



Using national data from 10,061 people patch-tested for allergens, a DHMC resident found that children and adults show allergic reactions at similar rates—but to different substances.

Brain wave: New insight into development

This has been an extremely humbling experience,” marvels physiologist Val Galton, Ph.D., a member of the DMS faculty since 1961. She’s referring to a recent finding that challenges a piece of conventional wisdom in the field she’s worked in for nearly 50 years. Galton began her career by studying thyroid hormone (TH) in the frog—an ideal model for TH studies because of its simplicity; the sole purpose of TH in frog development is to trigger the differentiation that turns tadpoles into frogs. If they lack TH, tadpoles neither grow limbs nor absorb their tails.

Since then, she’s developed a long-term collaboration with endocrinologist Donald St. Germain, M.D. They now work with more complex animal models, primarily looking at how TH regulates brain development in mice. “We went from studying shrinking tails to [studying] growing brains,” observes St. Germain.

Poor: As a clinician, he has long sought to develop better treatments for hypothyroidism—a TH deficiency in humans. Children who grow up lacking TH develop cretinism, a condition characterized by mental retardation, short stature, and other features of poor development.

There are two thyroid hormones, T4 and T3; the latter is the active form. It is

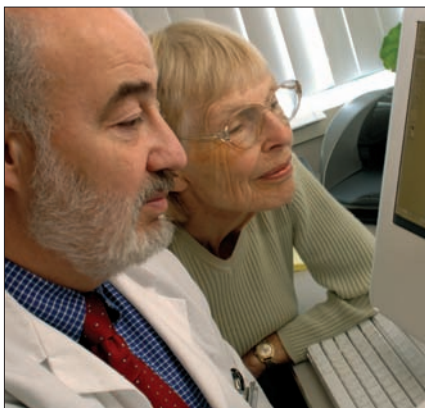
the job of enzymes called deiodinases to maintain the right ratio of the two. Proper development requires “receiving the right amount of thyroid hormone at the right time,” says St. Germain. Recognizing TH’s apparent role in brain development, he and Galton began using genetic techniques to wipe out deiodinases in mice, to see the effect of their absence.

Deiodinases are like switches that can be turned on and off to ensure the right balance of T3 and T4 during critical stages of development. The accepted view of TH regulation has been that T3 in the brain is produced there from T4 by a deiodinase known as type 2 (D2).

For their latest study, published in *Endocrinology*, Galton and St. Germain used a mouse model lacking D2; such mice are known as D2KO (the “KO” stands for knockout). The results strongly imply that the current view of TH homeostasis in the brain is incomplete. According to that view, D2KO mice should suffer from severe developmental problems. However, they exhibited only relatively mild functional impairment, plus some difficulties hearing and regulating their body temperature. But infants born with an untreated TH deficiency develop cretinism.

Role: So Galton and St. Germain have proposed the existence of important compensatory mechanisms that may minimize functional abnormalities in the absence of D2. “The more we learn about the role of the thyroid hormone in the developing brain, the more optimal a treatment we can offer pregnant mothers and infants suffering from hypothyroidism,” explains St. Germain.

Now, armed with mouse models deficient in various combinations of deiodinases, he and Galton are determined to unveil more of the mystery surrounding thyroid hormone regulation during brain development. TINA TING-LAN CHANG



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St. Germain and Galton have collaborated for years.

Making the cut

Surgery trumps physical therapy, steroid injections, and drugs in relieving pain from a slipped vertebra and a narrowing spinal canal, according to the latest paper from the seven-year, \$21-million Spine Patient Outcomes Research Trial. “We suspected surgery produced better results, but we had little objective data to support that,” said James Weinstein, D.O., M.S., chair of orthopaedics at Dartmouth and lead author of the study, published in the *New England Journal of Medicine*. “We can now discuss much more fully the surgical and non-surgical options available to our patients so that they can make an informed choice.”

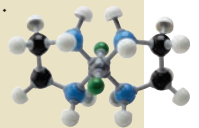


Function junction

Hunting for better ways to combat cancer, a DMS team examined the expression patterns of 241 microRNAs (miRNAs) in 59 cancer cell lines. Since miRNAs regulate gene expression and protein production, knowing how they function is “essential . . .

for designing effective strategies for cancer prevention and treatment,” note Arti Gaur, Ph.D., and her

coauthors in *Cancer Research*. Understanding miRNAs may also offer insight into how a “limited number of genetic alterations . . . result in the profound physiologic changes that characterize all malignant tissues.”





Who decides where elective surgery is performed? A recent Dartmouth study of 500 Medicare patients found that in 31% of cases, the doctor was the primary decision-maker.

Findings cast iron as heart un-healthy

Buyer beware! Iron-fortified foods and vitamins with iron could be hazardous to your cardiovascular health, especially if you're a man or a postmenopausal woman. Too much iron promotes the creation of free radicals—highly reactive molecules that can damage arteries, particularly in the early stages of arteriosclerosis.

But don't despair. A recent Dartmouth study, led by Leo Zacharski, M.D., and published in the *Journal of the American Medical Association*, suggests that lowering excess body stores of iron—through drawing blood—can improve outcomes for some people with peripheral arterial disease (PAD).

Correlation: The story begins in 1981, when a pathologist in Florida observed a correlation between increased levels of iron in the blood and age- and gender-related heart attack rates. He hypothesized that premenopausal women—who regularly lose blood, and thus iron, through menstruation—as well as men who donate blood regularly have lower cardiovascular risk than men who don't give blood. Some later studies supported that hypothesis, though others have shown mixed results.

Zacharski, a DMS faculty member and a physician at the VA Medical Center in White River Junction, Vt., launched what he describes as “the first big study . . . to show in a controlled manner that having relatively low levels of body iron is associated with reduced disease risk.” The randomized clinical trial, conducted from 1999 to 2005 at 24 VA hospitals (including the one in White River Junction), involved 1,277 men and postmenopausal women aged 43 to 87 with symptomatic but stable PAD. About half were randomly assigned to a control group and received no iron reduction. The other half underwent iron reduction through phlebotomy; every six months, defined volumes of blood were removed.

“We wanted to bring their ferritin levels—meaning their body iron stores—down to the level of premenopausal women,” Zacharski explains. “So we drew blood off to lower the iron to a nadir of 25.” Ferritin levels in children and menstruating women average about 25 nanograms per milliliter of blood serum.

Significant: At first, the researchers found no statistically significant difference between the two treatment groups. Then they analyzed the data from the younger patients—those aged 43 to 61. This time there was a significant difference in the iron-reduction group: 54% fewer deaths from all causes.

“If we could just lower the amount of iron in our system, we could . . . lower the risk of vascular disease,” Zacharski says. While he acknowledges that further controlled studies are needed to clarify the role of iron in cardiovascular disease, he points out that “iron has been implicated in other diseases,” too.

He expects to publish results from a new study, one that focuses on iron's effects in another disease, in the very near future. **LAURA STEPHENSON CARTER**



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Iron, cautions Zacharski, including from fortified food and vitamins, can be too much of a good thing.

Aging well

A new fountain of youth for yeast was reported by DMS biochemists in the journal *Cell*. Previously, the best known way to prolong life in yeast, as well as more complex organisms, was by calorie restriction. But Charles Brenner, Ph.D., and colleagues have found a new vitamin



that prolongs life in yeast. “If we could do this in humans,” he says, “we would be able to provide some of the benefits of calorie restriction, which are pretty striking in model organisms.” The findings may one day help people with neurodegenerative diseases and other conditions associated with aging.

Needlepoint

Administering vaccinations against measles, mumps, rubella, and chicken pox may soon be easier in developed and developing nations alike. Pediatric researchers at Dartmouth recently evaluated a combination vaccine that only needs to be refrigerated, not frozen, and found it to be just as good as its frozen counterparts. Adopting the refrigerator-stable formulation “will lessen the burden of distribution and storage on pediatric practices, increase the ease of vaccine administration, and allow additional global expansion of current recommendations throughout the world,” the authors wrote in the journal *Pediatrics*.





DMS geneticists explained in the journal *Science* how cells' circadian clocks sense light and thus pace their daily cycle. It's a mechanism that has implications for mental illness and cancer.

Schizophrenia: Haunted by the past

Many studies have shown that childhood abuse or other adversity is linked to physical and mental health problems in adulthood. But a recent Dartmouth-led study, published in *Psychiatric Services*, was the first to evaluate that link in schizophrenia. Researchers from DMS, the University of Medicine and Dentistry of New Jersey, and Columbia found that high rates of childhood adversity contribute to worse health outcomes in adults with schizophrenia.

Events: "We felt that probably it was the combination of schizophrenia and adverse childhood events that was even more toxic" than schizophrenia alone, says lead author Stanley Rosenberg, Ph.D., a professor of psychiatry at DMS.

Schizophrenia—a severe mental illness characterized by distorted thinking, hallucinations, and a reduced ability to feel normal emotions—affects about 1% of the U.S. population, says the National Institute of Mental Health. The illness tends to strike men in their late teens to early twenties and women in their mid-twenties to early thirties.

The researchers interviewed 569 adults with schizophrenia, asking them to recall adverse events during their first 16 years of life—such as being the victim of physical or sexual abuse; having parents who were divorced or mentally ill; witnessing domestic violence; or being in foster care. The participants were receiving treatment for schizophrenia through mental health systems in New Hampshire, Connecticut, Maryland, or North Carolina.

Half: About 14% of the patients reported no adverse events, 18% reported one, and nearly half—46%—said they'd experienced more than three. The researchers found a correlation between cumulative exposure to adverse childhood events and adult psychiatric problems, such as suicidal thoughts or post-traumatic stress dis-

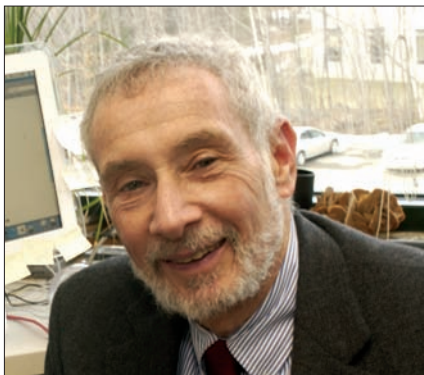
order; substance abuse; physical health problems, including HIV infection; and poor social functioning, such as homelessness or involvement in the criminal justice system. These problems are often misattributed to schizophrenia alone, according to Rosenberg.

"When you are looking at people with major mental illness, their life is a kind of perfect storm for trauma," he says. "So we started looking more intently at the whole issue of how violence and violent victimization affect this population."

The findings confirm what the researchers had long suspected—that appropriate treatment of schizophrenic patients means confronting lasting effects of adverse childhood events. But this isn't the current approach, Rosenberg says. "What caretakers are mostly concerned about . . . are the ravages of schizophrenia," not childhood trauma.

Past: The researchers acknowledge that since this study was retrospective, there's a chance that participants might have underreported past adversity, and that they may not be representative of all clients in the mental health system. Even so, Rosenberg sees a need for "tailored interventions" for those with schizophrenia to "address the consequences of adverse childhood events." **KELLEY MECK**

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Rosenberg studied an often "toxic" combination.

Walkabout

Elderly men, but not women, who live in pedestrian-friendly neighborhoods have lower rates of depression, found a study led by a new DMS faculty member. Even after taking into account factors such as income, education, age, ethnicity, smoking status, and chronic diseases, the association persisted. "One consequence of a poorly walkable neighborhood may be more depressive symptoms, particularly in older men," wrote Ethan Berke, M.D.,



M.P.H., in the *Journal of the American Geriatrics Society*. So, the authors wondered, should clinicians suggest that "older patients . . . live, if possible, in more-walkable areas?"

High sign

Higher malpractice awards and premiums go hand in hand with higher Medicare spending, note DMS health-policy analysts. In a state-by-state comparison of Medicare data from 2000 to 2003, they found that rising liability costs were associated with increases in physician services. "Our estimates do not imply that [the association is due to] 'defensive medicine,'" the authors wrote in *Health Affairs*. But they identified an especially strong link between higher liability costs and more imaging procedures, which are "often believed to be driven by physicians' fears of malpractice." ■

