high levels of the toxicant.

Top: Margaret Karagas, PhD, and Brian Jackson.

Bottom: Baby tooth being analyzed in Earth Sciences lab.



Eli Burakian

Rob Strong

This seminal work served as the foundation for the Dartmouth Children's Environmental Health and Disease Prevention Research Center, which Karagas created and has led since 2010. Part of a national network of research centers focused on identifying and mitigating environmental threats to children, the consortium has, for many years, relied on joint funding from the EPA and the Department of Health and Human Services' National Institute of Environmental Health Sciences, part of which has recently been ended (see sidebar).

"Traditionally, most research funding has gone to finding cures for disease rather than prevention, and comparatively very little has focused on environmental influences on children's health—the kind of longstanding support that we've had to date has been crucial to our efforts to change that paradigm," says Karagas, who is the James W. Squires Professor and chair of the Department of Epidemiology and a professor of community and family medicine at Dartmouth's Geisel School of Medicine. She also directs the Center for Molecular Epidemiology at Dartmouth.

One example of the center's growth and broadening impact came in 2012, when Karagas received a Center of Biomedical Research Excellence award from the National Institute of General Medical Sciences to set up a biorepository and biospecimen resource facility at Dartmouth. The facility, which has processed and archived more than 30,000 biologic samples to date, is speeding up the pace of research for Dartmouth's multidisciplinary teams of scientists and clinicians, as well as for collaborating investigators at other centers.

Mark Washburn

Juliette Madan, MD, MS, with young CF patient Tate LaPoint and his mom, Taylor.

Having this capability helped lead to the center receiving a National Institutes of Health award in 2016 through the Environmental Influences of Child Health Outcomes program to conduct a long-term study involving more than 50,000 children in the U.S., which is following them from the time they are in utero up to young adulthood. Importantly, funding from this program includes the opportunity for Dartmouth and other rural centers—that are often underrepresented in studies—to be part of a national pediatric clinical trials network.

Today, Dartmouth faculty, as well as the graduate and undergraduate students who are engaged in research at all levels with the center, are poised to lead the nation in defining how to optimize children's health. Their vision is to reduce the occurrence of the most common chronic diseases that affect children and adults—including cancer, autism, diabetes, obesity, cardiovascular disease, asthma, and allergies; inspire future innovators and equip them with the tools needed to solve emerging health concerns; and translate their science into action by informing policy makers, healthcare providers, and the public.

To this end, over the past 10 years they have made a number of important discoveries that have advanced the science of disease prevention—influencing public policy and community health.

The center's researchers have discovered that exposure to arsenic, from contaminated well water or foods such as rice and apple juice, increases pregnant mothers' risk for hypertension and gestational diabetes while negatively impacting fetal growth, immune system function, and changes in gene expression. And the cumulative intake of arsenic from drinking water early in life may be associated with the high bladder cancer rates found in New England.

Findings like these have led the FDA to propose new guidelines for acceptable levels of arsenic in baby rice cereal and prompted the American Academy of Pediatrics to change their infant first-food guidelines, including exposing babies to a wide variety of healthy foods. And just recently, New Hampshire became only the second state in the U.S., after New Jersey, to lower the acceptable arsenic levels in public drinking water from 10 to 5 parts per billion, due in part to research by Karagas and her colleagues.

"This action by the New Hampshire Department of Environmental Services and the governor, in signing this legislation, is a great example of the partnership between sound research, good policy, and effective risk management," says Carolyn Murray, MD, MPH, director of the center's Community Outreach and Translation Core. "We hope this motivates more residents who are on private water systems to get their wells tested."

For a number of years now, Murray and her colleagues have been engaged in outreach activities—including surveys, focus groups, newsletters, grand rounds presentations, and public events—to help educate primary care and pediatric providers and families about the dangers of arsenic and what can be done to help reduce exposure risks. They found, for example, that providing well-water test results to families in the birth cohort prompted them to reduce their intake and use of contaminated water by more than half.

"I think we're making good progress in raising awareness about this important public health threat—but more needs to be done," she says. "We're continuing to work with rural providers more broadly, including the OB/GYN community in New Hampshire, to help them make it a routine part of their practices."

Another important area of research for the center is the human microbiome—the overall communities of microbes that colonize the gut and have been shown to be important in immune system development and health outcomes.

"Our studies focus on the most critical window of development for the microbiome, in the neonatal and infant period when the immune system is being programmed for lifelong health," says Juliette Madan, MED '00, an associate professor of pediatrics and of epidemiology at Geisel and a neonatologist at Children's Hospital

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at Dartmouth-Hitchcock. "As one of the largest groups in the country studying early life microbiome, we're starting to understand how very typical exposures like infant feeding practices and mode of delivery, as well as more complex exposures such as maternal stress, environmental toxicants, diet, and antibiotics impact the microbiome."

Babies born by cesarean or who are formula-fed are at an increased risk for later health problems like obesity, allergies, asthma, autism, and autoimmune diseases.

Additionally, the center has given Madan and her colleagues a unique opportunity to investigate the differences between newborn babies with healthy microbiomes and those with Cystic Fibrosis (CF)—a high-risk population she has been enrolling since 2009. "By identifying the missing microbes in CF that are important to training the immune system, we hope to create probiotic treatments to benefit infants with CF, giving them a better chance at a long, healthy life," she says.

With a growing body of valuable data and specimens, the center allows investigators to ask important research questions from a variety of different perspectives.

"It's really exciting as a young investigator to be able to come into a pregnancy and birth cohort that's so well developed," says Megan Romano, PhD, an assistant professor of epidemiology at Geisel who joined the Dartmouth community three years ago. "With some of the kids getting older, we've been able to start thinking about early childhood outcomes."

Romano studies endocrine-disrupting chemicals that interfere with hormonal pathways in the body. Commonly found in consumer products and in contaminated food and water—these chemicals can have adverse effects on pregnancy, infant feeding behaviors, and early life growth.

"One of the most exciting developments in our field are silicone wristbands, a passive, non-invasive tool that can measure more than 1,500 chemicals in the environment," she explains. "We ask the pregnant moms in the birth cohort to wear them for a week at about 12 weeks' gestation. That allows us to compare our findings with the urine and blood samples that we collect and also understand much more about the totality of what they're being exposed to."

Last year, Romano and her colleagues conducted a study looking at the levels and effects of perfluoroalkyl substances, commonly known as PFAS, found in the plasma of 1,000 women in the birth cohort. This research, together with their community outreach efforts working with state agencies to educate the public about the dangers of PFAS, helped provide the impetus for NH to recently adopt among the strictest limits in the country for PFAS chemicals in drinking water.

The center also provides researchers with an opportunity to study environmental health factors that may be more common in rural settings, such as exposure to high amounts of indoor air pollution. This is an area of focus for Laura Paulin, MD, MHS, a pulmonary and critical care physician at Dartmouth-Hitchcock and assistant professor of medicine and of epidemiology at Geisel.

"Here in New England, a lot of people use wood and gas stoves for heating and cooking and that can lead to high concentrations of pollutants like particulate matter and nitrogen dioxide," says Paulin. "One of our projects involves adding air pollution monitoring to the homes of pregnant women, so we can look at the exposures to the moms during their third trimester of pregnancy. The goal is to expand on that to include air pollution monitoring at different points in pregnancy and in childhood. Then we can begin to look at early life predictors of lung

health and function for both healthy and high-risk children and come up with interventions that may help them."

The air quality monitoring devices, which are deployed for about a week in the homes, will soon include the ability to measure ultrafine particulates. "Size is important in terms of where it goes in your body," she says. "The smallest particulates can travel deep into the lung and be incorporated into the systemic circulation, causing a host of potential health problems."

Just as with the wearable devices for children and the wristbands for pregnant women, the air monitors are mailed to the homes and include easy-to-follow instructions. "One thing that's nice about Margaret's studies is that she's been very mindful of minimizing any disruption people may feel to their lives and to their privacy as study participants," adds Paulin.

"We appreciate how thoughtful and thorough Dr. Karagas and her team have been in working with us and communicating the study results," says Gubbins, whose well-water tests have been normal, and who limits the amount of rice products that the boys eat.

"To be honest, with Noah there were times when I felt exhausted and didn't want to have to do one more thing, but I did it anyway because it was for such a good cause," she says. "Then with Zachary, it was so much easier. But I've never thought of it as a burden—having kids just makes you want to do anything you can to make them healthier."

For more information about the Children's Environmental Health & Disease Prevention Research Center, visit **www.protectkidshealth.com.**

TIM DEAN IS A SENIOR WRITER FOR *DARTMOUTH MEDICINE.*

Megan Romano, PhD, advising grad student Brett Doherty.

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REGIONAL SUCCESS, FEDERAL CHALLENGES

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For centuries, arsenic was a poison known for being deadly and hard to detect. That's why it was a favorite murder weapon in the 18th and 19th centuries. Today, the dangers and consequences of arsenic for most people are more subtle and long-term, as researchers from the Children's Environmental Health and Disease Prevention Research Center at Geisel have shown. Multiple studies from the center's investigators have linked arsenic—a common contaminant in drinking water, rice products, and apple juice—with cancer, gestational diabetes, immune system problems, fetal growth, and neurodevelopment. Policy makers regionally are taking note.

In July 2019, New Hampshire became the second state in the nation, after New Jersey, to lower the allowable level of arsenic in public drinking water from the federal standard of 10 parts per billion to 5 parts per billion. Other states are expected to follow suit.

At the federal level, such policy changes will likely be harder to achieve. This year, the Environmental Protection Agency discontinued funding to all 13 Children's Environmental Health and Disease Prevention Research programs nationwide.

"Good science should inform good policy," says Carolyn Murray, MD, MPH, director of community outreach for Geisel's Children's Environmental Health and Disease Prevention Research Center. "What's worrying me is that, at the federal level, good science keeps being called into question. That's disconcerting, but I do see the states stepping up."

The federal cuts translate to a loss of $1.2 million per year to the center. While the center has many sources of grant funding, the cut will slow down and potentially halt certain lines of data collection and analysis and strip away all funding for translation of the research to the public. That translational work includes educating primary care doctors about the potential dangers of arsenic in private well water and common food products fed to babies and young children, such as rice cereal and apple juice.

To learn how you can support the Children's Environmental Health and Disease Prevention Research Center, visit dartgo.org/campaign-children or e-mail robert.d.holley@dartmouth.edu.

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