



McGill

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RESEARCH, DISCOVERY AND INNOVATION AT MCGILL UNIVERSITY

The Aging Issue

**Olga is 92.
Will you age
this well?**

From brains to bones to
blood vessels: A special report
on McGill research into how
we can grow old, healthier.

headway

Research, discovery and innovation
at McGill University

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ON THE COVER:
Olga Kotelko is a
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The Aging Issue

Research Innovation



Message from the Vice-Principal (Research and International Relations)

Aging touches everyone's life in profound ways. When I returned to Montreal from Calgary in 2010 to become VP (RIR) at McGill, I quite literally moved back home, temporarily taking up residence with my elderly parents. This was a learning experience, as I saw first-hand their needs in terms of their health, mobility and care. I learned from my parents that it's the little things, particularly related to the social environment, that can make a big difference. For example, seeing how they have embraced technology to communicate and maintain their social relationships has been wonderful. As researchers, we need to focus our efforts just as much on these small yet impactful innovations as on the "big problem" of aging itself.

Which is not to underestimate just how "big" this aging problem is. We may not be getting any younger, but we are living longer. Heart disease, cancer, AIDS and other afflictions are no longer the automatic death sentences they once were, but as we prolong life, other challenges become more prevalent, including degenerative diseases, dementia and social problems. These challenges are going to be shared by an unprecedented number of Canadians, too, as our oldest demographics exponentially swell with golden age baby boomers. There's nothing new about getting old, but aging is most definitely a subject that is taking on increased urgency — and so it is the focus of this issue of *Headway*.

I can't imagine a topic that better captures McGill's interdisciplinary research spirit. Our world-class researchers continue to pursue innovations, whether they are technological, scientific, or social, with an insatiable passion and resolve. These pages highlight just some of the University's wide-reaching efforts to mediate the ravages of time. Our researchers are working to mitigate the effects of cognitive disorders, and to understand the cellular workings of the aging process. They're trying to strengthen aging bones, and to bolster weakened hearts. And, importantly, they're connecting with the people they want to help, to improve the quality of life for Canadians across the country — and, indeed, for seniors around the world.

I sometimes think about what my parents' life would be like if they didn't have their children and extended family and friends to offer them our love, support and guidance. We are lucky to have a McGill geriatric medicine specialist in the family! As people have fewer children, and as adult family members are less likely to live near their parents, their built-in support systems are smaller, and the responsibility for the welfare of the elderly falls to others in society. The old adage says that it takes a village to raise a child. Doesn't it make sense that it also takes a village to support an elder?

McGill is proud to be part of the village of support. It is through research, the very kind that happens at McGill, that we can solve problems like these, and share our discoveries with our partners in government, industry, health care, non-profit and academia around the world.

Dr. Rose Goldstein
Vice-Principal
(Research and International Relations)

Joelle Pineau

In 2002, Joelle Pineau was contributing to a multi-university project called Nursebot, which built mobile robotic personal aides for people living in nursing homes. Nursebot got Pineau thinking about the countless ways human-robot interaction could improve the lives of people with limitations — such as decreased mobility. Five years ago, the McGill associate professor of computer science (and co-director of the Reasoning and Learning Lab) began collaborating with professor Paul Cohen's team at École Polytechnique de Montréal. Pineau's specialty is coding algorithms, while the Polytechnique crew are focused on engineering challenges. Their new "smart wheelchair" senses obstacles and can use programmed maps to self-navigate specific terrains. Now in the prototype stage, their smart wheelchair would not only benefit current users of motorized wheelchairs; because of the smart wheelchair's capability to be programmed, and to understand spoken commands, it could also open up previously off-limits mobility options for many people who lack the cognitive abilities to operate conventional motorized wheelchairs. Beginning this fall, the researchers will begin a pilot project at Place Alexis-Nihon in downtown Montreal. The field project will investigate how well the smart chair can autonomously navigate the shopping centre's busy hallways, and respond to the needs and interests of its occupant. (These field

tests are just part of a much larger project that is using the mall as a "Rehabilitation Living Lab" to explore issues of social inclusion and participation for people with physical disabilities. The Living Lab is an initiative of the multi-university Centre for Interdisciplinary Research in Rehabilitation of Greater Montreal, co-directed by McGill associate professor Eva Kehayia.) "What makes our study different from other smart wheelchairs," says Pineau, "is that it's the only one that has undergone a clinically relevant test. We have used the Wheelchair Skill Test, which was developed by researchers at Dalhousie University, to quantify people's performance with the wheelchair under different circumstances. It's this close tie with people in clinical practice which has helped get this project so far in only four years."

■ This research is funded by an NSERC Collaborative Research and Development Grant in conjunction with Sunrise Medical, a manufacturer of products for home care and extended care. The "Rehabilitation Living Lab" project at Alexis-Nihon is funded by the Fonds de la recherche en santé's Projects for Innovative Strategic Development program, in partnership with Homburg Invest Inc.

Joelle Pineau in her McConnell Engineering Building lab, on May 26, 2011. Photographed by Owen Egan.

Standard-issue joystick controller. The researchers are experimenting by replacing it with a gaming joystick. "This may offer richer ways of providing commands to the robot."

The chair is one of two prototypes, both modified versions of commercially available Sunrise Medical powered wheelchairs.

Two laser rangefinders (one in front, one in back) give accurate measurements of any obstacles within 40 metres. The lasers can respond to hazards (such as stopping the chair from going down stairs) and correlate what the robot "sees" with a map loaded into its CPU. Pineau foresees one day being able to download a map through a smartphone app, then wirelessly transmitting that info to the chair.

Computer stack: "The brain of the chair. It interfaces with the controllers."

The touchscreen provides feedback to the user. "The user can verify that the robot has understood their commands before it takes any action," says Pineau. "If they asked the robot to turn left, and the touchscreen says, 'I'm going to turn right,' then they can stop it before it turns."

The user can issue vocal commands through a microphone; the commands are then translated into motion. This could be especially useful for people with very limited motor skills.



David R. Colman, director of the Montreal Neurological Institute and Hospital, passed away unexpectedly on June 1, 2011. His many friends and colleagues were shocked and saddened by this tremendous loss.



Remembering David Colman (1949-2011)

Liliana Pedraza worked closely with David Colman for 18 years, first as a postdoctoral fellow in his Mount Sinai School of Medicine lab. In 2003, she joined him when he moved to the Neuro, where she is an assistant professor specializing in neural-glial interactions. Here she reflects on her dear friend and mentor.

I would have followed Dave to the end of the world.

When we first met, I was at a difficult time in my life and career. I had just finished a post-doc at NYU and was supposed to go back to my home in Argentina, where I held a position at my university. Last-minute changes in my husband's career plans meant staying in New York and, of course, finding a job. I had a newborn baby, my working permit had expired, and I was in Manhattan, where people work crazy hours, and my work hours were limited — so my chances were very narrow for finding a second post-doc. But, even though we'd only met a few times at conferences, Dave had faith in me.

Since then, I've been unconditionally by his side. When he moved to the Neuro, I had good options to keep working in New York. But I couldn't see not working with Dave: He was the kind of person you'd be fortunate to come across just once in your lifetime.

There are many good scientists. But brilliant is something else, and Dave was brilliant. Part of it was his curiosity. I was always amazed at his knowledge of everything. He could talk about ancient Greece, philosophy, mythology, astronomy, music, Shakespeare.... He could talk about any possible thing and transmit his knowledge like it was the most natural thing. He wasn't a show-off. He was just interested in the world.

That enthusiasm transformed me. My PhD is in biochemistry, but joining Dave's lab turned me into more of a cell biologist. Biochemists break everything apart — we do subfractionations of different parts of a cell, run gels, look at what proteins are here and there — but Dave wanted to keep things intact and watch what was happening. It's one thing to look at static images of central nervous system tissue under a microscope, but he really wanted to see the event as it developed in real time. One time in the mid-90s, Dave came back from a symposium where someone presented on fluorescent protein technology, which was brand new at the time. He was so excited because he immediately envisioned a tool that would permit us to be a voyeur, to spy on the secret life of a cell while it's happening. Making myelin proteins fluorescent ended up opening yet another chapter of the story of the Colman lab.

Dave could see beyond what everyone else was seeing — and, for me, that's what distinguishes a real genius. We had a post-doc, Allison Fannon, who was trying to figure out the arrangement of cadherin-mediated adherent junctions in the central nervous system. She'd already published a beautiful paper on cadherins in the peripheral nervous system myelin, but now she was struggling because the structures are smaller, and therefore harder to visualize, in the central nervous system. Allison thought her images weren't good because they were covered with a dot pattern. We were all looking in the microscope, but it was Dave who realized that what Allison was seeing, without realizing she was seeing it, were synapses — and this was another huge contribution of the Colman lab, that cadherins mediate synaptic junction adhesion.

Dave was the type of person who always made you feel like you have value, that what you were doing was important. He was proud of everyone's work in the lab, and he always made it clear how much he valued the team. One time, at a conference, he presented data I had collected regarding axo-glial interactions. People were really excited about it. Someone asked, "What microscope are you using to get such beautiful pictures?" Dave said, "It's not the microscope, it's the person behind it. Liliana is a virtuoso. When she's operating a microscope, every confocal becomes a Stradivarius." I wish he had put that in writing! I don't think anyone will ever appreciate my work in that way again.

I keep his photo on my computer desktop. When I look at the eyes, *that* was Dave. His smile always started with his eyes, with that mischievous expression.

Every time we had a one-to-one meeting, we'd spend the first few minutes talking about the research and then start talking about something else. And it was always so interesting, sparking unexpected new ideas, that I never wanted that time to be over.

For 18 years, we had so much fun. We spent our lives at the microscope, night and day, and it was fantastic. Life after Dave. I still can't think about it. ■

From hospital to nursing home...eventually

For many elderly people, the transition from hospital ward to long-term-care facility can bring with it resignation, even depression — but what happens when this important life change is drawn out over multiple moves?

In early 2011, **Tamara Sussman** began a longitudinal study of elderly Quebec people as they transition from hospital care to long-term care. Sussman is an assistant professor in McGill's School of Social Work. Her study was sparked by the implementation of Quebec's Program 68, which dramatically revises the procedure for how older adults make this change. In the past, if elderly hospital patients were deemed in need of long-term care, they were moved to the hospital's nursing home care evaluation

wing, where they lived until there was an availability in the long-term facility of their choice. Under Program 68, which was piloted in two Montreal hospitals and is now being rolled out in the greater Montreal area, patients are subjected to many more moves. Within 72 hours of being deemed acutely stable, yet in need of long-term care, they're moved to an evaluation bed at a nursing home, then into a transition bed at a different home, and only later into their final long-term-care home of choice.

Working with St. Mary's Hospital Center, Sussman is following patients as they move through the new transition system. She wants to learn about their experiences, as well as those of their families. "What are the actual movements?" she wonders. "Are people following the new policy or circumventing the moves? And how do the moves impact people? Are more moves worse than fewer?" The study will run until everyone in the cohort completes the transition into their final long-term-care facility (approximately two years), but Sussman has already observed that the process seems hardest on the family members.

"The older people may be depressed about giving up their own homes, but they've given their day-to-day planning over to their family members," she notes. "It's the family members who are showing a lot of stress and anxiety. Some of this comes from having to make big decisions in very short time periods. And some of it actually seems to come from seeing their family member adjust and do well in their new transitional setting, while knowing that they won't be staying there. The new policy seems to be interfering with their own adjustment."

■ This research is funded by the Fonds de la recherche en santé du Québec.



FRSQ grant to further personalized medicine at RI-MUHC

The Research Institute of the McGill University Health Centre (RI-MUHC) is one of three winners in the 2011-2012 Fonds de la recherche en santé du Québec competition. The RI-MUHC won a four-year grant of \$1.4M for innovative strategic development in developing personalized medicine. An interdisciplinary research team will combine recent advances in bioinformatics, state-of-the-art technologies and new information about how biological systems interact, to create a new competitive program in translational research. The researchers will focus on non-alcoholic fatty liver disease and non-alcoholic steatohepatitis, two diseases that are emerging as potential health care crises. One of the project's goals is to identify new biomarkers to allow physicians to understand and predict the progression of NAFLD and NASH — possibly leading to new diagnostic tests and treatments.

"NAFLD and NASH will serve as a model for this new approach to treating disease and will provide the tools to better diagnose and manage a patient's disease or predisposition to it," explains lead investigator **Tommy Nilsson**, director of the Proteomics and Systems Medicine Program at the RI-MUHC, and professor in McGill's Faculty of Medicine. "This will form the basis for personalized medicine in the future."

"If successful, this work will create the road map to building personalized medicine programs across a spectrum of diseases that could lead to changes in health care delivery," adds **Vassilios Papadopoulos**, director of the RI-MUHC.

■ The Fonds de la recherche en santé du Québec is a funding agency dedicating to supporting excellence and innovation in university- and hospital-based research into human health.

Take two of these placebos and call me in the morning

Before he was a psychiatry professor and researcher, **Amir Raz** was a magician — and the two occupations aren't as different as you might think. As a researcher at the Lady Davis Institute at the Jewish General Hospital, Raz is interested in deception and how people's physiology is influenced by their expectations of what is about to happen. He recently led a survey of physicians and psychiatrists at Canadian medical schools and found that one in five respondents has administered or prescribed a placebo. The study also suggests that psychiatrists place much more value on placebo power than other physicians: More than 60 per cent of psychiatrists believe in the therapeutic effect of placebos, and more than 35 per cent reported prescribing subtherapeutic doses of medication to treat their patients.

"While most physicians probably appreciate the clinical merits of placebos, limited guidelines and scientific knowledge, as well as ethical considerations, impede open discussion about the best way we may want to reintroduce placebos into the medical milieu," says Raz. "This survey provides a valuable starting point for further investigations into Canadian physicians' attitudes towards and use of placebos."

■ *This research was funded by the Canadian Institutes of Health Research, the Natural Sciences and Engineering Research Council of Canada and the Oxford-McGill Neuroscience Collaboration.*



Nicolas Morin

Vassilios Papadopoulos

Blood simple: Diagnosing Alzheimer's may be a needle prick away

The only definitive way to diagnose Alzheimer's disease was the most invasive procedure imaginable: a post mortem analysis of brain tissue. Now, thanks to a new study conducted at the Research Institute of the McGill University Health Centre (RI-MUHC), it may be possible to diagnose the insidious disease using a simple blood test.

The study, published in the May 2011 issue of the *Journal of Alzheimer's Disease*, focuses on a brain hormone called dehydroepiandrosterone (DHEA). The researchers were able to use oxidation to promote DHEA production in blood samples taken from people who do not have Alzheimer's. The same procedure, when performed on people suffering from the disease, did not result in increased DHEA levels. The correlation was clear, says senior author and RI-MUHC director **Vassilios Papadopoulos**. (The other authors are **Georges Rammouz** and **Laurent Lecanu**, also of the RI-MUHC, and Dr. Paul Aisen of the University of California at San Diego.)

"We demonstrated we could accurately and repetitively detect Alzheimer's disease, with small samples of blood," says Papadopoulos. "This test also allowed for differential diagnosis of early stages of Alzheimer's disease, suggesting this can be used as a test to diagnose the disease in its infancy." He believes the test may also be used to distinguish Alzheimer's dementia from other cognitive impairments.

There are several disease-modifying therapies at the clinical trial stage but, as with any therapy, successful implementation depends on a reliable diagnosis. Currently, the diagnosis of Alzheimer's follows the sequence of family history, information, mental assessment and the physical exam, focusing on neurological signs. A more definitive diagnosis, such as that promised by this new blood test, would be a welcome tool in the fight against Alzheimer's.

"An accurate, easy and specific non-invasive biochemical test that correlates with clinical findings is vital," says Papadopoulos. "We believe our results demonstrate that the DHEA-oxidation blood test can be used to diagnose Alzheimer's at a very early stage and monitor the effect of therapies and the evolution of the disease."

■ *This research was funded by the National Institutes of Health and Samaritan Pharmaceuticals. The Research Institute of the McGill University Health Centre supports over 600 researchers, and over 1,000 graduate students, post-docs and fellows devoted to a broad spectrum of fundamental and clinical research.*

Giving (photo) voice to indigenous people

What do Inuit, the Shipibo and Shawi peoples of the Peruvian forest and the Batwa Pygmies of Uganda have in common? They all depend on the land for their survival—and are therefore all especially susceptible to climate change. Led by McGill geography professors **Lea Berrang-Ford** and **James Ford**, a multidisciplinary team of scholars from Canada, Peru and Uganda is working with these at-risk populations to examine what climate change means for their health. The Indigenous Health Adaptation to Climate Change (IHACC) project is also piloting training initiatives and “bottom-up” interventions to help the communities adapt to current changes. One of their projects is PhotoVoice: Indigenous people were trained to use digital cameras as a way to tell stories about their changing worlds. They created images of stagnant water, of crops that aren’t as bountiful as in previous years, of the food staples in their new diets. “We’re doing climate change research, but we’re setting the term ‘climate change’ to the side and saying, ‘In order to understand this global process, we need to understand how

people interact with their local environments today,’” says Berrang-Ford. “This project uses current experiences as a proxy for the future. We are looking at the current and potential adaptive capacities in these communities. A traditional top-down approach might ask, ‘If the temperature changes by two degrees, what would be the impact on Inuit people?’ But we’re asking, ‘What environmental conditions matter most to people’s health?’ It may not be temperature change per se. Perhaps it is a delay in the freeze-up of ice by a week, more frequent flooding in the Amazon, or later rains that delay harvest in the Uganda communities. We can take this information back to the climate models to find out what climate change projections say about how these variables might change in the future.”

■ *IHACC is a five-year, \$2.5-million initiative funded by the International Development Research Council (IDRC) and the Canadian Institutes of Health Research (CIHR), the Natural Sciences and Engineering Research Council (NSERC) and the Social Sciences and Humanities Research Council (SSHRC).*



Courtesy IHACC

Bloomberg and Manulife promote active health



Toronto financier **Lawrence S. Bloomberg** is a fervent believer that active health is a key to reversing North America’s sagging health. By teaming up with Manulife Financial, the McGill grad (MBA’65) has helped to create a \$50,000 annual prize that recognizes research achievements in the area of active health. Through their generous \$1-million donations, Bloomberg and Manulife are also launching a series of fellowships in McGill’s Department of Kinesiology and Physical Education; the fellowships will help attract new research talent, and spearhead new initiatives aimed at enhancing Canadians’ health and physical activity.

Lawrence Bloomberg has been actively involved in numerous community initiatives related to health, including many years as chair of the board at Toronto’s Mount Sinai Hospital. These experiences led him to focus his energies on improving health care and finding ways to better educate the population on issues related to health. ■



Brenda Milner honoured again

Brenda Milner is a McGill institution. The British expat trained under McGill psychology pioneer Donald Hebb, and went on to blaze her own trails by merging psychology and neurobiology to create the field of cognitive neuroscience. Still going strong in her nineties, Milner's seminal research has provided landmark discoveries in the study of human memory and the brain's temporal lobes, which play a key role in emotional responses, hearing, memory and speech.

She's about to become \$100,000 richer, too. On November 2, 2011, Milner will receive this year's Pearl Meister Greengard Prize from Rockefeller University. The prize recognizes female scientists who have made exceptional contributions to biomedical science, a group that historically has not received appropriate recognition and acclaim.

"I am absolutely delighted and amazed to receive this special award and so proud and honoured to be representing women scientists in this context," says Milner. "I am very privileged for having been able to pursue my sense of curiosity within the culture of excellence at the Montreal Neurological Institute, as well as to train and encourage talented young students — driving forces throughout my career to which I attribute much of my success."

"Brenda Milner is a great neuroscientist, and the founder of the field of neuropsychology," says Paul Greengard, a neuroscience professor at Rockefeller University. "By virtue of her stature as a pre-eminent scientist, she has greatly advanced efforts to achieve acceptance and respect for women in science." Greengard and his wife, Ursula von Rydingsvard, established the Pearl Meister Greengard Prize in memory of his mother. The prize was funded in part by the proceeds of Greengard's 2000 Nobel Prize in Physiology or Medicine. ■

Stop pain, improve brain

Back pain brings with it a host of problems — but brain damage? It's quite possible that chronic back pain doesn't just inflict agony, it also impairs cognitive function, and actually reduces grey matter, in certain parts of the brain. But a new study reports that alleviating the pain can reverse those brain changes.

In a longitudinal study published in May 2011 in the *Journal of Neuroscience*, a group of pain researchers from McGill University and the McGill University Health Centre (MUHC) followed a group of patients who underwent spinal injections or spinal surgery to alleviate their low back pain. MRI scans were conducted on each subject before and six months after their procedures. The scans measured the cortical thickness of the brain and brain activity while the subjects performed a simple cognitive task.

"When they came back in, we wanted to know whether their pain had lessened and whether their daily lives had improved," said the study's senior author, **Laura S. Stone** from McGill's Alan Edwards Centre for Research on Pain. "We wanted to see if any of the pain-related abnormalities found initially in the brain had at least slowed down or been partially reversed."

Not only did the team observe recovery in the anatomical function of the brain, but also in its ability to function. After the subjects were treated, researchers found increased cortical thickness in specific areas of the brain that were related to both pain reduction and physical disability. And the abnormal brain activity observed initially during an attention-demanding cognitive task was found to have normalized after treatment.

While more research would be needed to confirm whether chronic pain actually causes these changes in the brain, Stone hypothesizes that chronic low back pain, at the very least, maintains these differences:

"If you can make the pain go away with effective treatment, you can reverse these abnormal changes in the brain."

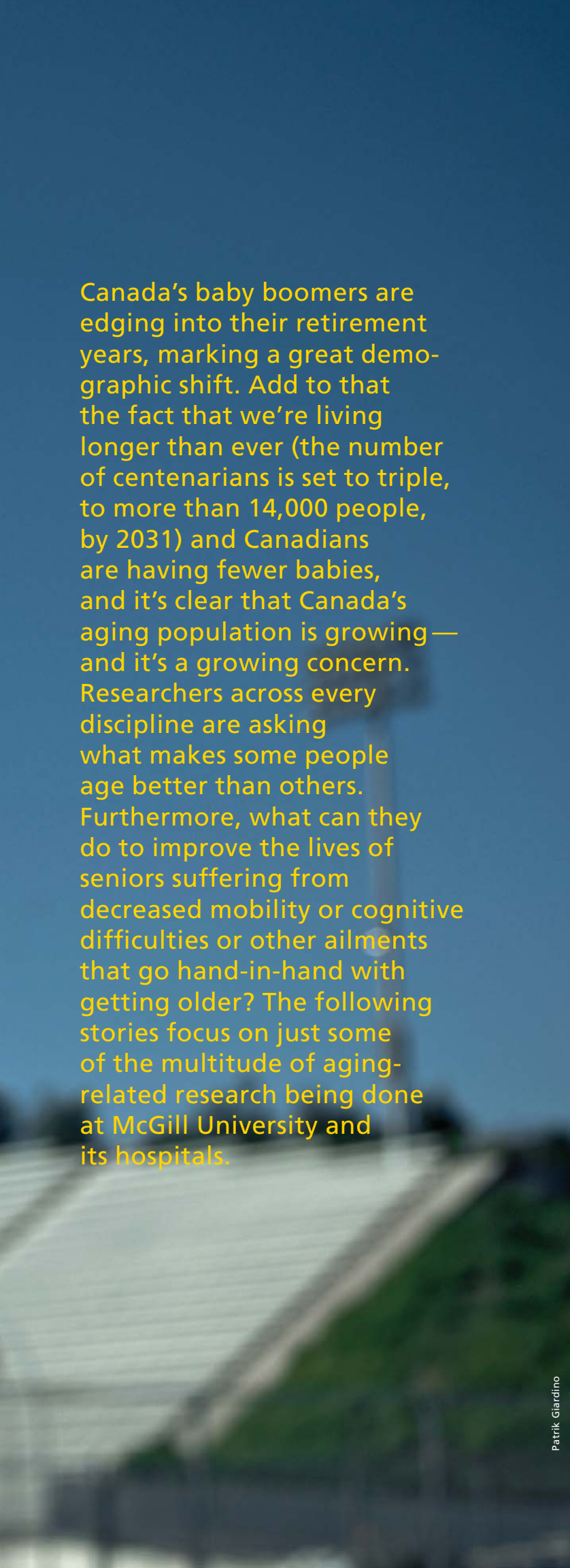
■ *This research was funded by the Louise and Alan Edwards Foundation, the Canadian Institutes of Health Research, the International Association for the Study of Pain and the Fonds de la recherche en santé du Québec.*



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The Aging Issue





Canada's baby boomers are edging into their retirement years, marking a great demographic shift. Add to that the fact that we're living longer than ever (the number of centenarians is set to triple, to more than 14,000 people, by 2031) and Canadians are having fewer babies, and it's clear that Canada's aging population is growing—and it's a growing concern. Researchers across every discipline are asking what makes some people age better than others. Furthermore, what can they do to improve the lives of seniors suffering from decreased mobility or cognitive difficulties or other ailments that go hand-in-hand with getting older? The following stories focus on just some of the multitude of aging-related research being done at McGill University and its hospitals.

In September 2009, Tanja Taivassalo went to Finland to watch her 70-year-old father run the World Masters Championships marathon. Keijo Taivassalo did well, finishing fourth in his age group. But everyone's eyes were drawn to Olga Kotelko, a petite 90-year-old woman from West Vancouver, B.C., who set no less than eight world records during the games—and, in total, holds more than 30 world track-and-field records. (As if that alone isn't impressive enough, Kotelko only started her athletic career at the age of 77.)

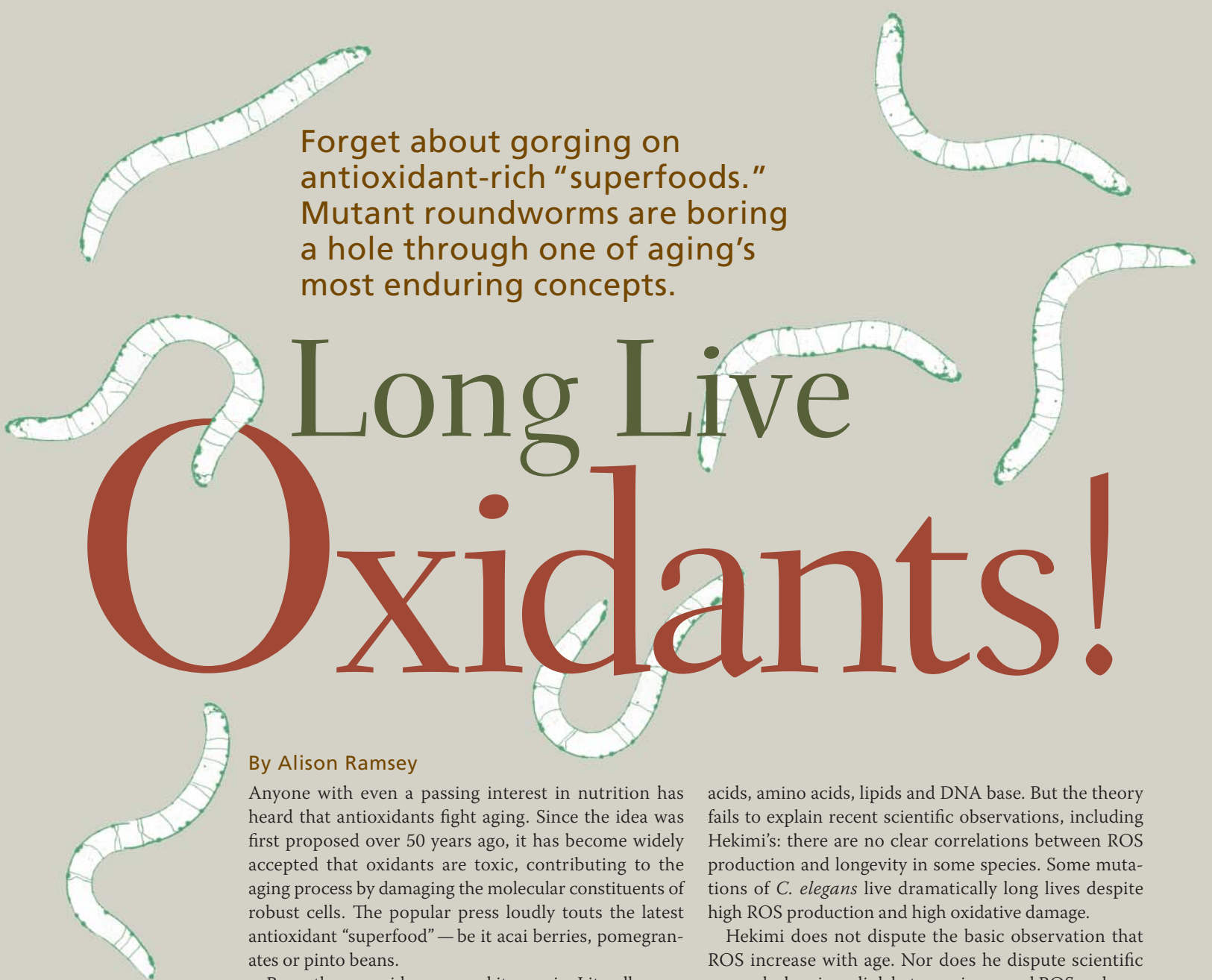
Taivassalo is an associate professor in McGill's Department of Kinesiology and Physical Education. Her research interests usually skew young; specifically, she studies genetic mitochondrial disease, in which people's cellular "batteries" are so weak that a walk around the block causes levels of fatigue normally seen after an 800-metre sprint. The disease affects around one in 8,500 people, and there's no cure—but Taivassalo wonders if Olga might hold a key. "There's no question Olga is remarkable," says Taivassalo. "What we're trying to understand is whether it's her genes or how she's been training that makes her remarkable. Was she born or was she made?"

To answer that question, Taivassalo invited Kotelko to her lab at the Montreal Chest Institute in March 2010. The McGill researchers tested Kotelko's aerobic capacity while she exercised and found that, although her ability to take in and consume oxygen was what one might predict for a nonagenarian endurance athlete (that is to say, it's very good—and equivalent to that of a sedentary 80-year-old), it wasn't off the charts. She does, however, seem to have exceptional muscle fibres that allow her to excel in power sports.

Russell Hepple, associate professor in the Department of Kinesiology and Physical Education and the Department of Medicine (Critical Care Division), is doing an ongoing analysis of a muscle biopsy taken during Kotelko's visit. Hepple doesn't agree with the common belief that people lose type 2 muscle fibres (the fibres responsible for power and strength, as opposed to the aerobic-focused type 1 fibres) as they age. Olga Kotelko just might prove him right, "because she is, after all, a power athlete doing powerful things." As we age, we lose both the neurons that activate muscle fibres, as well as the nerve terminals connecting to muscles. Hepple's team has new data, currently under review, that posits that almost all aging-related muscle atrophy occurs in denervated muscle fibres. "That's a big finding," he says, "because it means that understanding the basis for neuronal death is the key to preventing most of aging muscle atrophy. I'm interested in learning whether Olga is protected from this neuronal death—and, just from looking at the size and shape of her muscle fibres, I already suspect that's the case. If that's true, the next question will be: Why?" (Hepple adds that better protection from age-associated neuronal death may also explain Olga's sharp wit: "So much for the stereotypical dumb jock!")

Hepple and Taivassalo are keen to bring Kotelko back to McGill for a second round of tests—but perhaps nobody is more curious about Olga's secret than Olga herself. "Well, I still have the energy I had at 50," she told the *New York Times Magazine*. "More. Where is it coming from? Honestly, I don't know. It's a mystery even to me."

■ This research is funded by the Natural Sciences and Engineering Research Council of Canada and the Canadian Institutes of Health Research.



Forget about gorging on antioxidant-rich “superfoods.” Mutant roundworms are boring a hole through one of aging’s most enduring concepts.

Long Live Oxidants!

By Alison Ramsey

Anyone with even a passing interest in nutrition has heard that antioxidants fight aging. Since the idea was first proposed over 50 years ago, it has become widely accepted that oxidants are toxic, contributing to the aging process by damaging the molecular constituents of robust cells. The popular press loudly touts the latest antioxidant “superfood” — be it acai berries, pomegranates or pinto beans.

Recently, a new idea wormed its way in. Literally.

For the past decade, McGill biology professor Siegfried Hekimi has been breeding roundworms (nematodes of species *Caenorhabditis elegans*) with a surplus of oxidants, free radicals that are also called reactive oxygen species (ROS). If the antioxidant theory held true, then the mutant *C. elegans* should have been shorter lived. Instead, they lived longer.

“We can sometimes completely uncouple oxidative stress from how long an animal lives,” asserts the Swiss-born scientist.

Similar experiments with mice further bolstered his results, and gave rise to Hekimi’s own theory, that ROS are produced as a stress response to the damage caused by aging. In study after study, published in journals including *Genetics*, *Science*, *Developmental Cell*, *Aging Cell*, *PLoS Genetics* and most recently in the December issue of *PLoS Biology*, Hekimi’s work further erodes oxidative stress theory while leaving the door open to his own theory. (A new paper is currently being revised.)

The oxidative stress theory, first posited in 1954, is largely based on the observation that ROS gradually increase with age. It proposes that aging is caused by ROS damage to macromolecules, including proteins, nucleic

acids, amino acids, lipids and DNA base. But the theory fails to explain recent scientific observations, including Hekimi’s: there are no clear correlations between ROS production and longevity in some species. Some mutations of *C. elegans* live dramatically long lives despite high ROS production and high oxidative damage.

Hekimi does not dispute the basic observation that ROS increase with age. Nor does he dispute scientific research showing a link between increased ROS and age-dependent diseases such as cancer, heart disease and diabetes. He does, however, have a different interpretation of those facts.

“There is mounting evidence,” he notes, “that ROS can stimulate beneficial responses to cellular stresses produced by aging.” It may act as a signal in young mutants that triggers changes of gene expression that help prevent or delay the effects of aging. To a point: Over time, ever higher ROS levels may eventually overwhelm those beneficial responses, now harming where once they helped. Hekimi, a fit 54-year-old, describes his work with dynamic energy indicative of the professional athlete he once was. Before earning his PhD in biology at the University of Geneva, he cycled professionally full-time for more than six years, competing in the Tour de France and the Giro d’Italia. Slowly, however, he concluded that “professional sport is not a sport, it’s a profession. After awhile it became not fun. The professional mentality is: what counts is success, whatever the means, and not whether the path is interesting or pleasurable.” Hekimi’s current path is interesting, and something more. “Scientific research is like a shock wave,” he says. “You always feel lost, everything is always new. But if it were



not like that, it would not be science. Of course,” he shrugs, “it makes you suffer. You feel like you don’t know what you’re doing all the time.”

Hekimi had no clue that unseating a tenet of aging was in store when he was a post-doc at the government-run Laboratory of Molecular Biology in Cambridge, England, in the late 1980s. While attempting to find new mutants that affect nervous system development in *C. elegans*, he noticed one clone with a modified *clk-1* gene behaving oddly.

“I saw worms that should have been adult, but they were tiny,” he says. “I thought, ‘Oh, they’re terribly sick and probably will never grow up.’” Yet, a few days later, the runts were healthy adults. He was stunned.

His curiosity piqued, Hekimi began studying those aspects of the worms that normally followed a strictly structured timetable. There were many. “They defecate every 50 seconds — *ping!*” he describes. Egg-laying, wiggling, pumping — each has its timetable that produces a classic, bell-shaped distribution curve.

The *clk-1* mutants, however, broke the rules. Though perfectly healthy, some took two or even three times longer to develop. “They gave a completely flat distribution, which is completely weird. There was no peak, no favoured length of development time, which makes no sense whatsoever.” *Clk-1* mutations in both worms and mice, he observed, have increased ROS levels, yet the animals live longer: a direct contradiction of the oxidative stress theory of aging.

But do tests on worms and mice unhinge the theory of how oxidative stress affects humans? Hekimi responds vigorously: “The oxidative stress theory proposes that oxidative stress is *the* cause of aging” in organisms, regardless of species. “You can’t say, ‘Oh, there’s an exception for *your* mutant.’” Don’t expect to see nutritionists recanting anytime soon, however. The oxidative stress theory has become too well entrenched, in both the scientific community and the public consciousness.

“It has become like a dogma in a religion,” explains Hekimi. Not to mention a huge industry comprising food, supplements and cosmetics.

“It’s a reasonable theory based on plausibility, and the human brain cannot help but love those,” explains Hekimi. “The sun comes up every morning, therefore the sun goes around the Earth, right? There’s a big pile of correlative data on oxidative stress. When a theory appears to be supported by a big pile of data, and you want to say that the data is right but the theory is wrong, people find it hard to believe you.”

Having realized that he “can’t pursue every question,” Hekimi is focusing on two. The first question is: If ROS can lengthen lifespan, how does it do it? “By what pathway? What other genes are involved that transmit the signal? There’s a business end to this mechanism we don’t know about yet.” The implications of decoding that

“When a theory appears to be supported by a big pile of data, and you want to say that the data is right but the theory is wrong, people find it hard to believe you.”

— SIEGFRIED HEKIMI

business end? “Everything!” says Hekimi. “We don’t really know what causes aging. Finding out how ROS can moderate the rate of aging could allow us to do the same in a medical context.”

One thing he is certain of is that neither his nor anyone else’s research will suddenly create extremely long-lived people.

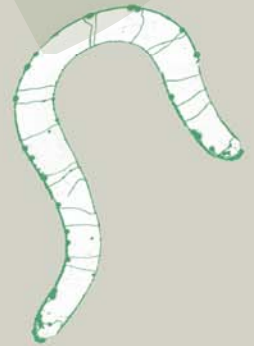
“In the past 300 years, average lifespan has increased three-fold, but not due to genetic research, vaccinations or medicine,” he says. It’s thanks to better sanitation, more abundant food, and generally having an easier life. Even 300 years ago, he adds, some people were long-lived. “We’re not living any longer, it’s just that now, everyone does! We have a limit. In theory, we could intervene on this limit. Maybe in a couple of centuries, we’ll live a bit longer... There will be no big step, and to propose it is quackery.”

Having nipped a hole in oxidative stress theory, Hekimi’s second question takes on another medical principle of mythic size: that inflammation is bad for you.

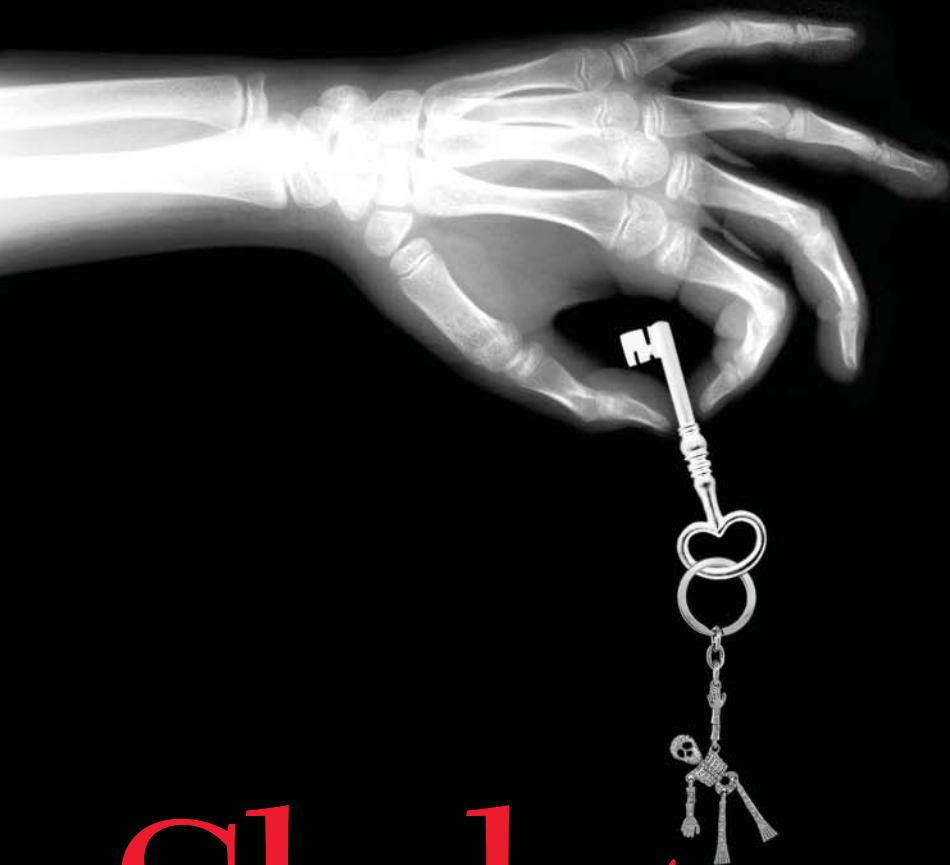
“Scientists believe that everything going wrong in us is inflammation gone awry, and it certainly is the source of some types of pain and maybe aspects of heart disease and cancer. But I believe that it could be that it is mostly good for you. It can get out of hand sometimes, but most of the time, it’s good.” His preliminary research indicates that aging biomarkers are reduced in mice with elevated immune system function.

Hekimi has made one other discovery in the past 27 years. Science isn’t anything like professional cycling. It’s a more lasting kind of fun.

■ *Siegfried Hekimi is the Robert Archibald and Catherine Louise Campbell Chair in Developmental Biology. His laboratory receives funding from the Canadian Institutes of Health Research (CIHR), the Canada Foundation for Innovation (CFI) and the Canadian Cancer Society Research Institute.*



Rachel Granofsky



Skeleton

By Philip Trum

When older people talk about resting their weary bones, they're not waxing metaphoric: Decades of movement and support takes a natural toll on our bones—a toll that becomes even more pronounced when pathologies come into play. Based at McGill, and bringing together researchers from across Quebec, the Centre for Bone and Periodontal Research is searching for better ways to treat two diseases that make our aging bones even more weary (and painful): osteoporosis and osteoarthritis.

In Shakespeare's *The Tempest*, Prospero venomously vows to "Fill all thy bones with aches, make thee roar / That beasts shall tremble at thy din." The threat sends his insolent servant scurrying, and rightly so: As millions of Canadians in their sixties and seventies will readily attest, bone pain can be excruciating.

Osteoporosis is a disease characterized by a progressive loss of bone strength. It usually makes itself known around age 60 to 65, but may begin even earlier; about 70 per cent of osteoporosis patients are women. If left unchecked, the disease can decimate bones to the point that they are extremely susceptible to fractures. In his research, Dr. David Goltzman has helped uncover some surprises about osteoporosis.

Goltzman is director of the Calcium Research Laboratory of the MUHC, and a professor of medicine and physiology in the Faculty of Medicine. Among his studies in osteoporosis, he is exploring the relationship between osteoporosis and cardiovascular disease, two ailments that

Keys?

are common in the plus-65 set. He suspects that the same mechanisms that put calcium into bone (a good thing) also conspire to calcify blood vessels (a bad thing). This means, unfortunately, that standard osteoporosis treatment (bone-boosting dosages of calcium and vitamin D) may put people at higher risk for vascular calcification. Translation: Curb your osteoporosis and you open the door to heart disease and stroke. "It may be that what is good for one isn't good for the other," Goltzman says, "but there may be an optimal level of osteoporosis treatment that doesn't put you at increased risk for cardiovascular disease." Determining how calcium and hormones such as vitamin D work, and what the optimal levels are for their effectiveness, is currently a major preoccupation of his research team and should help in the understanding and treatment of both diseases.

That isn't the only recent change to how we think about—and, therefore, treat—osteoporosis. As the director of the Centre for Bone and Periodontal Research—a collaboration between McGill's faculties of Dentistry and Medicine that brings together basic scientists and clinical investigators from several Quebec universities—Goltzman heads the Canadian Multicentre Osteoporosis Study (CaMos). The prospective cohort study has been following some 10,000 individuals, from nine cities, for almost 14 years. (It's the largest ever Canadian osteoporosis study.) CaMos has generated a wealth of data that is helping to

better diagnose the disease. In fact, the study has suggested that bone mineral density, as an indicator, may not be all it's been cracked up to be. "Bone mineral density (BMD) used to be the *sine qua non* for diagnosing osteoporosis," Goltzman says. "If BMD was low, you treat. But, as we analyzed all this detailed CaMos data, we started to find that most of the osteoporotic fractures occurred in people who did not have very low bone density. Low bone density isn't inconsequential, but it doesn't have the same implications for a 40-year-old that it has for a 60-year-old."

So what is the red flag for osteoporosis? It all depends on the person. That's why CaMos, in collaboration with Osteoporosis Canada, worked with the World Health Organization to create a new online tool for determining which risk factors put an individual at risk for an osteoporotic fracture. Launched in Canada in 2010, this tool, dubbed FRAX, takes into account patient specifics — such as age, BMD, smoking, weight, height, previous fractures — to calculate the risk of a patient suffering a hip, humerus, wrist or spine fracture in the next ten years. Goltzman would like to see clinicians use FRAX to help determine what kind of treatment, if any, a patient requires.

Although osteoporosis therapies are becoming increasingly effective at halting the disease, preventing from 30 to 70 per cent of fractures, osteoarthritis cannot be slowed or cured. Osteoarthritis is caused by the thinning of the shock-absorbing cartilage covering the ends of bones. Physicians have little recourse but to treat pain — or, as a last resort, to surgically replace problematic joints. "It's really an area that's ripe for new drug discoveries and therapies," says Goltzman.

That's exactly what Dr. John Di Battista and his colleagues at the Royal Victoria Hospital are working toward. Di Battista is a professor of medicine in the Faculty of Medicine. There are currently no reliable biomarkers for early detection of osteoarthritis, and no therapies for reversing or even slowing the disease's progression. (There are, however, drugs for modifying the progression of rheumatoid arthritis.) You therefore don't know you have the disease until you have symptoms, at which time it may be too late to do anything other than try to reduce pain, swelling and inflammation. "Basically, our treatments are rather primitive," says Di Battista.

Osteoarthritis usually affects weight-bearing joints, such as knees, ankles and hips. It usually strikes people in their sixties and seventies, and women are three to four times more prone than men (at least in terms of patients requiring remedial surgery). Because the disease can't be reversed, late-stage osteoarthritis sufferers are often left with no choice but to undergo joint replacement surgery; in Montreal alone, more than two thousand osteoarthritis-related hip and knee arthroplasties are performed each year.

Di Battista receives three or four surgical specimens from orthopedic surgeons every week (mostly from knee and hip replacements). One of the things Di Battista looks

at in each sample is the synovial membrane, which normally envelops the joint and contains joint-lubricating synovial fluid.

For something so important, a healthy synovial membrane is only one or two cells thick, and is modestly vascularized. In his surgical samples, though, Di Battista has been seeing a lot of inflamed membranes that are unnatural in both thickness and excessive blood vessel count. Increased vascularization acts as a gateway for immune cells to infiltrate the membrane. The problem with immune cells sneaking into places they shouldn't be? They signal the body to attack itself. In this case the victim is cartilage. After years of study, Battista has identified some of the mechanisms that activate this kind of inflammation-based osteoarthritis. He's now working to develop therapeutic interventions that would interrupt the process by blocking intermediary molecules.

"Right now, this type of osteoarthritis is the only case where we think we can modify the disease," he says. "From what we currently know, we can't stop osteoarthritis that's caused by injury, overuse or genetics — but 20 to 30 per cent of osteoarthritis cases are caused by inflammation, so it's still very important."

Di Battista's lab is also studying some possible genetic causes of osteoarthritis. "You'd think that a progressive disease that mainly strikes people later in their sixth or seventh decade of life wouldn't have a genetic component," he says, "but there are a few genes we're currently investigating that may predispose individuals to osteoarthritis." One such group is people who have hemochromatosis, a blood disease that causes iron overload. These people often develop osteoarthritis in their forties — some 20 years earlier than most osteoarthritis sufferers. What's more, their form of osteoarthritis, unlike "traditional" osteoarthritis, manifests itself symmetrically: Instead of just affecting one hip, for example, it affects both at the same time. Approximately one in 400 people have the genetic mutation that puts them at risk for hemochromatosis-influenced osteoarthritis.

"Right now, we can only treat the symptoms of people with established or even advanced disease," Di Battista says. "Our goal is, through the identification of biomarkers, to start preventative therapies before patients experience debilitating pain or loss of mobility, ensuring a better quality of life well into the seventh or eighth decade."

■ The CIHR recently renewed funding for the Canadian Multicentre Osteoporosis Study for five years. The study also receives support from Amgen, Lilly, Merck and Novartis-DG. Dr. Di Battista's work has been supported for some 20 years by funds from the CIHR and the Arthritis Society of Canada.

OSTEOARTHRITIS

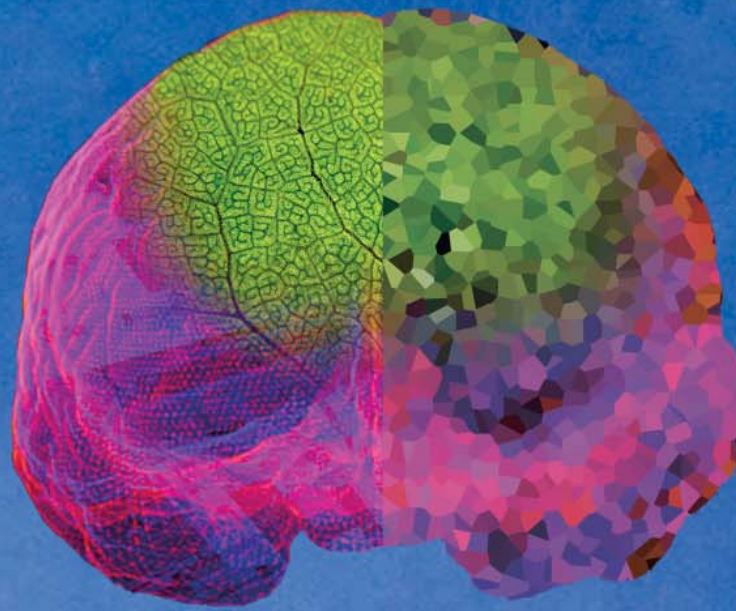
Osteoarthritis affects approximately one in 10 Canadians.

Osteoporosis affects one in four Canadian women over the age of 50.

OSTEOPOROSIS

Fighting Alzheimer's with 3D Technology

The older a brain gets, the more it's at risk for neurodegenerative diseases such as Alzheimer's. By getting a clearer picture (literally) of what a living Alzheimer's brain looks like as the disease progresses, brain imaging researcher Alan Evans is helping drive the development of new therapies that promise to change lives.



By Paul Atkinson

We're all too familiar with what Alzheimer's disease looks like from the outside. The classic symptom is disruptive memory loss, but there are other indications of a brain that just isn't working the way it once did. There may be extreme confusion over time and place. Debilitating problems with speech and language. Dramatic changes in personality, even. But what does it look like inside that misfiring brain? If you were to look at a police line-up of an Alzheimer's brain surrounded by healthy organs, could you ID the perpetrator based on physical characteristics alone? If so, what makes it stand out? Those are the questions that Alan Evans is trying to answer.

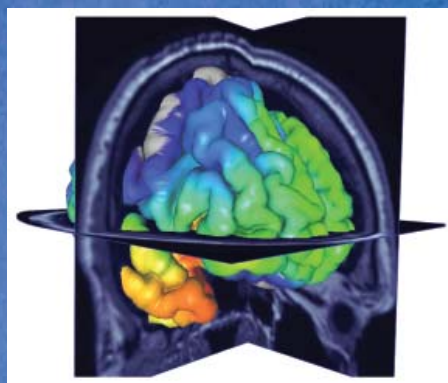
Evans is the director of the McConnell Brain Imaging Centre's ACE NeuroImaging Laboratory and the Montreal Consortium for Brain Imaging Research — and, as a specialist in three-dimensional modeling of the living brain, his goal is to understand neurological pathologies inside-out. "Ultimately, we're trying to understand the natural history of a disease," he says. "What parts of the brain exhibit abnormal changes in cortical thickness, for example, over the duration of Alzheimer's disease? How does that brain map relate to behaviours, such as a decline in language skills, that

we're able to observe? And then how might those two things relate to genetic factors?"

Originally trained in physics at Liverpool University, with a PhD in biophysics, Evans uses a technique developed at McGill that generates 3D MRI images of the living, developing brain — scans that can be repeated over time to facilitate longitudinal studies that follow disease progression. The new technology enabled him to discover the link between the thinning of the brain's cortex and mild cognitive impairment (MCI) as well as Alzheimer's disease.

"If you can start to understand the mechanisms of neuropathology as it evolves in living subjects, you have a better understanding of the process of the disease and can ultimately do something about it," states Evans. "Through imaging, we're getting a better handle on how a normal brain's networks change over time in comparison to the networks from a brain progressing to Alzheimer's."

Evans also serves as Principal Investigator of the national CBRAIN and international GBRAIN research networks. Funded by Canada's Advanced Research and Innovation Network (CANARIE), the networks bring together research from many brain imaging centres



DEMENTIA ON THE RISE

According to the Alzheimer's Society, one Canadian develops dementia every five minutes. By 2038, this will become one person every two minutes, totaling more than 257,000 people per year.

DEMENTIA ON THE RISE



around the world into a central, unified platform. Using seven supercomputers housed across Canada, the CBRAIN platform lets researchers share 3D and 4D (how a 3D image changes over time) brain imaging data from clinical trials and other large research projects, allowing researchers to explore existing data, process their own data, and add their findings to ongoing research. Remote users can apply their findings to large databases stored at remote locations and visualize the results as 3D maps in real time. Someone studying Alzheimer's disease or, at the other end of the age spectrum, autism, can measure the cortical thickness in hundreds of individual brains — or study the physiological changes in one brain over the span of milliseconds or even

its structural changes over years.

"CBRAIN is an engine for the common good," says Evans. "The techniques we are using are allowing us to build up large databases of information from across the globe to attack diseases such as Alzheimer's."

Evans points out that with CBRAIN and GBRAIN in place, researchers are able to conduct larger studies using thousands of subjects — studies that are simply impossible to do in a single lab. This shared resource also reduces the need for isolated researchers to duplicate work that's already been done elsewhere, allowing for more and larger-scale Alzheimer's-related research projects to see the light of day — helping researchers push ahead in understanding the mechanisms of the disease and how to attack it head-on.

"We're trying to combine three different domains of data acquisition — behaviour, imaging and genetics — in some multi-variant sense to see if there's a cluster of deficits that are most strongly predictive of disease progression," says Evans. "What are we seeing as someone progresses from having, say, mild cognitive impairment to Alzheimer's disease? That's what neuroscience is today."

■ *Alan Evans is a James McGill Professor of Neurology, Psychiatry and Biomedical Engineering and a CIHR Senior Scientist. He is the director of the McConnell Brain Imaging Centre's ACE NeuroImaging Laboratory and the Montreal Consortium for Brain Imaging Research. He is also Principal Investigator of the CBRAIN and GBRAIN projects, funded by Canada's Advanced Research and Innovation Network (CANARIE).*

NEUROLOG

Andréa LeBlanc has found what may be a crucial key for decoding Alzheimer's disease (where no one was even looking).

Degeneration

By Mark Shainblum

Persistence can pay off. For the better part of a decade, Andréa LeBlanc championed an unpopular, and even controversial, theory about the root causes of Alzheimer's disease. For most of that time, she and her team were virtually the only researchers in the world building a case against Caspase-6, an enzyme that plays a role in cell death and inflammation.

Her stance goes against the still widely held "amyloid theory," which fingers amyloid beta (Abeta) as the fundamental cause of Alzheimer's. Abeta forms the infamous "senile plaque" deposits, accumulations of amyloid protein in the grey matter of Alzheimer's sufferers. LeBlanc views Abeta not so much as a criminal mastermind, but Alzheimer's thuggish lackey, a serious demotion from cause to effect that many colleagues found hard to swallow. For the longest time, Caspase-6 wasn't even on anyone else's Alzheimer's agenda.

"Our research has shown that neurons, the type of cells mainly affected in Alzheimer's brains, activate Caspase-6 when stressed," explains LeBlanc, senior investigator at the Lady Davis Institute for Medical Research at the Jewish General Hospital. "We have also shown that otherwise healthy neurons degenerate when exposed to active Caspase-6."

"At the beginning, even my own students did not believe me," LeBlanc says with a laugh. "I would get excited whenever I saw new results, and they'd just look at me as if I was crazy."

The laughter started to die down as LeBlanc kept researching and publishing. By the time she and her colleagues had published over a dozen research papers and were demonstrating tangible and incontrovertible results, other researchers worldwide started to take notice. Some tried to replicate her results.

"We discovered that neural degeneration is totally independent of the production of Abeta," explains LeBlanc. "This again confirmed our theory that Abeta is a consequence and not a cause of the disease. Caspase-6 is much more upstream. In fact, active Caspase-6 increases the production of Abeta in human neurons and contributes to several other cellular defects associated with Alzheimer's disease."

Alzheimer's brains have extremely high levels of activated Caspase-6, while LeBlanc found virtually none in

the brains of older people who did not have the disease — or in anyone under the age of 45, for that matter. She also found elevated levels of the enzyme in the brains of some older people who did not suffer from Alzheimer's disease, but who had signs of memory impairment.

"We determined these normal people — who had active enzyme in the part of the brain thought to be first affected by Alzheimer's disease — also had lower cognitive scores," LeBlanc adds. "They had no clinical signs of Alzheimer's during their lifetimes but these



results indicated that they may have developed Alzheimer's disease if they had lived longer. This makes a very strong link between Caspase-6 and Alzheimer's disease."

If the Caspase-6 theory is proven correct, LeBlanc sees exciting implications for the development of new diagnostic tools and therapies. Existing psychiatric methods of diagnosing Alzheimer's are only effective once the disease has progressed past the point of no return, and there are no accepted biological or biochemical tests that can diagnose the disease in its early stages.

"Caspase-6 enzyme does not kill neurons, but it causes neurodegeneration," she says. "The implication is that this process of neurodegeneration might be reversible. At the very least it might help us identify individuals early enough to try different therapies that could prevent the progression of the disease."

■ *Andréa LeBlanc receives funding from the CIHR, the CFI and National Institutes of Health (U.S.).*

Grey Matter



Courtesy of John Breitner

Alzheimer's disease may have you long before you know that you've got it: By the time you've got symptoms, the disease is (for now) unstoppable. But Dr. John Breitner and researchers at the new Centre for Studies on the Prevention of Alzheimer's Disease are learning how to trace the progress of the disease in people who are not yet symptomatic—opening the door to early therapeutic interventions that might save millions of people from the creeping fog of dementia.

By Philip Trum

In June 2009, professor Judes Poirier phoned Dr. John Breitner with an offer. As an accomplished researcher in, and former director of, the McGill Centre for Studies in Aging, Poirier knew that McGill was the site of outstanding work in areas such as neurochemistry and brain imaging. What the University needed was someone who could help focus those strengths into a precise effort to prevent one of the worst scourges plaguing an aging population: Alzheimer's dementia. Breitner, a distinguished epidemiologist and geriatric psychiatrist known for his Alzheimer's research at Duke and Johns Hopkins Universities and the University of Washington-Seattle, was the man for the job. Breitner also knew what McGill brought to the table, and it excited him. "I told Judes I needed a few days to think of any reasons why I wouldn't be interested," he recalls. He moved to Montreal barely a year later.

Alzheimer's disease, as it's now currently understood, is an extended, chronic process of changes in the brain that ultimately produce dementia. What may begin with relatively benign memory lapses can steadily progress to the point where dementia sufferers lose not only the ability to use language, but even to coordinate any kind of movement.

"End-stage Alzheimer's leaves people vulnerable to pneumonia and similar health threats of immobility," says

Breitner, now a professor in McGill's Department of Psychiatry and Behavioural Sciences and director of the Centre for Studies on the Prevention of Alzheimer's Disease (STOP-AD) at the Douglas Mental Health University Institute. He also holds the inaugural Pfizer Professorship in Prevention of Dementia. "Make no mistake about it: The proportion of older people with Alzheimer's dementia is extraordinary, and the rates of new disease double with every five years of age. When we're looking at people in their late eighties or nineties, a third to half have some form of Alzheimer's dementia. It's one of the leading causes of death in late life. And it's on the rise. The statistics are quite frightening."

Although the disease usually doesn't announce itself until its victim's twilight years, it has long roots that may twist as far back as early adulthood. Its insidious nature makes preventing the disease a tall order. Perhaps, suggests Breitner, impossibly tall. Which isn't to say nothing can be done. "It's not necessary to prevent the disease altogether. The trick is to interrupt the disease process when people don't have symptoms and thereby prevent the later development of dementia."

Alzheimer's patients can suffer from confusion, irritability and mood swings, but the most characteristic feature, by far, is dementia. Not only is dementia devastating for the patient, but it can wreak havoc on family

and friends who watch helplessly as they lose loved ones to this terrible fog. (Alzheimer's isn't the only cause of dementia, but it is the leading cause.) But, long before there's any outward manifestation of Alzheimer's — or, if there are cognitive difficulties, that are a long way from dementia — there are identifiable changes in key areas of the brain. That's what interests Breitner.

In the early 1990s, Breitner and his colleagues at Duke University were exploring environmental factors associated with increased risk of Alzheimer's dementia. They noted that people who were regularly taking common anti-inflammatory agents (e.g., ibuprofen or naproxen) to treat arthritis pain had less dementia. Was there a causal connection? Only a randomized control trial would answer that question. So Breitner's team, now at Hopkins, gathered 2,500 healthy people who were at increased risk for Alzheimer's. (People with a parent with Alzheimer's are two to three times more likely to develop the disease.) Some were given an anti-inflammatory drug, others a placebo. The 12-year trial still has another 18 months before results will be available, but the researchers have already discovered that the people taking the drug experienced chemical changes in their cerebral spinal fluid (CSF). Short of surgically removing samples of the brain, the biomarkers found in CSF — attained through the simple and benign procedure of lumbar puncture — are the best indicator of what's going on in brain physiology.

"What's become clear of late is that the same chemical changes in CSF that characterize the presence of Alzheimer's dementia can be seen in normal people," says Breitner, "and that those people who have the changes are the ones who typically go on in later years to develop cognitive deficits and dementia. We think that changes in the chemistry of the CSF is a warning beacon that bad things are going on in the brain, sometimes long before people have begun to develop symptoms." Breitner's research showed that people who were given anti-inflammatories in the trial had "better" CSF chemical profiles — that is, fewer portents of looming dementia — than those taking the placebo. "This opens up a whole different way of thinking about things: if it becomes possible to detect evidence of the disease in people who are not yet symptomatic, it should be possible to modify those signals with treatments. We think this is a sensible way for us to test potential preventative agents."

With the anti-inflammatory trial nearing completion,

"The trick is to interrupt the disease process when people don't have symptoms and thereby prevent the later development of dementia."

– DR. JOHN BREITNER



Breitner is setting up “the next stage of this life’s work.” He’s currently recruiting a cohort of healthy yet at-risk people, age 60 and older, for a new study that will test five such potential therapies. (See sidebar.) Up to 500 people will be followed for one or two years; changes in brain physiology (as measured by CSF tests and MRI scans) will be benchmarked against their cognitive performance. Breitner hopes to begin the study late this year.

“I came to McGill because there’s a vision here,” he says. “There’s a recognition that the next phase of work needed to conquer Alzheimer’s disease is in the area of prevention. And the big problem in the prevention of Alzheimer’s dementia is the identification of treatments and interventions that are likely to work. In the past, a lot of money has been spent on things that don’t work. The preliminary evidence for the effectiveness of ginkgo biloba as a memory booster, for example, was weak but that didn’t stop people from spending upwards of \$35 million testing it—and it didn’t pan out. That’s all

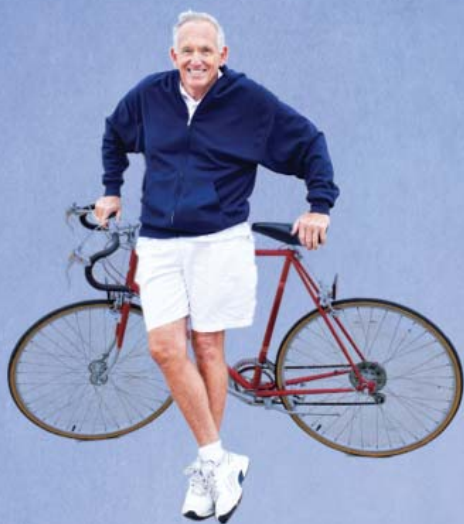
FACTS ABOUT AGING

600,000 Canadians have Alzheimer’s, and almost 100,000 die from the disease each year. The cost of Alzheimer care in Canada is between six and eight billion dollars.

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well and good if we had unlimited resources—but we don’t have unlimited resources. Dementia is already a public health crisis, and it could grow to catastrophic proportions in coming decades, so it’s time we started testing things for which there is evidence that they’ll really work.”

■ *This research is supported by the Douglas Mental Health Research Foundation.*



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Novel dementia prevention

The longer you live, the greater the chance you’ll develop Alzheimer’s disease. By some researchers’ estimates, up to two-thirds of people in their nineties will show AD symptoms. But, even if the disease is an inevitable byproduct of aging (and the jury is still out on that one), it doesn’t mean that its primary symptom—dementia—can’t be kept in check. The new PREVENT-AD cohort study will soon begin to explore five promising interventions:

■ **Anti-inflammatory drugs.** This study will say a great deal about the “whys and wherefores” of the long-term trial that Dr. John Breitner helped launch while at


Johns Hopkins University, and which is nearing completion. “Those findings are very exciting,” says Breitner, “so we want to independently confirm and extend them.”

■ **Insulin.** Studies have shown that spraying a very small concentration of insulin into the nostrils has powerful effects on cognition and chemical changes in the brains of people already suffering from Alzheimer’s dementia. Might the same treatment slow, or even prevent, the onset of dementia in people not yet showing symptoms?

■ **ApoE inducers.** One of the most important risk factors for Alzheimer’s is a variant form of a gene called apolipoprotein E (apoE). When people have this variant, they make less of the apoE protein. Some drugs can promote the synthesis of more apoE. “Will these drugs slow the development of Alzheimer’s symptoms? We need to find out.”

■ **Exercise.** Two hours of heart-rate-elevating physical activity per week, already known to improve cognition, may actually stave off dementia.

■ **A “Mediterranean” diet.** Cut down on sugars or simple starches, cut down on saturated fats...cut down on Alzheimer’s dementia? Could be. Breitner points to comparative studies between genetically similar populations, one in Nigeria, the other in Indianapolis. “The American population surely ate much more fast food, and they were two to three times more likely to develop Alzheimer’s dementia. It’s worth exploring the possible correlation.” ■



Communication Breakdowns



Interdisciplinary research across McGill—including the Bloomfield Centre for Research in Aging, the School of Communication Sciences and Disorders and the Centre for Research on Language, Mind and Brain—is exploring how language works...or doesn't.

By Thierry Harris

As young children move through their early years, their command of language undergoes an incredible growth spurt. Vocabularies swell. Sentence construction becomes increasingly elaborate. It becomes easier to navigate those areas—such as sarcasm or irony—where the unspoken speaks louder than the words themselves. And, although we never again enjoy such amazing rates of improvement, our language skills do tend to keep on getting better—after all, unless we're hermits, we're constantly honing our language skills.

But, sometimes, aging has other ideas—and words fail us.

Howard Chertkow, Director of the Bloomfield Centre for Research in Aging at the Lady Davis Institute for Medical Research, is sitting in his office at the Jewish General Hospital looking at pictures of a bear and a

hippopotamus. “When I show a bear to a patient with Alzheimer’s disease, they’ll say it’s a dog. A hippopotamus, that’s a pig.”

People suffering from Alzheimer’s dementia often have difficulty remembering words and, as in Chertkow’s example, regularly call things by the wrong name. It’s one way that the aging process can complicate speech and communication, things most of us take for granted.

Chertkow’s research focuses on the impact of dementia (Alzheimer’s-induced and otherwise) on semantic memory, the brain’s long-term storage of concepts, words and meanings. Using brain imaging technology, he’s attempting to understand the structure of language in the “normal” brain. By finding the location—or, perhaps, locations—of semantic memory, and learning how it is organized, he hopes to relate physical changes in the brain to cognitive difficulties—and, with any luck, to develop therapies for improving the cognition of dementia patients.

In the past ten years McGill has seen a significant increase in cross-faculty, interdisciplinary research partnerships to study the mind and how language works. “There is a very strong neurology group and cognitive neurologists interested in language disorder,” says Chertkow. “Through our teaching hospitals, we have access to patients. The Montreal Neurological Institute provides both imaging technology and expertise. So we’ve got cognitive neurology, we’ve got brain imaging, and we’ve got the basic brain and language scientists all in the same place with the potential to interact in multiple ways.”



Institute, recently received a CIHR grant to study further the effects of aging and bilingualism. “Much of the literature on aging, and age-related changes in communication and language, uses probes or measures of language processing that maybe lack nuances and sensitivity,” says Titone. Her team will instead gauge language comprehension by measuring eye movement using an eye tracker, which

tracks pupil fixation. Eye movement has “exquisite temporal resolution,” meaning it is sensitive to the real-time processing of language, which happens on the order of milliseconds; it is an excellent measure of whether someone is understanding what is being said.

Baum doesn’t just explore problems understanding words, either: She’s also researching why some older adults have difficulty recognizing key changes in intonation, rhythm and phrasing. Such prosodic processing deficits can result in severe misunderstandings. Take, for example, the sentence “John said Mary was the nicest girl at the party.” Without appropriate prosody, it’s difficult to determine whether John made his comment at the party, or was distinguishing Mary’s shining qualities from those of all the other girls at the party. “Intonational cues disambiguate the sentence,” she says, “but if you have an impaired ability to understand prosodic cues, you may misinterpret the meaning of the sentence.” With funding from two CIHR grants, Baum and Karsten Steinhauer, a neurobiology professor in the CRLMB, are using event-related potential (ERP) measurement techniques to understand what exactly goes wrong when such problems occur. By making electroencephalography (EEG) recordings of the brain’s electrical activity while a person is listening to speech, ERP measures millisecond-by-millisecond information about how prosodic cues change the way in which that person processes a spoken sentence. “One potential misconception is that older people may simply miss the prosodic cues because of hearing deficits,” says Steinhauer, “but our research, along with that from other labs, suggests otherwise. Adults aged 65 to 80 years vary a lot in how they interpret, or rate the meaning of, spoken sentences. Difficulties, or differences compared to young adults, may not be due to problems in perceiving prosodic patterns. For these early processing stages, our ERP data show very similar brain signatures in young and older adults.” On the other hand, Steinhauer’s team found ERP evidence that the aging brain may have problems integrating prosodic patterns with other types of information, such as the sentence structure. “As these difficulties occur at later processing stages and partly rely on memory capacity,” Steinhauer concludes, “this may explain why people with Alzheimer’s often struggle with prosodic processing as well.” ■

Better cognition through science: Howard Chertkow (left) is studying how non-invasive stimulation of the brain might reduce the effects of dementia, while Shari Baum (right) is exploring how bilingualism might improve cognitive reserve capacity.

As with many afflictions, early detection is important — and Chertkow’s seemingly simple tests with animal pictures provide an early warning of language problems.

“Animals are particularly difficult for people with Alzheimer’s disease, because they have no particular function. So the system for distinguishing animals is pretty sophisticated and is quite likely to break down early on when you get damage to these areas,” says Chertkow.

Chertkow sees new therapies opening up for older people suffering from Alzheimer’s disease once the early warning signs appear. “We are finding that there are areas of the brain that are affected in Alzheimer’s disease such as the temporal lobe. But other parts of the brain, such as the parietal lobe, are not only preserved, but can compensate for the compromised areas.” This compensation, known as cognitive reserve, may be improved through therapies such as transcranial magnetic stimulation, a procedure that uses electromagnetic induction to generate a painless electric current across the scalp and skull. “If we stimulate these compensatory areas they actually seem to improve patient’s picture naming,” says Chertkow.

Cognitive reserve capacity may also improve through training. Shari Baum, James McGill Professor at the School of Communication Sciences and Disorders (SCSD) and former founding director of the Centre for Research on Language, Mind and Brain (CRLMB), and Debra Titone of McGill’s Department of Psychology are studying executive functions with bilingual older adults. Executive functions are a collection of processes which deal with things like pursuing a goal, inhibiting distracting information and maintaining knowledge and working memory to store things in your immediate consciousness and manipulate them in various ways. As we get older, these functions decline. Baum and Titone are building on research by Ellen Bialystok of York University in Toronto, who has suggested contentiously that bilingualism effectively acts as weight training for executive functions — and may stave off the onset of Alzheimer’s dementia by as much as four years.

Titone and Baum, along with Denise Klein, a clinical research scientist from the Montreal Neurological



FACTS ABOUT AGING

Alzheimer's disease is the cause of 63 per cent of all dementias. The Alzheimer Society of Canada estimates this number may increase to 68 per cent by 2034.

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AGING

C. Jensen, Thinkstock

The 3D Heart

How a computer simulation of the aorta could help surgeons make better, quicker decisions.

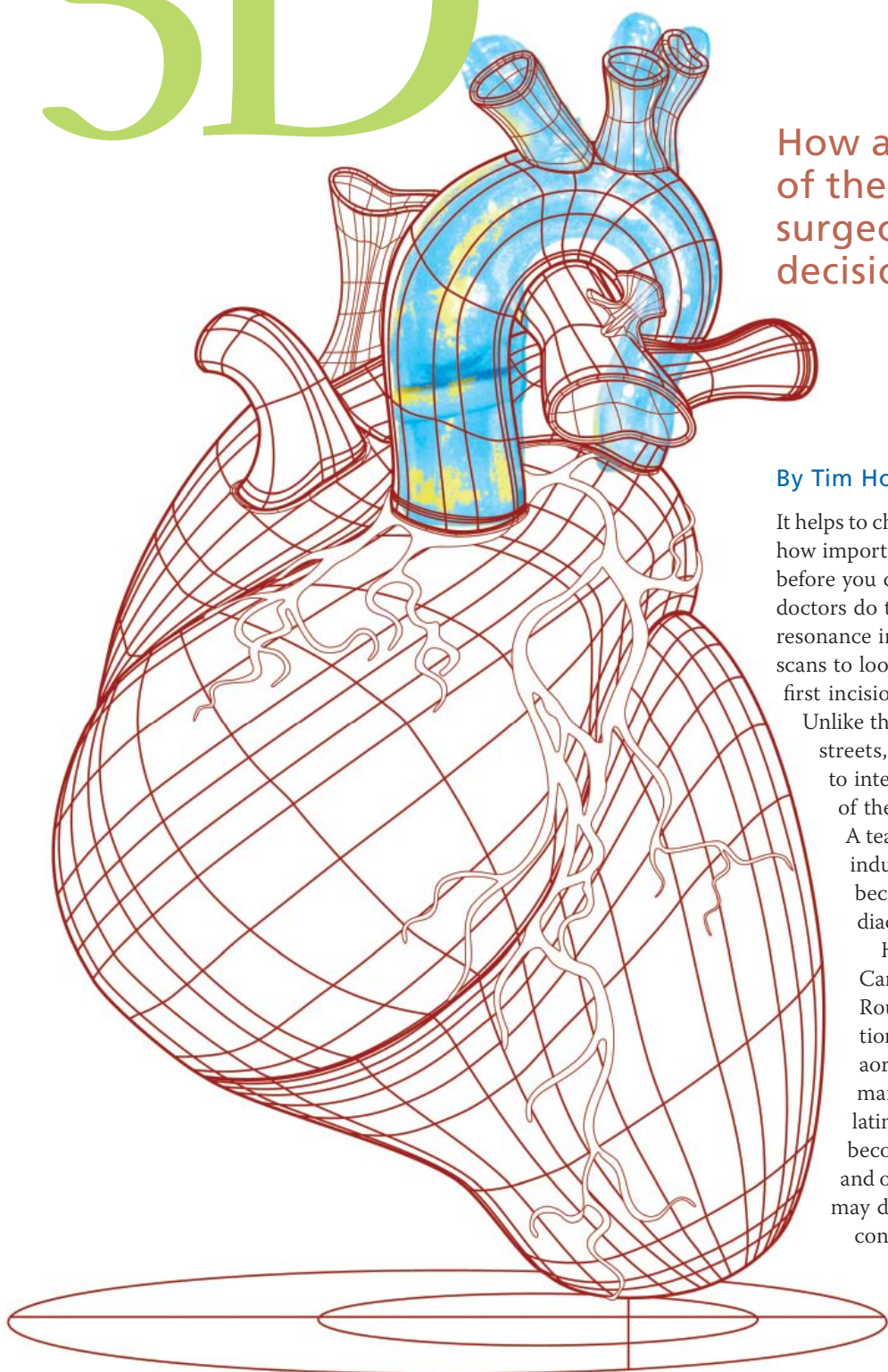
By Tim Hornyak

It helps to check a map before starting a road trip, so imagine how important it is to know the lay of the land, so to speak, before you crack open someone's chest. That's exactly what doctors do to prepare for heart surgery: They use magnetic resonance imaging (MRI) and computed tomography (CT) scans to look at what's inside the patient before making the first incision. The technology, though, is far from perfect.

Unlike the precise satellite images we use to navigate city streets, these heart images are often noisy and tricky to interpret. But what if doctors could have a 3D map of the aorta before the patient goes under the knife? A team of McGill researchers is collaborating with an industrial partner to develop technology that could become an essential decision-making tool for cardiac surgeons.

Heart disease remains one of the top killers of Canadians, and is a particular threat to older people. Roughly one-third of all heart surgeries are conditions involving the heart's valves. One such ailment, aortic valve disease, affects the gateway to the body's main blood vessel. It occurs when the valves regulating blood flow from the left ventricle into the aorta become compromised due to bulges in the aorta wall and other complications. To fix the problem, surgeons may dilate or implant grafts in the ascending aorta, a conduit just above the heart that's shaped somewhat like an umbrella handle.

Rosaire Mongrain of the Department of Mechanical Engineering points toward a colourful 3D mesh on his computer screen. It looks like a wire-frame tree trunk with a thick



stalk growing out of a bulbous base. This is a model of an actual ascending aorta, based on MRI and CT scan data. When Mongrain clicks his mouse, the tree begins to pulsate with an invisible liquid. The model is replicating the function of the aortic root.

“We are extracting the 3D anatomical shape of a patient’s heart and we reconstruct it on the computer and then assign mechanical properties to it,” Mongrain explains. “The surgeon may replace some parts of the aorta with artificial structures. These grafts do not have the same properties as the natural structures, and the surgeon will want to understand the impact on the blood flow.”

“The software gives doctors some options to think about prior to surgery,” says collaborator Richard Leask of the Department of Chemical Engineering. “We can tell them, ‘OK, if you put that coronary ostia up at this level, this is how much flow you are going to get.’ Before they go into the operating room, they can get an idea of how they will do the surgery based on the actual flow parameters, whereas up until now they just do it based on an image. Ultimately, the idea is to improve the post-surgical outcome of these patients.”

Mongrain and Leask have been working with Raymond Cartier, a heart surgeon at the Montreal Heart Institute. Inspired by Cartier’s work on aorta surgery and seeking to better understand the flow features of the aorta, Mongrain and Leask began the project six years ago and have gradually made their model more sophisticated. There are other efforts to produce computer models of the human body, such as the large-scale European HUMOS project to create a “numerical human” for applications such as car crash simulations, but few are as tissue-specific as the McGill biomechanical model of the aorta. In 2010, Mongrain, Leask and Cartier received a three-year grant from the Natural Sciences and Engineering Research Council of Canada to build the aorta model.

The researchers have shown that their basic concept is valid. They have taken about 120 aorta samples from cadavers or surgeries, and tested them for flexibility and other mechanical and biochemical properties. Then, they replicated them as CAD models using their software as well as commercial simulation products such as Comsol, LS-DYNA and 3D-Doctor. To verify the validity of a model, they send its CAD file to a rapid prototyping machine to manufacture a life-sized mockup of the aorta in transparent elastic silicone, complete with sinuses, arch and upper branches. Using a technique called particle image velocimetry, the team can then check the flow parameters of a fluid coursing through the ersatz aorta by using laser light to reflect off titanium oxide particles. Though there were some differences between the silicone model and flow results from the actual organ

using echocardiography, the pair says they should diminish as the software is improved.

“Computationally, these simulations are very intense, and they can take weeks to converge,” says Leask. “To get good results you need a very fine mesh, meaning millions of nodes. But we hope to get the computation time down to a number of hours or to a day.” To achieve that, the researchers will have to develop tools to automate the process of turning the raw imaging data into a useful graphical model of the aorta. They will also see how much the resolution of the model can be reduced, so it can be rendered more quickly without affecting its usefulness as a guide.

Since aortic repair surgeries are elective, surgeons have time to plan the operation with X-rays, MRI and other means. Running a scan of the aorta and then simulating how it will behave if a certain graft or valve is implanted would be part of pre-surgical preparation. Mongrain even envisages his aorta model as a standard feature on imaging equipment that shows various surgical possibilities to doctors.

“For example, on a GE MRI machine you could have a little subroutine on the console with the command ‘simulate surgery’ and it starts to generate the model and the flow,” says Mongrain. “It’s a little like Star Trek.”

The researchers plan to make the simulated aorta available to two types of end users in two years. One type is surgeons. They may require some assistance from engineers in interpreting certain data, but

the system would have a simple graphical user interface as a surgical planning tool. The other end user is corporations. Coroneo, a private-sector biomedical company in Montreal, is the industrial partner in the research project. It wants to use the software model in the design of its devices such as aortic annuloplasty rings, which are placed around the aorta to prevent aneurysms.

The main technical problems with developing the model have been resolved. Refining the system, and incorporating various pathologies of the aorta to make it increasingly realistic, is the next step. While corporate users will want a more unrefined version of the system so they can hack around with it, the team is now focused on making the software more user-friendly, polished and smooth for surgeons.

“We need to automate the system for medical doctors,” says Leask. “Heart surgeons have no time to spare. They have many patients and no patience.” ■

FACTS ABOUT AGING

Age and obesity are the two biggest factors for heart disease. By some estimates, the growth of heart disease deaths in Canada, by 2031, will be seven times the national population growth.

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Golden

There are over two million drivers aged 65 and up on Canada's roads. Yet the science of evaluating motorist fitness is inexact — and that's not good for the many safe drivers who rely on their cars to be independent. Researchers in McGill's School of Physical and Occupational Therapy are part of a nationwide project to better decide which drivers get the green light.



By Billy Shields

Imagine living in a country where you had to get a medical exam to keep your licence to drive. After five years, you'd need another doctor's note, and then another, and another. And what if there wasn't consensus about whether things like blood pressure, cognitive faculties or reflexes were the best predictors for driving ability, anyway?

Would it surprise you to learn you live in that country already?

Enter Isabelle G  linas, an associate professor in the Faculty of Medicine's School of Physical and Occupational Therapy (SPOT). G  linas is overseeing the Montreal site of Canadian Driving Research Initiative for Vehicular Safety in the Elderly (CanDRIVE), a groundbreaking study that promises to create new metrics to precisely gauge motorist fitness — a crucial breakthrough for seniors who depend on staying on the road to connect with the world and enjoy life in later years. CanDRIVE is a five-year, pan-Canadian multicentre longitudinal study. For the Montreal site, G  linas is working with SPOT colleagues associate professor Nicol Korner-Bitensky and assistant professor Barbara Mazer, as well as research associates Minh-Thy Truong and Felice Mendelsohn Wise, and research assistants Rivi Levkovich and Susie Schwartz. The project is now in its second year.

According to Transport Canada, almost 2.8 million Canadians aged 65 and older hold a driver's license. Yet the science of determining a driver's competence remains extremely inexact. Given that in 25 years about one-fifth of Canada's drivers will be more than 65 years old, there's an increasing urgency to refine the evaluation process. The researchers aim to develop assessment standards that

would help general practitioners keep safe drivers on the road. CanDRIVE researchers also hope to offer up customizations to the licensing process — such as day-only or no-highway driving — and minor accommodations for seniors who could retain safe driving skills by making changes in their driving style.

"We do change with age, but most seniors are good drivers, adjust their driving and keep up with changes," G  linas says. She explains that an average driver's crash-per-kilometre ratio generally makes a U-shaped graph, with high ratios at the beginning and end of one's driving career. While the poor performance of young drivers is often explainable by distractions and inexperience, she says, aged driving is a more complex phenomenon. Some studies demonstrate that a driver's crash-per-kilometre ratio doubles after age 70, but G  linas is quick to note this is often the result of accumulated conditions that are not necessarily due to the number of years on a person's odometer: Declines in visual attention (not eyesight, but how well one pays attention to visual stimulus in the environment), longer reaction times and declining motor functions all can contribute to a driver's performance. When seniors become unfit to drive, she explains, "it's not because you're old, it's associated medical conditions" that people traditionally infer are due to old age.

The McGill researchers are working with more than 100 Montreal drivers aged 70 and older in an effort to graph driving performance across a wide swath of the senior population. (Overall, the study involves almost 1,000 participants in seven test cities: Hamilton, Montreal, Ottawa, Thunder Bay, Toronto, Victoria and Winnipeg.) CanDRIVE participants must be at least 70

Gears



years old, live in Canada for at least 10 months of the year (no snowbirds allowed), and be free of certain serious health conditions such as macular degeneration. A few times a year, researchers test the seniors on a host of data points including physical, behavioural, cognitive and clinical factors. There are two shorter follow-up appointments.

The researchers also use an in-car recording device (ICRD) to collect detailed data about the drivers' everyday habits. With a global positioning system aerial that sits near the windscreen, the ICRD records the types of roads a driver uses, braking habits, and even whether the driver gets into an accident in a shopping centre parking lot—a potential red flag in driver fitness.

General practitioners asked to fill out forms from Canada's provincial licensing agencies increasingly turn to occupational therapists like SPOT research associate Felice Mendelsohn Wise for advice on what to look for in driver fitness evaluations. "Seniors shouldn't be targeted because of age. It's not age itself that makes a driver unsafe," she says. "There are conditions that can compromise our strength, conditioning and reaction times. It's very difficult to say why someone can't continue to drive. We have people in their nineties who are enrolled in the study and are so sharp." (A driver can go even beyond their nineties—there are seven centenarian drivers in Quebec—and still retain enough mental and motor skills necessary to drive.)

Potential drivers with mild cognitive impairments (known as MCIs), such as memory loss, are in an especially precarious position in Quebec, she said, because the services available to assess their driving

fitness are scarce. "If you have an MCI there's nowhere public for those people to get this assessment," she says, adding that private assessments for MCI patients can cost upwards of \$500.

So far governments have been encouraging. Recently the Canadian Council of Motor Transportation Administrators, comprised of federal and provincial driving safety researchers, launched a task force calling for this sort of research. Getting the study off the ground hasn't been easy, as research assistant Rivi Levkovich noted during a visit to the Kirkland CanDRIVE centre. She looked at the ICRD she planted in the steering column of a navy blue Ford Taurus SEL. It's one of more than 100 such small boxes that have been installed in Montreal-area cars.

One of the biggest obstacles the study hit may offer an unscientific argument for keeping seniors on the road—researchers struggle to keep up with the participants. Many seniors in the study are so active and so mobile that they leave the ICRD behind when they change cars. "You have no idea how many times a senior citizen buys a new car," Wise laughs. "And every time they do, we have to de-install the device and reinstall it into the new car."

■ *CanDRIVE is principally funded by a \$1.1-million grant from the Canadian Institutes of Health Research. The universities participating in CanDRIVE are Lakehead University, the University of Manitoba, McGill University, McMaster University, the University of Ottawa, and the University of Victoria. The University of Michigan and Monash University (Australia) are also partners.*

By James Martin

The stress of aging

Allen McInnis



Interview with Jens Pruessner, director of the McGill Centre for Studies in Aging

Jens Pruessner studies the psychoneuroendocrinology of aging. Much of his research focuses on biomarkers—such as the hormone cortisol, heart rate and blood pressure—to assess your levels of stress and their relationship to neurodegeneration. “The long-term goal,” he says, “is to hopefully understand the mechanisms behind neurodegeneration and prevent it from happening.” The last five years have seen his work—and, indeed, much of that done at the McGill Centre for Studies in Aging (MCSA) at the Douglas Mental Health University Institute, where he’s served as director for the past two years—switch from finding a cure to such preventative interventions. “We’ve realized that efforts to intervene once someone has a disease such as Alzheimer’s have not been very successful,” he says. “The changes in the brain have been so great that all we can do is maybe slow the progression, but we can’t stop it. If we can start the process earlier, we have a chance to prevent full-blown onset—and to do that, we need reliable biomarkers and better methods to detect who is normally aging and who is moving toward disease.”

How does stress affect aging?

If you’ve been chronically exposed to high levels of stress over the course of your life, there’s a chance that this has chronic effects on your cortisol regulation—which greatly increases your chances of developing a host of health problems. Our work investigates the link to

develop dementia and neurodegeneration as a consequence of life-long stress, and how it affects our brain. We are still only beginning to understand that link, and all the factors which are involved, but it seems that there is a systematic relationship that warrants further investigation.

How do you define stress in your studies?

We use the definition by Richard Lazarus which involves comparing your available resources with the demand of the situation at hand. If you feel you’ve got what it takes to cope with a certain situation—whether it’s the daily hassle of getting your children to school on time, or a major occurrence like losing a loved one—you’re not stressed. You may be challenged, but you can do it. We’re studying the stress response that happens when you feel that you don’t have what it takes.

Is that response the same for all types of stressful situations?

No, there are two stress systems. Fight-or-flight is the stress of facing a wild lion. The other one, the hypothalamic pituitary adrenal axis, is more about responding to social situations—the end product of that axis is the hormone cortisol, and that’s what we’re studying. It’s particularly important for aging research as it has been shown to have neurotoxic properties, which might influence how our brain ages.

What is social stress?

A big part of it now is insecurity about losing status or rank as a consequence of a negative outcome. The psychological term is “social evaluative threat.” If you failed to complete an assignment at work, for example, you could lose the respect of your co-workers when they realize you’re not on the top of your game. It’s a very powerful source of stress for your hormonal system.

Why the focus on social stress? Is it just because it’s more predominant, or does it have more effect on the aging process?

Social stress is the worst stress to have. Fight-or-flight seems to be more transient: Adrenaline levels skyrocket but go back to baseline very fast. Social stress is longer lasting; we’re observing cortisol changes that last for hours, which puts your whole system in a state of extreme defensiveness and the consequences last longer before you return to the baseline.

■ *Jens Pruessner’s research is funded by the Canadian Institutes of Health Research, the Natural Sciences and Engineering Research Council of Canada, the Alzheimer Society of Canada, Fonds de recherche en santé du Québec and the donors of the McGill Centre for Studies in Aging.*

Making Headway

McGILL RESEARCH FACTS

McGill biochemistry professor J.B. Collip was searching for new sex hormones. He enlisted Hans Selye, a 29-year-old Austro-Hungarian post-doc, to inject lab rats with bovine ovary extracts, then look for changes to their sex organs. What Selye observed, however, weren't the expected changes. Curious, Selye injected the rats with extracts prepared from other cow organs—and observed the same set of strange reactions. He ran the rats on a revved-up treadmill, and put them on a frigid rooftop. Again and again: the same reactions.

If it wasn't a hormone causing this uniform set of changes, then, what was it? Selye remembered a pet idea from his undergraduate days at the University of Prague. During a second-year lecture, a pre-eminent internist was presented with five hospital patients, all unknown to him. In a flashy display of diagnostic prowess, he asked a few questions of each patient, then correctly identified their unrelated maladies: stomach cancer, tuberculosis, measles.... It was a tour-de-force of logical interrogation and precise observation. But young Selye was left pondering why no mention was made of a "ridiculously childish and self-evident" commonality: Each of the patients was tired, without appetite, lethargic. Selye thought of these shared symptoms as "the syndrome of just being sick."

"I wondered why nobody had ever given this syndrome any special attention," he later wrote in his 1979 memoir, *The Stress of My Life*. "This struck me as the most fundamental problem in medicine."

It struck Selye's professors and classmates as stupid, and they ridiculed his theory. Years later, it didn't fare much better at McGill. Could the changes to the lab rats be due, not to what he was injecting, but the trauma of injection—or treadmills, or cold? J.B. Collip tried to talk his protege out of studying "the meaningless side effects of disease": "I am even tempted to look upon your work as the pharmacology of dirt!"



Hans Selye before he "discovered" stress (left) and after (right).

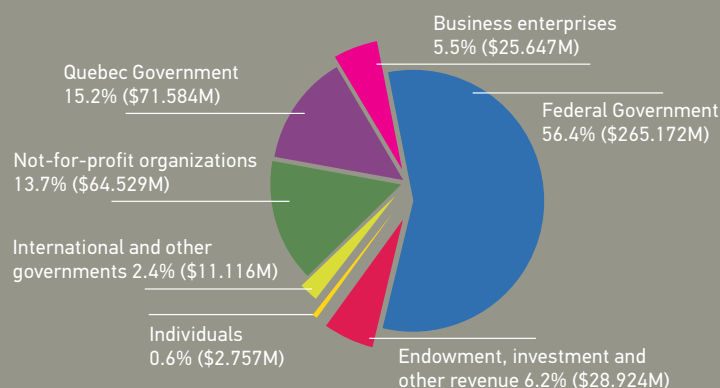


Turning Point 1936

Selye pushed on. In 1936, *Nature* published a short letter in which he quietly introduced what would become a major medical concept: "biological stress." Despite its false starts, this time the idea caught on in a big way. Selye, who later joined the Université de Montréal, published extensively on stress during his long and distinguished career. Stress became a focal point for psychologists and biologists alike, as well as a hallmark of modern life.

Selye's one regret, however, was the name, which he'd borrowed from physics. Although he was fluent in many languages, in 1936 he still struggled with some of the finer distinctions of English. In physics, "stress" is the thing that acts upon a resistant body, not the induced changes. By the time Selye realized what he called his "regrettable oversight," his misnamed idea had gained traction around the world. If he could've done it differently, today frazzled people would be complaining about how "strained-out" they are.

McGill's research funding sources 2009-2010: \$469.729 million*



*McGill and affiliated hospitals



Take the pulse of global research issues and trends (and read the latest McGill research news) at the new *Headway* blog: publications.mcgill.ca/headway

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