

SRI MAGAZINE

SUNNYBROOK RESEARCH INSTITUTE 2017

THE TRAUMA ISSUE

SRI MAGAZINE 2017

Inventing the Future of Health Care

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In This Issue



12 THE TRAUMA ISSUE

14 IN-DEPTH WITH DR. BARRY MCLELLAN
Reflections on trauma at Sunnybrook

16 YOU ONLY GET ONE SHOT
When it comes to transporting a severely injured patient to hospital, there are no second chances

20 BLOOD NOT SO SIMPLE
Preventing trauma patients from bleeding out is one of the most challenging tasks a trauma team faces—but so is ensuring they don't get lethal blood clots

26 PUTTING HUMPTY BACK TOGETHER
Orthopaedic trauma surgeons repair badly broken bodies and are changing practice through their work

28 MILD BRAIN INJURY? THAT'S A MISNOMER
Yes, there are degrees of severity when the brain is hurt, but concussions can have life-altering repercussions

30 INSIDE TRAUMA AT SUNNYBROOK
Photos from the front line

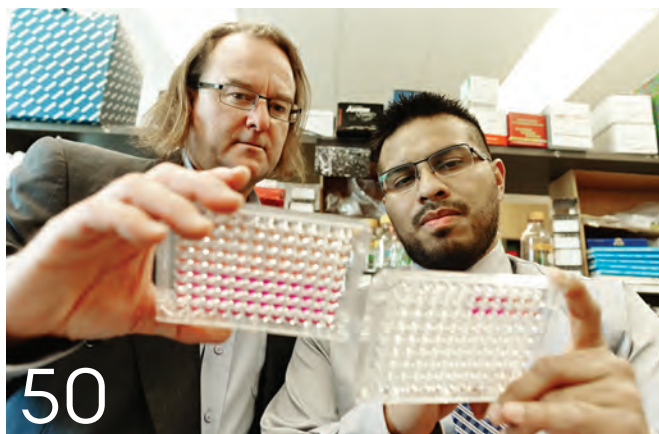
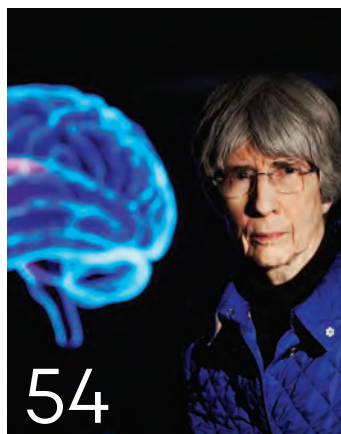
38 A FINE BALANCE
For patients vulnerable to developing sepsis while in hospital, how to balance the need for antibiotics against prudence in the face of increasing microbial resistance? Two docs take up the challenge

42 ALL POCUS, NO HOCUS
Bedside imaging, also known as point-of-care ultrasound (POCUS), is emerging as a powerful, evidence-based tool in the ER

44 UNDAUNTED: JOURNEY THROUGH TRAUMA
One man's story of survival and healing

48 A MATTER OF PERSPECTIVE
Study illuminates surprising source of collisions

Also in This Issue



FEATURES

50 RESTRAINING NATURAL KILLER CELLS
Landmark discovery brings researchers closer to vanquishing virus

52 ENGINEERING TOMORROW'S CARE
Two architects of medicine are reconstructing how surgery is done

54 NO CURE
And few—or no—treatments for these devastating brain diseases: Why not?

58 BE STILL MY BEATING HEART
Study is the first to enable biochemical reactions in the heart to be seen with MRI using a novel contrast agent

DEPARTMENTS

MESSAGES FROM SENIOR LEADERSHIP
03 Transformative research

DIGEST
04 Abstracts and News

SHORT STORIES
08 A New Angle on Pain
Tool gives voice to women's discomfort during labour

09 Culture Change
Policy slashes rates of baseless urine screening before hip or knee replacement surgery

10 That Syncing Feeling
Seasonal rhythms affect gene expression in the brain; they also are linked with daily rhythms—and both are disrupted in Alzheimer's disease: study

CONNECTED TRAINEES

60 No Doubt
Doctoral student finds his calling in science, mentoring and medicine

ASK A SCIENTIST
62 What is the biggest misconception about being a scientist?

FACTS & STATS
63 Quick Statistics

Q&A
64 Dr. Carol Schuurmans

Inside Back Cover
THROUGH THE WORMHOLE
Journey into a different time in medical science

Messages

Transformative Research



WHAT A YEAR 2016 was, and what an exciting issue of the *SRI Magazine* this is. Sunnybrook has achieved notable advances across all of our Programs and Strategic Priorities. As of press time, the world's first clinical trial testing the use of focused ultrasound to open the blood-brain barrier in people with Alzheimer's disease is well underway. This noninvasive technology, pioneered by a Sunnybrook scientist, shows promise to transform the treatment landscape, not only for brain diseases, but also for many other diseases. You can read more about this research on page 4, research that was central to our designation as a Centre of Excellence in Focused Ultrasound, the first in Canada.

The Trauma Strategic Priority, the focus of this issue, continues to make care better for the roughly 1,350 patients who rely on us each year to attend to the severest injuries. From clinical trials to determine the ideal transfusion strategy to studies to improve functional outcome, our clinician-researchers are delivering innovative approaches from resuscitation to rehab.

As we say every year, for this is a critically important point, none of the transformative advances our scientists and their talented teams achieve is possible without the support of our community. We extend our gratitude to each person and organization in that diverse community. Among these are the visionary philanthropists and funding agencies that invest in our researchers. Above all, we have our patients and their families to thank: for their support and the trust they place in us when it matters most.

Blake Goldring

Chair, Board of Directors
Sunnybrook Health Sciences Centre

Barry A. McLellan

President and CEO
Sunnybrook Health Sciences Centre

"DISCOVERY TO CLINICAL impact through the medical market place" is the mantra that fuels the evolution of SRI. A simple concept at first blush, it merits unpacking in preface to the stories in this year's magazine.

"Discovery" is straightforward. It underpins our ability to invent the future of health care.

The scope of "clinical impact" is broader than perhaps obvious. It highlights our goal to lead in the development and implementation of health care advances that form the foundation of precision medicine, broadly defined as targeted interventions tailored to the person; and image-guided therapeutics. It also captures the world-first innovations we are achieving, as well as the strategic integration of the research and clinical domains of Sunnybrook that make achieving these accomplishments possible.

"Through the medical market place" highlights the dozens of private sector partners through which SRI supports the high risk and high cost of technology development and commercialization, in most cases, the only way to get our discoveries to our patients.

It would not be hyperbole to say that this conceptual foundation uniquely positions SRI within the constellation of hospital-based research institutes. Our accomplishments this past year exemplify the power of this foundation in enabling us to have paradigm-changing impact on clinical care.

Health care is at the precipice of profound change. Here, the journey is well underway and Sunnybrook's leadership role, validated internationally, is our legacy.

Welcome to *SRI Magazine 2017*, with its focus on trauma. We hope that you enjoy the captivating stories. As you read, know that we are bringing discovery to life, to ensure our patients will benefit from breakthroughs faster than ever.

Michael Julius

Vice-President, Research
Sunnybrook Research Institute &
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Professor, Departments of Immunology & Medical Biophysics
Faculty of Medicine, University of Toronto

Digest

A round-up of notable advances
at Sunnybrook Research Institute

LAUNCHED: FIRST CLINICAL TRIAL OF FOCUSED ULTRASOUND FOR ALZHEIMER'S

IN MAY 2017, researchers and neurosurgeons at Sunnybrook made history when they became the first to use focused ultrasound technology to open the blood-brain barrier (BBB) in a person with Alzheimer's disease. In a packed MRI control room in the heart of Sunnybrook Research Institute (SRI), they tracked the procedure on a monitor, sharing smiles when it was clear the procedure had worked. With the success, they knew this first step would be one for the archives and, they hoped, the history books as-yet unwritten.

In Canada, 564,000 people are thought to have Alzheimer's disease. In the U.S., the number tops five million. Treatment options are lacking, and none stop progression. One medication after another has failed to show an effect in clinical trials. The thinking is that this might be down to the bouncer of the brain—the BBB—doing an effective job at barring entry of the study drugs. A layer of tightly packed cells, the BBB is important. It prevents toxic substances from infiltrating our most precious organ. The problem is, it blocks potentially beneficial substances, like 97% of medications.

Among the researchers overseeing the procedure was Dr. Kullervo Hynynen, director of Physical Sciences at SRI. He pioneered the technology in collaboration with industry. Also there was Dr. Nir Lipsman, a neurosurgeon and principal investigator of the trial and Dr. Sandra Black, director of the Hurvitz Brain Sciences Research Program and a co-principal investigator of the trial. The procedure works like this: the patient is fitted with a helmet-like device and positioned in an MRI scanner. Microbubbles, harmless bubbles of gas, are injected into the bloodstream, where they travel to the brain. Then, focused ultrasound is

applied through the helmet at very low intensities to a precise area previously identified. This causes the bubbles to vibrate, which in turn prompts the BBB to open only at the small, targeted area. Contrast dye previously injected into the patient shows up on MRI and enables the researchers to monitor what happens in real time. During the study, they saw the BBB open precisely where they wanted it to open. Roughly eight hours later, the BBB closes, which the researchers verify the next day with a follow-up MRI scan.

The trial follows a painstaking process of technology development and lab experiments—two decades' worth. Hynynen and Dr. Isabelle Aubert, a neuroscientist at SRI, were the first to show preclinically that focused ultrasound enables the delivery of anti-amyloid drugs, genes and stem cells into the brain safely and precisely. Moreover, they were also the first to show in mice that focused

ultrasound alone, without any drugs, restores working memory and sparks the growth of new neurons.

The first stage of the trial—as is the case with all “first-in-human” studies—is evaluating safety and feasibility. No drugs are being used. Looking ahead, the researchers have a few plans in mind, depending on the outcome of this trial. These include targeting the hippocampus, a vaguely seahorse-shaped structure where we store and process memories. They also hope to start delivering small amounts of drugs. As exciting a development as this trial is, it is but a baby step. Much more research is needed. Nonetheless, it is the thought of those living with Alzheimer's, and the millions of people who take care of them, that keeps the researchers' eyes trained on taking all the baby steps needed until, well, one giant leap. **SR**



DR. KULLERVO HYNYNEN (third from left), DR. NIR LIPSMAN (centre-back), DR. SANDRA BLACK (far right) and the rest of the team in the MRI control room as they deliver low-intensity focused ultrasound to a patient, not seen here, during the world's first clinical trial of this technology to open the blood-brain barrier in Alzheimer's disease in May 2017.

That's a Relief

THERE ARE MORE than 60,000 knee replacements in Canada annually, making it the most common surgery in the country after C-section delivery. During the operation, systemic pain relief is given intravenously, with or without a femoral nerve block, which silences movement and sensory signals from the femoral nerve that runs from the spine all the way down the leg. Such blocks are effective, but they can also cause weakness, which delays physiotherapy and increases the risk of falls. In contrast, a regional technique called local infiltration analgesia (LIA) doesn't cause motor block, thereby enabling faster recovery and discharge from hospital.

About 30% of patients who have a knee replacement are beset with chronic pain. Doctors are unsure which approach best relieves suffering and improves outcomes. To address this knowledge gap, Dr. Stephen Choi, a researcher in the Holland Musculoskeletal Research Program at Sunnybrook Research Institute, led a trial comparing LIA with a femoral nerve block that was given once, and one that was given continuously for 48 hours. One hundred and twenty people who had the surgery were randomly assigned to one of the three interventions. Neither the participants nor health care providers knew which method was used.

There were no significant differences in pain between the three methods two days after the operation. In a study published in *Anesthesia & Analgesia*, Choi and colleagues concluded that the optimal means of relief depends on many factors, and that most patients without chronic pain or who are not taking opioids daily will have satisfactory results using any of the three means. **AK**



"Any improvement since I brought the balloon?"

THE POWER OF CHOICE

ACCORDING TO THE Canadian Women's Health Network, about 60,000 cases of ductal carcinoma in situ (DCIS) are diagnosed each year and many patients receive radiation therapy in addition to breast-conserving surgery. What Dr. Eileen Rakovitch, a scientist in the Odette Cancer Research Program at Sunnybrook Research Institute, and her colleagues have found, however, is that radiation therapy may not be required for all women.

Rakovitch and her colleagues set out to validate a test to identify the women in need of radiation therapy after surgery, and determine which patients are at low risk of recurrence and in a position to bypass the additional treatment. To do so, they used the Oncotype DX DCIS Score, a test that evaluates the expression of 12 genes in breast tumours to reveal the risk of recurrence. The higher the score, the greater the chance of the cancer's return; the lower the score, the lesser the likelihood of the cancer's recurrence. They looked at 1,260 women diagnosed with

DCIS in Ontario who between 1994 and 2003 either had breast-conserving surgery alone, or surgery plus radiotherapy. Samples of their tumours were tested to produce a score.

The results showed low-risk women treated by breast-conserving surgery alone had a local recurrence risk of 10.6% at 10 years and only a small benefit from radiation therapy. Alternatively, women with higher scores had a local recurrence risk of 25.4% after surgery and experienced a greater benefit from radiotherapy.

If validated, the findings would arm doctors with greater knowledge and equip women diagnosed with DCIS to select a treatment approach specific to their needs. With such a test, patients would no longer be reliant on a generic estimate, but instead have the information required to elect an individualized plan. **MP**

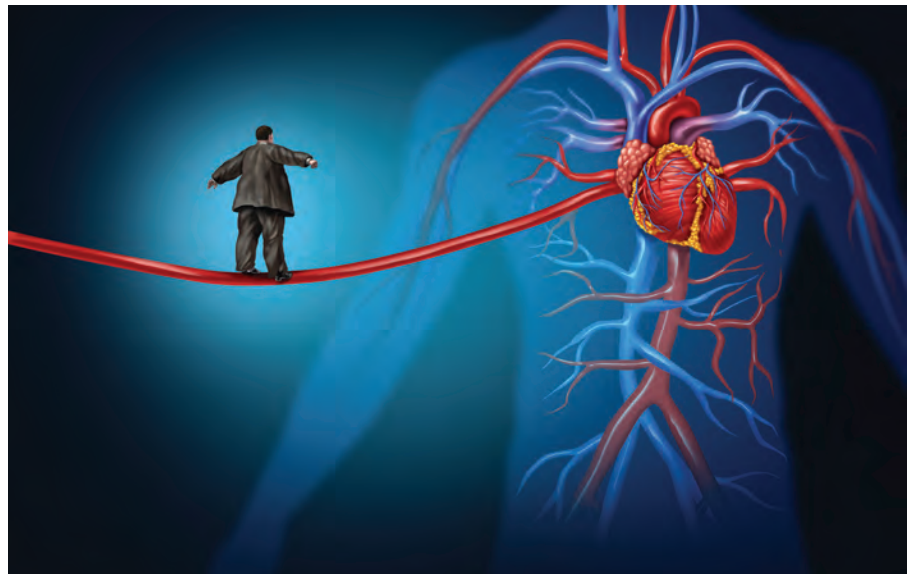


A Win-Win Situation

EACH YEAR ABOUT 5,200 Canadians are diagnosed with pancreatic cancer, which is referred to as a “silent killer” because by the time symptoms appear, the disease is advanced. For those who are diagnosed early, surgery offers the best chance of survival.

Surgery to remove pancreatic tumours involves excising the head of the pancreas and nearby lymph nodes, the gallbladder, and parts of the small intestine and stomach. Researchers at Sunnybrook Research Institute, led by clinician-scientist Dr. Natalie Coburn, are studying how to prevent a common complication of surgery called pancreatic fistula. Characterized by leaking fluid, a pancreatic fistula is an abnormal connection between the pancreas and other organs and spaces in the body that can cause infection, bleeding, longer hospital stays and even death.

Coburn and colleagues analyzed the cost-effectiveness of giving pasireotide, a drug that, while pricey, decreases the incidence of pancreatic fistulae. They compared the cost of giving the drug versus not giving it in patients who’d had the surgery. In spite of the drug’s high cost, giving it was associated with an average reduction of one-and-a-half days in hospital and a savings of \$1,685 due to shorter stays and fewer readmissions. They looked only at hospital costs, and not broader costs, such as rehabilitation services and lost productivity of patients and caregivers; had these been factored in, the savings from treatment would have been even greater, the researchers noted. Thus, they said, due to benefits to patients and cost savings, giving pasireotide to patients undergoing pancreatic resection should be considered. **AK**



Challenging "Good" Cholesterol's Role in Heart Health

FOR DECADES PEOPLE were told that high-density lipoprotein (HDL) was “healthy” and low-density lipoprotein (LDL) was “lousy.” Research by Dr. Dennis Ko, a scientist in the Schulich Heart Research Program at Sunnybrook Research Institute calls this binary doctrine into question.

He has shown that high levels of HDL do not protect against cardiovascular disease. In a study published in the *Journal of the American College of Cardiology*, he examined the HDL cholesterol levels and outcomes of more than 600,000 people in Ontario aged between 40 and 105 years. Following up this group four years after the study started, the researchers

analyzed deaths from cardiovascular diseases, cancer and other causes. People with lower HDL were at higher risk of death from both cardiovascular and non-cardiovascular conditions. If HDL were truly a marker for cardiovascular health, then it shouldn’t be implicated in other causes of death, the researchers reasoned. That wasn’t the case. Moreover, people with the lowest and highest levels of HDL cholesterol had a higher overall risk of death from all causes than those whose HDL cholesterol levels were average.

The study was named the fifth most influential paper of more than 1,000 papers published in 2016 by the journal, which is top-ranked in cardiology. **AK**

Non Sequitur

Cashmere has been combed out from the underdown of moulting goats for thousands of years. It originated in the Kashmir region of South Asia, better known today as a hotly contested no-go zone. Once combed out, the coarse hair is separated from the fine hair and washed, before being dyed and spun into yarn. For weavers in Indian-run Kashmir, who produce ultra-fine cashmere, it is still a source of industry, but one that is struggling owing to the threat posed by cheaper products produced elsewhere. **SR**

Technologies Developed In-House Approved for Clinical Use

MEDICAL DEVICES SPUN out of research done at Sunnybrook Research Institute (SRI) are poised to improve care. Dr. Brian Courtney, a clinician-scientist at SRI, developed an intracardiac echocardiography system that makes 3-D pictures inside the heart in real time. It is the first catheter-based ultrasound system that is forward-viewing and can provide 2-D and 3-D images of the heart. Conavi Medical, a spinoff that Courtney co-founded, announced in March 2017 that it received approval from Health Canada to sell its intracardiac imaging system in Canada. The device provides guidance during minimally invasive procedures to treat structural heart disease and arrhythmia, when the heart beats irregularly.

Dr. Stuart Foster, a senior scientist at SRI, founded VisualSonics in 1999 based on his work in micro-ultrasound for preclinical imaging. This is imaging that is done at high

frequencies to produce clear pictures of minute structures within tissue, and physiological details, like blood flow in a tumour, for example. The company, which was acquired by Fujifilm, also received Health Canada approval in January 2017 for its ultra-high-frequency ultrasound system. It is the first

Focused ultrasound safely and effectively improved symptoms and quality of life of patients with essential tremor.

technology of its kind to be used in people. Applications include imaging very small blood vessels in newborns, studying early joint changes in rheumatoid arthritis and examining skin changes in dermatology.

The regulatory body also autho-

rized focused ultrasound for treatment of essential tremor, a progressive and debilitating disorder that causes shaking, and afflicts millions worldwide. Focused ultrasound, which is completely noninvasive, uses MRI to guide high-intensity sound waves deep in the brain to destroy disease-causing tissue and to monitor the effects of the treatment as it is delivered.

The approval brought things full circle for Dr. Kullervo Hynynen, director of Physical Sciences at SRI, who worked on the technology for 20 years. Health Canada's decision was based on results of a multi-centre, randomized controlled trial published in the *New England Journal of Medicine*. The study's lead authors, including SRI scientist Dr. Nir Lipsman, showed that MRI-guided focused ultrasound safely and effectively improved symptoms and quality of life of patients with essential tremor who were resistant to medication. **AK**

THE MEDICAL DEVICE SECTOR IN CANADA

\$6.7B



The value (USD) of the medical device market in 2014.

10%

Percentage of medical device companies that have spun off from Canadian research organizations.



Canada's largest trading partner is the U.S. In 2015, medical device exports to the U.S. totalled \$1.8 billion.

\$6.3B

The amount more that Canada spent on medical device imports versus exports in 2015.



The industry is based primarily in British Columbia, Ontario and Quebec.

Source: Industry Canada https://www.ic.gc.ca/eic/site/lsg-pdsv.nsf/eng/h_hn01736.html

A New Angle on Pain

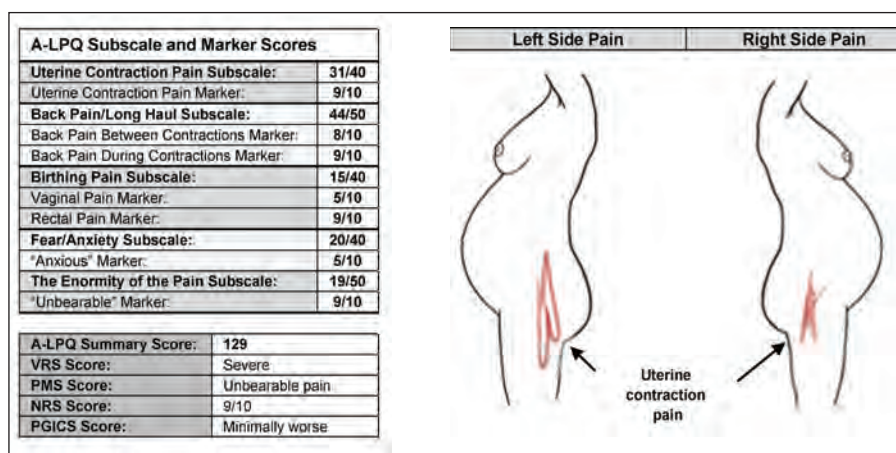
Tool gives voice to women's discomfort during labour

DR. PAMELA ANGLE has spent more than a decade learning the language moms-to-be use to describe their pain during childbirth in the birthing unit at Sunnybrook.

"Labour pain is more than one kind of pain. It consists of different types of pain. These differ in their presence, severity and levels of associated distress between women, and even within the same woman over time. You can't really use the kind of scales we have now to understand it," says Angle, director of the obstetric anesthesia research unit at Sunnybrook Research Institute and an associate scientist in the Women & Babies Research Program. "Existing tools were not developed out of a deep understanding of this phenomenon."

The only multidimensional pain tools available for labour pain assessment derive from the McGill Pain Questionnaire, which did not include labouring women during its earliest phase of development. This gap led Angle and her team to develop the Angle Labour Pain Questionnaire (A-LPQ). The tool measures the five most important dimensions of women's childbirth pain: enormity of the pain, fear and anxiety, uterine contraction pain, birthing pain and back pain/long haul. A companion tool, the Angle Pictorial Pain Mapping and Ranking Tool (A-PPMRT), is also available. It permits women to draw and name the different types of labour pain they are experiencing using anatomic diagrams and a list of pain names originally generated by labouring women.

Angle has conducted three validation studies for the A-LPQ. The first, published in the *Clinical Journal of Pain*, assessed the test-retest reliability of the tool during early active labour in 104 women without pain relief. Test-retest reliability assesses if the measure is



The A-LPQ tool measures the five most important dimensions of labour pain. Women use the Angle Pain Mapping and Pain Ranking Tool to draw and name the different types of pain they experience.

stable over time. The study also looked at the scale's sensitivity to change—its capacity to detect change when it occurs—as well as the A-LPQ's responsiveness to minimal changes in pain over time. The second study, published in *Anesthesia and Analgesia*, examined the scale's sensitivity to change in women who received epidural pain relief.

"These studies showed that the A-LPQ had excellent test-retest reliability, was sensitive to change and was extremely responsive to minimal changes in pain," says Angle, who is an associate professor of anesthesiology at the University of Toronto.

Results from the third study, which will be submitted soon for publication, found that women in early active labour have excellent recall of the pain they experienced just before receiving an epidural, when they were asked to rate that pain within 20 to 30 minutes of receiving an epidural. That's important, says Angle, "because it's very difficult to study women in pain, particularly when that pain is severe. We have a great gap in our knowledge of women's physical pain

experiences during late labour and in women with obstructive labour." Multidimensional measurement of women with this type of pain is typically done much later, after delivery, because women are simply unable to answer the questions.

Taken together, the findings suggest that the scale will be useful in clinical trials and other studies of pain during labour, says Angle. Further, she notes that the approach is groundbreaking, and will soon be used in practice globally to help clinicians understand, manage and treat labour pain. "The A-LPQ and the A-PPMRT were developed directly from the voices of women, from their words, their pictures, their experiences—the women have been my teachers, and this new approach to understanding their pain will allow them to teach others to better care for them," she says.

ELENI KANAVAS

Angle's research is funded by an AFP Innovation Award at Sunnybrook, the Langar Foundation (Toronto), and the Ontario Ministry of Health and Long-Term Care.

Culture Change

Policy slashes rates of baseless urine screening before hip or knee replacement surgery

CHOOSE WISELY: IN hospitals it's a mantra underpinned by evidence and motivated by concern for patients, resources and the health care system writ large. Much research has shown that some tests should not be ordered, either because the results will not influence the decisions made, or, worse, because they could do harm.

Sunnybrook's Holland Orthopaedic and Arthritic Centre does about 3,300 surgeries every year. Until May 2015, screens of urine cultures were routinely ordered before patients had their joints replaced. The thinking was that if the cultures tested positive for bacteria, then patients should be treated with antibiotics before having surgery to reduce the odds of getting a joint infection. The wrinkle in this thinking? "I've been doing joint replacements for over 30 years. I don't think I've ever had a patient develop an acute postoperative infection from a urinary organism," says Dr. Jeff Gollish, medical director of the Holland Centre.

Added to a lifetime of surgical experience are data—or a lack thereof. “We have not had prospective studies demonstrating that if you [order urine cultures and find bacteria] and then treat the urine that you can reduce the risk of infection in the joint replacement surgery,” says Dr. Jerome Leis, medical director of infection prevention and control at Sunnybrook, and an associate scientist at Sunnybrook Research Institute.

Thus Leis and Gollish were prompted to figure out how to change practice. Education, they surmised, wasn't enough. "What we did was slightly different; we implemented a system change," says Leis. They developed a policy such that urine screening was not done automatically. They removed it from the standard set of tests ordered before surgery. For specimens received by the lab there

was “a little bit of a hard stop,” says Leis. “The lab upon receipt of the specimens would not automatically process them.” Instead, anyone who wanted the culture done had to call the lab to request it within 24 hours.

As detailed in a March 2017 article in *Clinical Infectious Diseases*, it worked. The researchers evaluated 3,523 patients undergoing a first total knee, hip or shoulder replacement during two years leading up to the policy change. They compared them to 1,891 patients who had surgery after the policy change. Before the change, 3,069 screening urine cultures were ordered over the two years, all of which were processed; of these, 352 were positive. After the change, 126 cultures were ordered, only 10 of which were processed; none were positive. This corresponded to a 99% relative reduction in the screening rate of urine cultures. “The system change led to a dramatic shift in practice, and not only dramatic, but



After launching a policy change, routine ordering of unwarranted urine cultures before joint replacement surgery dropped.

rapid—within a month,” says Leis.

They also found no significant year-over-year increase in joint infections after the change. “In fact, among those that we did find, they were caused by bacteria that do not originate from the urinary tract, suggesting they were unrelated to this change in the intervention,” says Leis.

The results also have societal reverberations. “Antibiotic stewardship and avoiding inappropriate use of antibiotics is critical to avoid developing organisms for which we have no treatment,” says Gollish. “We are starting to see the development of multi-drug-resistant bacteria where we have limited treatment options, and anything we can do to scale back unnecessary antibiotics is essential,” Leis says.

Gollish notes that while it is standard practice at the Holland Centre not to order urine cultures unless patients have symptoms that warrant testing, this isn't the case elsewhere. "If I talk to my colleagues across the country, virtually everybody is still doing this in most hospitals." He hopes to move the change into wider use through his work with the National Standards Committee of the Canadian Orthopaedic Association.

Working to achieve consensus on the change was pivotal to success. “This is an example of what we can accomplish when we collaborate between clinical services, including orthopaedics, infectious diseases, infection control, antimicrobial stewardship and microbiology,” says Leis, then adds, “by all being at the table and coming up with a process that everyone agrees on and acknowledges is a better use of resources, we can make system changes that are more impactful and sustainable.”

STEPHANIE ROBERTS

That Syncing Feeling

Seasonal rhythms affect gene expression in the brain; they also are linked with daily rhythms—and both are disrupted in Alzheimer's disease: study



ABOVE WHERE THE left and right optic nerves cross are two tiny structures that serve as command central for our brain's internal "clock," or circadian rhythm. The size of the head of a pin, these structures are called the suprachiasmatic [soo-pra-ki-az-ma-tik] nuclei. They contain thousands of neurons that receive information about light to help regulate sleep and wake patterns, body temperature and the release of hormones like melatonin and cortisol.

Circadian rhythms, which follow a 24-hour cycle, as well as seasonal rhythms, are found in all kinds of living things. "If you look across the animal kingdom, there are seasonal rhythms in

animals that hibernate, and in plants with flowering and leaf growth. Similarly, there are circadian rhythms that permeate the natural world. Almost all animals have sleep and wake cycles," says Dr. Andrew Lim, a neuroscientist at Sunnybrook Research Institute and neurologist at Sunnybrook.

An avid cyclist, Lim travels to work almost always on two wheels. (Only during snowstorms does he leave his bike at home.) Having just biked in, he is still in his cycling gear as we chat about his research. Lim notes that there are daily and seasonal rhythms in brain functions like mood and cognition; for instance, times of the day when people feel more

alert. Another example of rhythmic brain function in action is seasonal affective disorder, a brain disease where people become profoundly depressed in the winter. Circadian and seasonal cycles are vital to our health, yet little is known about what drives them.

To shed light on the biology behind these rhythms, Lim and his colleagues in the U.S. analyzed the brains of 757 deceased people who volunteered for long-term studies on aging and memory. In particular, the team examined patterns of gene expression in a brain region that's important for thinking and mood. They used a technique called RNA sequencing, which is a read-out of all the RNA in a cell.

Since RNA mirrors the DNA from which it was copied, RNA sequencing can tell researchers where a gene is turned on or off, and the amount of gene activity, or expression. With this technology he and his colleagues were able to assess the levels of expression for every single gene in the genome in each brain. "We were able to construct a chart for each one of the 20-something-thousand genes, showing what the pattern of expression of that gene is across the day. Is it higher at night, in the morning, or in the afternoon?" says Lim, who is also an assistant professor of medicine at the University of Toronto.

The first thing they found is that there are indeed seasonal rhythms of gene expression. This discovery had never before been made in any human organ, and suggests there is a biological basis for brain disorders that are influenced by the seasons. "Nobody had ever asked the question whether our brains, at a deep molecular level, are different in the winter than in the summer. It isn't that we merely feel different; our brains are fundamentally different at different times of the year, and at different times of the day," says Lim.

Next, they discovered that daily and seasonal regulation of genes were tightly linked, so much so that "you could, to some degree, predict how a gene would behave across seasons if you knew how that gene behaved across the day and night cycle," he says.

The team also found there were differences in the timing of gene expression in the brains of people who had Alzheimer's disease (AD) compared to those that didn't have the disease. Daily rhythms of gene expression in people with AD were advanced by one-and-a-half hours, while seasonal rhythms were delayed by two weeks. Abnormal rhythms of gene expression in AD may account for difficulties with sleep and increased behavioural problems that begin late in the day, says Lim.

The groundbreaking study opens up different avenues of research into the biology of daily and seasonal rhythms. Basic scientists can look at gene expression patterns across days and seasons in preclinical models to uncover the specific mechanisms regulating those patterns. Meanwhile, translational researchers, who have clinical impact in mind, can

"Our brains are fundamentally different at different times of the year, and at different times of the day."

look for changes in gene expression in conditions like seasonal affective disorder to identify genes linked to the disease that could serve as drug targets.

The capacity to examine gene expression in the human brain was a confluence of favourable circumstances, Lim notes. The study hinged on access to a large sample of postmortem brain tissue. Moreover, only in the last few years has the technology to do RNA sequencing at a global level become available. Finally, he and his lab were able to engineer tools to process staggering amounts of data. "Each analytic run could take many days to a week at a dedicated super-computing facility. A lot of the work we did was to develop the algorithms to make it possible to do this large-scale data analysis even with the latest in computing tools," says Lim.

Computer programming and data analysis are major aspects of his group's research. He is leading the Ontario Sleep and Brain Health Study, which looks at the impact of sleep on cognition. His team is examining sleep patterns of people in their thirties and forties to determine

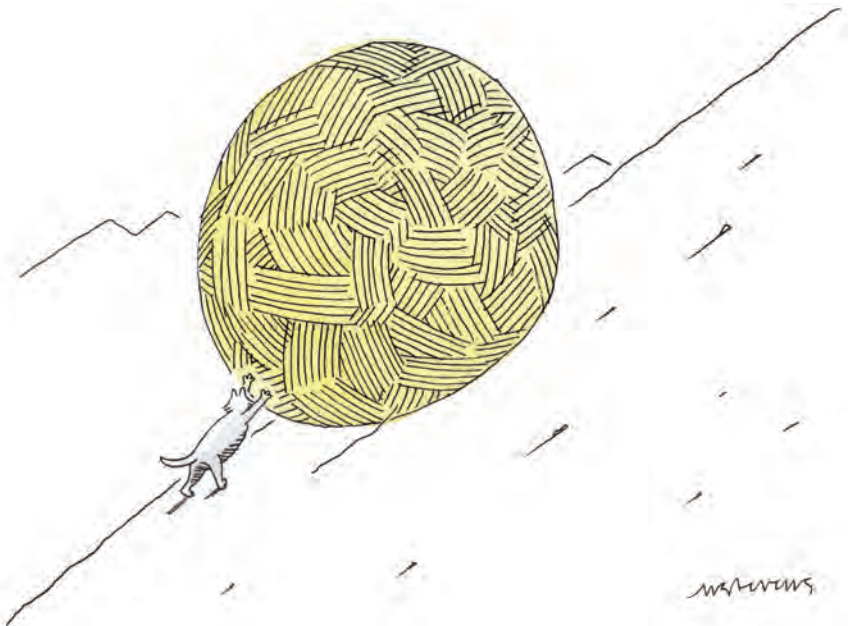
whether insufficient shuteye is linked to changes like damage to blood vessels in the brain and brain shrinkage. He is also studying whether poor sleep has an immediate effect on mental performance and if it increases the risk of dementia long-term. "The big issue is that nobody sleeps enough," says Lim. He acknowledges that his own sleep is erratic because he works on call overnight every week. He is not alone. Parents of young children and people who do shift work also tend to have irregular sleep patterns.

Research Lim published in 2013 has already established a link between sleep disruption in older adults and increased risk of AD. Thanks to studies like this, more people are appreciating the importance of a good night's slumber.

It's about time.

ALISA KIM

Lim's research is supported by the Canadian Institutes of Health Research, National Institutes of Health, and Ontario Ministry of Research, Innovation and Science.



There is one thing that doctors want people to know: that trauma doesn't happen only to others—it could happen to you. Each year, it happens to more than 1,300 people who are brought to Sunnybrook.

What is trauma? Apart from non-discriminating, it is a serious life- or limb-threatening condition where each second counts. It's the teenager who drank too much and thought it would be cool to corkscrew into the—as it turned out, shallow—pool. It's the man who was stabbed during a fight over nothing very important, in the end. It's the worker who wasn't wearing a harness when he lost his footing and plummeted three stories onto concrete. It's the woman who was texting while crossing the road and got hit by a car whose driver was likewise engaged.

It is graphic and devastating and irrevocable.
It is not pretty. It is mostly preventable.

At Sunnybrook, it's a strategic priority. Twin pillars of care and research support it. It starts at the scene, with our partners in prehospital medicine, who stabilize and get injured people here stat. Once here, the trauma team assesses and resuscitates the patient. There can be upwards of a dozen medical professionals from a mass of specialties tending to one person. As that person continues his or her journey, likely to the OR, possibly to the ICU, almost certainly to rehab, the circle of care widens.

This trauma issue aims to show how each piece of this care has been informed by research and, every day in the field, trauma bay and throughout the hospital, continues to be informed by it. Research is changing practice here, regionally and around the world. It is having an impact. More patients are surviving their injuries. The bad news is that a return to a good life is not a sure thing. Even non-life-threatening trauma is life altering. That's why researchers are not content to pause, instead recognizing that much remains to be done along the spectrum of prevention, treatment and rehab.

Welcome to the trauma issue of the *SRI Magazine*.



14 In-Depth With Dr. Barry McLellan
Reflections on trauma at Sunnybrook

16 You Only Get One Shot
When it comes to transporting a severely injured patient to hospital, there are no second chances

20 Blood Not So Simple
Preventing trauma patients from bleeding out is one of the most challenging tasks a trauma team faces—but so is ensuring they don't get lethal blood clots

26 Putting Humpty Back Together
Orthopaedic trauma surgeons repair badly broken bodies and are changing practice through their work

28 *Mild* Brain Injury? That's a Misnomer

Yes, there are degrees of severity when the brain is hurt, but concussions can have life-altering repercussions

30 Inside Trauma at Sunnybrook
Photos from the front line

38 A Fine Balance
For patients vulnerable to developing sepsis while in hospital, how to balance the need for antibiotics against prudence in the face of increasing microbial resistance? Two docs take up the challenge

42 All POCUS, No HOCUS

Bedside imaging, also known as point-of-care ultrasound (POCUS), is emerging as a powerful, evidence-based tool in the ER

44 Undaunted: Journey Through Trauma
One man's story of survival and healing

48 A Matter of Perspective
Study illuminates surprising source of collisions

IN-DEPTH WITH DR. BARRY McLELLAN

He is not only president and CEO of Sunnybrook, **DR. BARRY McLELLAN** is the hospital's former director of the trauma program, emergency services and trauma research; he was also a trauma team leader and trained in the field here. Later, he oversaw the base hospital (paramedicine) program. Oh, and somewhere in there he did a 10-year stint in the coroner's office.

It's not hard to see why more than a few people refer to him as the father of trauma at Sunnybrook, though it's a moniker he likely would eschew, pointing instead to a legacy of pioneers that set the stage, including Al Harrison, Marv Tile and Bob McMurtry; and, above all, a highly enabling team environment. Here, he talks to **STEPHANIE ROBERTS**, editor of the *SRI Magazine*, reflecting on times past and relinquishing nothing about his future as his near-decade-long tenure at the helm of Sunnybrook comes to an end June 30, 2017.

Trauma is all about the team. What is it about trauma that makes this so?

The question might be, what is it about Sunnybrook that makes this so? Sunnybrook as an organization has been built around team function. There is a culture of collegiality and cooperation. When the trauma program at Sunnybrook started in 1976, a lot of the building blocks were already in place. You had an organization that was already thinking about how to work together to advance patient care.

Through the '70s and '80s, it crystallized into a comprehensive program. It not only includes depth in specialty areas, but as we say, we have a care chain, and if you have a weak link anywhere in that chain, then care of the patient is going to suffer—so right from resuscitation in the field and the response of the paramedics, and the air ambulance transport, right through the trauma room, surgery and critical care—if any one of those is weak, right through rehab and follow-up, then the outcome is less than optimal.

That thinking wasn't in place to start with. It developed here. When we talk about the trauma system that's in place more broadly, we have taken what was learned here and the creation of the program and disseminated it across the country and beyond. A lot of the trauma system thinking across the world came from some of the early work here. The

impact of that team approach is amazing. It's great for patients here, but it's also affected patient care across the world.

Why did you choose trauma?

I trained here in the early '80s in emergency and critical care. Sometimes you get drawn in by what you see. I could see excellence in the work that was being done, and I could see great team function.

Mentorship is so important. When you start out in medicine, you are bombarded with choices. This can be wonderful. It also can be paralyzing.

It is. You are very much influenced by those who train you and what you see. I could see great care being provided and opportunities in research and education. The leaders that were around at that time in trauma were very much pioneers in their field.

What was the hardest aspect of your work as a trauma physician?

Seeing injuries that were in large part preventable. Trauma patients are generally young, heavily skewed toward the male population. Early, much of it was related to motor vehicle [crashes], and much of that was preventable, whether it was because of alcohol, speed, other risk-taking behaviour or not wearing a seatbelt. You would be caring for someone who had a very bad head injury, had a spinal cord injury, and you would realize

that a bad decision that was made would have an impact for the rest of their lives.

It's one of the reasons that we became involved in injury prevention. It evolved from our early experience and research determining where prevention would be of most benefit in the system.

You've been here 10 years. When you look back at your accomplishments, of what are you most proud?

We've become more focused on a smaller number of areas—and you're going to make the biggest impact if you select and grow a small number of specific areas of strength. I would say that's one of the real strengths of our strategy: focus, and the impact comes out of that focus.

At Sunnybrook, there is TECC, which is broader than trauma.

It's a really important distinction to make between the TECC—Trauma, Emergency & Critical Care—Program and the trauma strategic priority. Each of the five strategic priorities at Sunnybrook has been very carefully defined around a clear grouping of patients and associated research and education, so when we talk about the trauma strategic priority we are speaking about those that have serious, life-threatening injuries and serious burns—that is really a relatively small subset of all the patients that go through TECC Program. When we're

talking about traumatic injury and burns and what's made us internationally renowned, it's around that subset. Bringing the other areas in, emergency and critical care, it's a logical grouping, but it's more than the trauma strategic priority.

Did it go by in a flash, these last 10 years?

Yes, but as you get older, Stephanie, all time goes by in a flash. It went by very, very quickly. When you reflect on what's happened, you realize why it's taken 10 years, but when you think back to 2007, it doesn't seem that long ago.

There's a long view behind you. How do you feel looking back?

I feel that the organization is poised for a great future, and when you are leaving and passing the baton, that's what you would like to think is the case.

What are some of the challenges that remain?

Our biggest challenge is staying on focus at a time when there are so many demands on the total hospital. We don't have a turnstile. We can't control what comes in through the door. That relentless focus on making sure that we're there when it matters most for patients is going to require ongoing attention to controlling volumes of activity and making sure the resources are selectively directed to strategic areas.

If you come to Sunnybrook and you have an illness or injury that is diagnosed and requires scheduled care a few weeks or months down the road, it might not be provided here. We need to be there for those patients that really rely on Sunnybrook, when it matters most.

As chief coroner, what question did you get asked most often?

Probably the most common question was, 'why would you ever do that?' The answer is a pretty simple one. The coroner's system is all about advancing public safety. It's learning from individual deaths and the analysis of many deaths to make the province safer. It is very gratifying, because much of our policy, many of our safety initiatives, including in hospitals, have developed through the death investigation system. For me it was a natural segue from my interest in prevention, because much of it is about preventing injury and death.

What are some examples?

Many of the changes around the use of helmets and bicycle safety developed through coroners' investigations. Much of the safety around school buses and children, and travel back and forth to school came through coroners' investigations. Policy changes related to speed and design of motor vehicles came through death investigations. It's a long list.

The magazine's theme is that trauma could happen to you. What is the biggest misconception about trauma?

The biggest one is that it is an inevitable event and it was not likely preventable. Not all trauma is preventable—but most of it is. The other thing I think is a misconception is that when you have a serious injury there's very little that can be done. In fact, there are great treatment advances, right from resuscitation through to surgery and critical care through to rehab. The outcomes from serious injury can be excellent. I also think many people don't appreciate that in order to have that optimal outcome you need to be treated in a trauma centre.

Does the system know to get to a trauma centre?

Yes, and I will admit that I had something to do with that. If you're picked up by paramedics anywhere in the GTA, the fact that you are taken to the nearest appropriate hospital—which means if it's a serious injury to a trauma centre—is based on triage guidelines and protocols that were first developed years ago. There's also a provincial distribution of trauma cases, so if someone has a serious injury anywhere in this province, it is clear as to where they should be sent.

It seems obvious that you should take people to where the expertise is. Why wasn't that happening?

It wasn't always appreciated for some injuries that outcomes would be better in a trauma centre. If someone had a serious head injury, then it might have been recognized. If they had a combination of less serious injuries without a bad head injury, however, then it wasn't initially recognized that your outcome was that much better if you were sent to a trauma centre.

It also wasn't appreciated how important time to receiving life-saving care was, and that the time from injury until you get your emergent care is very important

with respect to both survival and functional outcome.

What needs to happen now?

An important next step will be to conduct more research focused on functional outcome, to make sure that it's about more than survival. It's not that we have not paid any attention to this. We just haven't paid as much attention as we could have. Total trauma care should be right through to that rehab and follow-up, and we are well poised at Sunnybrook to contribute.

What would you say to a young you who was beginning his career in trauma?

First of all, I would say that it's exciting work, it's gratifying work, and there are great opportunities to continue to improve care. I would recommend focusing a research career on follow-up care and functional outcome.

You are given a wonderful gift, untethered. You can do something toward fixing the health care system, and you can do something toward fixing the health research system. They're not in competition. You have equal funds for each, let's say \$100 million.

I'm concerned that excellent research opportunities are being lost because they are not being funded. One hundred million dollars would go very quickly if it weren't carefully allocated, so I would want to develop a clear investment strategy where you'd see the most impact. I'd have to think of exactly what that best allocation would be, because it's too great a gift to waste with a quick answer!

What I would love to see at Sunnybrook, though, is a sustainable research operation that is not dependent on a range of uncertain funding sources as is the case at present.

What next?

You know what? I don't know [laughs].

You've dedicated your life to health care in one form or another.

I have. You're right.

I can't imagine that would change.

I can't either.

Visit sunnybrook.ca/research for an extended version of this conversation.



You Only Get *One* Shot

AN AIR AMBULANCE lands at Sunnybrook with a trauma patient on board.

When it comes to transporting a severely injured patient to hospital, there are no second chances

By **BETTY ZOU**



The adage “time is of the essence” is true for many areas of medicine but it is arguably most germane in trauma. Trauma care often focuses on what happens when a patient arrives at the hospital—blood transfusions, CT scans, surgeries—but it actually begins much earlier. The clock starts ticking the moment a person is injured. How long it takes for paramedics to reach them, what procedures are done at the scene or en route, how quickly they can be transported to a hospital that is capable of dealing with their injuries—these are all prehospital factors that directly affect a patient’s outcome.

The past decade has seen a dramatic shift in prehospital trauma care. “We used to believe that many procedures ought to be done in critically injured patients right then and there,” says Dr. Richard Verbeek, an emergency physician and head of the base hospital program at Sunnybrook. This approach, referred to as “stay and play,” has paramedics perform procedures such as intubations and starting an IV line to stabilize the patient at the scene. “In the last 10 years, we’ve done a total about-face,” he says. “Now we say to paramedics, ‘we don’t want you to spend time doing these things at the scene. We want you to safely get them in the back of the ambulance and do all of your critical interventions on your way to the hospital.’” The switch from “stay and play” to “scoop and run” highlights the recognition that for severely injured patients, the earlier they arrive at a trauma centre, the better their outcomes.

Speed, however, is not the whole story. As one group of Sunnybrook researchers looks for ways to shorten the time from scene to hospital, yet another is trying to integrate potentially life-improving interventions into existing prehospital strategies. Their common goal: to give each patient the best chance of surviving and returning to his pre-injury life.

“There are a lot of moving parts to get patients to Sunnybrook in a timely fash-

ion,” says Dr. Brodie Nolan, a fifth-year emergency medicine resident at the University of Toronto. As one of only two adult Level 1 trauma centres in the Greater Toronto Area (St. Michael’s Hospital is the other), Sunnybrook receives some of the most severely injured patients from the farthest locations. “Because there are so many moving pieces, I think there are a lot of opportunities to find ways to either improve or expedite care,” says Nolan.

One area where he identified potential for improvement is aeromedical transport. In Ontario air ambulance services are provided by Ornge, a provincially run, nonprofit organization that operates the largest fleet of air and critical care land ambulances in Canada. Ornge helicopters pick up a patient directly from where he is injured, in what is known as a scene call, or from a non-trauma centre where the patient was initially brought.

Using trauma registry data from Sunnybrook and St. Michael’s Hospital, Nolan and his co-authors examined the records of 911 patients who were brought to Level 1 trauma centres by helicopter between 2012 and 2014. Between 62% and 74% of the transportation delays they identified were caused by modifiable factors, meaning that these wait times can be reduced or eliminated. Most setbacks occurred either at the scene or sending hospital. For example, in nearly one-quarter of the cases, air transport was forced to wait because the sending physician was doing a procedure that might not be critically important to survival. Doctors ordering imaging like CT scans was the cause of additional delays. Others happened en route—the weather was poor, a patient went into cardiac arrest—or at the receiving end; for example, the aircrew had to wait for a land crew to escort the patient from the helipad to the hospital, or for the trauma team to assemble.

The study, the first of its kind in Canada, also found that there was a group of patients for whom the wait time was extended because the initial air ambulance call while en route was cancelled and then dispatched again later. “It would

have been better for the patient and for the system if we had the opportunity to transport the patient when first called; with severely injured patients, there is often only one chance to do it right,” says study co-author Dr. Homer Tien, an associate scientist in the Trauma, Emergency & Critical Care (TECC) Research Program at Sunnybrook Research Institute (SRI) and trauma surgeon in the Tory Regional Trauma Centre. The registries didn’t have the level of detail to say why this happened, but it’s clearly an area for targeted improvement. “If we can figure out how to avoid those cancellations, particularly the ones that get called back later, I expect that there would be better outcomes and system savings,” says Tien.

Nolan points out that while their study was not designed to detect differences in outcomes caused by transportation delays, evidence from other published research shows that the earlier these patients can get to a trauma centre, the better their recoveries. “Bringing patients to the trauma centre as quickly and as efficiently as possible is usually in their best interests,” he says.

As chief medical officer for Ornge, Tien is particularly interested in how the province’s aeromedical resources can be used more effectively, given that only 7% of Ornge dispatches are for trauma scene calls. “The helicopters aren’t just for

trauma,” he says. “If we’re called away to a trauma scene—these calls are deemed to have the highest priority—that’s another case [somewhere else] that we can’t go to.” These other cases are the interfacility transfers that comprise most of Ornge’s air ambulance dispatches. In such a move a patient is relocated by land or air to a hospital that is better suited to deal with his medical needs.

Tien recently collaborated with Dr. Avery Nathens, director of the TECC Research Program at SRI, and Sunnybrook’s surgeon-in-chief and medical director of trauma, to assess the strategies hospitals use to transfer trauma patients from one facility to another. “We know that patients cared for at a trauma centre like Sunnybrook have a lower mortality rate and a greater return to their pre-injury level of function. They clearly have better outcomes than patients cared for in non-trauma centres,” says Nathens. “Patients are injured anywhere in the province—and not necessarily close to a trauma centre. How do we ensure access to care for those patients so they have a higher probability of good outcomes?”

Using a novel approach that combined the province’s trauma registry data with maps showing routes and distances, the researchers were able to follow 7,702 severely injured patients to their various destinations, including community hospitals and trauma centres. They also

probed which hospitals used an optimal transfer strategy by choosing a destination and mode of transport with the shortest overall travel time, and how consistent facilities were in selecting their strategies.

The researchers found that 30% of severely injured patients across the region were transported using an ideal strategy. Only 12% of sending hospitals transferred more than 90% of their trauma patients optimally. “We found that decisions about how best to transport a patient and their transport destination were more or less random,” says Nathens, who is a professor of surgery at U of T. “There are no guidelines that the emergency doctors have at their disposal to help them make decisions about who they should be calling, land versus air, and what would be the right hospital to send patients to.”

While their selections didn’t always lead to the shortest transfer times, hospitals were more consistent in which receiving trauma centre and mode of transportation they chose. Most transfers occurred between a community hospital and a specific trauma centre, suggesting there might be pre-existing relationships that can be capitalized upon to improve the quality of care and flow of patients through the system.

The results drove Nathens and Tien to develop and implement initiatives to improve the movement of severely injured patients from the referring hospital to a trauma centre. Much of their effort targets the regional trauma network, a hub-and-spoke model connecting trauma centres to community hospitals. “The trauma centre is viewed as the hub of a wheel, and the spokes are the different pathways by which the community hospitals refer their patients,” says Tien, who is also an associate professor in the department of surgery at U of T. “As the hub, we have a responsibility to meet with our referring centres and discuss ways of improving care in the system.”

For example, in the air ambulance study, Nolan and Tien found that a cause of delay was physicians ordering procedures like CT scans. These time-consuming steps are often unnecessary because the receiving centre will perform its own tests if needed. To address this and other concerns, Nathens started issuing information back to community hospitals to provide feedback on how long it took hospitals to send patients to



DR. BRODIE NOLAN helped lead a study quantifying why patient transport was delayed.



FIRST RESPONDERS transfer a patient from air ambulance to land ambulance at Sunnybrook. They play a critical role in conducting research to advance prehospital care.

trauma centres. The goal is to streamline the transfer process by minimizing the number of interventions done at the sending facility and choosing the fastest mode of transportation for each case.

In a second project, Nathens launched a partnership between the trauma and base hospital programs at Sunnybrook to provide feedback to paramedics. “We’ve started issuing individual letters to paramedics about patients they bring in to Sunnybrook,” says Verbeek. “The letter outlines what injuries were detected in the trauma unit here and the broad outcomes.” He notes that for most paramedics the details of trauma cases are often etched in their minds. Reports like these allow them to compare their perception of a patient’s injury to what was actually found and, Verbeek hopes, guide them to make a more informed decision about whether the next patient’s injuries are severe enough to warrant being taken to a trauma centre, or whether he can be well cared for at a community hospital.

First responders also play a vital role in conducting research to drive prehospital care forward. “Paramedics are doing an excellent job recruiting patients in the field under stressful and challenging situations,” says Dr. Barto Nascimento, an associate scientist in the TECC Research

Program at SRI. He is one of the investigators in a study looking at a novel way to improve long-term neurologic outcomes in patients with moderate-to-severe traumatic brain injury (TBI).

“Trauma is the number one killer in young people, but among those that die, what do they die from?” asks Nascimento. “Half of trauma deaths are related to TBI.” In patients with TBI, the two most urgent concerns are getting enough oxygen to the brain and controlling cerebral

bleeding. Tranexamic acid (TXA) helps to prevent further bleeding by maintaining the clots that form in damaged vessels to stop blood from leaking out. A previous in-hospital trial in trauma patients demonstrated that those who received TXA within the first hour after injury had a 13% lower mortality rate. “If you give TXA within three hours of injury, it’s beneficial,” says Nascimento. “If you give it after three hours, the hazard ratio goes in the other direction—that of harm.”

In the current randomized controlled trial Nascimento and his colleagues at St. Michael’s Hospital have partnered with regional paramedics to determine if administering TXA in a prehospital setting, either at the scene or en route to hospital, can help patients with TBI make a better recovery. They will look not only at the drug’s effect on survival, but also its impact on neurological functioning six months after injury. Results from the study are expected later this year.

“It could change the way we resuscitate these patients in the field and in hospital,” says Nascimento. “If it does, then it’s going to change protocols. That’s going to be huge.”

Research Funding

Nascimento: American Heart Association, Canadian Institutes of Health Research (CIHR), Defense Research and Development Canada, Heart and Stroke Foundation of Canada, National Heart, Lung and Blood Institute, and U.S. Army Medical Research and Material Command. Nathens: CIHR and the De Souza Chair in Trauma Research. Verbeek: CIHR, National Institutes of Health and Ontario Centres of Excellence Program.



Blood Not So Simple

Preventing trauma patients from bleeding out is one of the most challenging tasks a trauma team faces—but so is ensuring they don't get lethal blood clots

By **BETTY ZOU**

Ten minutes before our meeting, an email from Dr. Jeannie Callum pops up on my screen: “Multiple traumas right now. I won’t be able to talk—sorry.” Moments earlier a Code Omega call had been broadcast over the hospital’s intercom system. Someone was bleeding to death in the trauma bay, and Callum needed to be there.

After head injury, bleeding is the leading cause of death among trauma patients. “The estimate is that somewhere around half of [trauma] deaths are related to poor hemorrhage control,” says Callum, who is an associate scientist in the Trauma, Emergency & Critical Care (TECC) Research Program at Sunnybrook Research Institute (SRI) and Sunnybrook’s director of transfusion medicine. Doctors must work quickly to replenish the fluids that have been lost and staunch the flow of blood to prevent patients from bleeding out. “On Friday [during the Code Omega], in a period of four hours, we issued 300 components of blood for a single patient,” she recalls.

The injuries and blood transfusions they receive, paradoxically, make these patients more prone to developing blood

clots, or emboli, that could be lethal if they lodge in the lungs. “In the past, it was not uncommon for patients to die of a pulmonary embolism—where the clot dislodges from a vein in the leg and then prevents blood flow to the lung,” says Dr. Avery Nathens, director of the TECC Research Program at SRI and Sunnybrook’s surgeon-in-chief. “It’s always been a very challenging area because of balancing the risk between bleeding and clotting.”

Hemorrhage control and embolism prevention, then, are two sides of the same crimson coin. To give their patients the best chance of survival, Callum, Nathens and clinician-scientists at SRI are defining best practices that help physicians strike the right balance between these two seemingly opposite strategies.

In a test tube, blood looks like a

homogenous, thick, dark red liquid, but it is actually a mixture of four main components: red blood cells that deliver oxygen; white blood cells that fight infection; platelets that clot at the site of injury; and liquid plasma that carries everything through the body.

“When you lose blood, you lose everything,” says Dr. Barto Nascimento, an associate scientist in the TECC Research Program at SRI and a trauma hospitalist at Sunnybrook who specializes in the care of patients in hospital. “You’re bleeding red blood cells. You’re bleeding plasma, which has all the clotting factors, including platelets.” Before a transfusion, doctors typically rely on blood tests to determine the best ratio of blood components to mix together for each patient. Some may need more red blood cells; others, more plasma. The downside to





DR. JAMES BYRNE (left) and DR. AVERY NATHENS published definitive results on how to prevent pulmonary embolism after trauma.

this approach is that the tests take a long time. When a patient is bleeding out on the stretcher, each minute becomes as valuable as every drop of fluid dripping through an IV.

In an effort to start transfusions earlier, some doctors began using higher fixed ratios of blood products. The U.S. Army was the first to adopt so-called damage control resuscitation in its battlefield hospitals. Patients were automatically transfused with a balanced 1:1:1 ratio of plasma to platelets to red blood cells. Initial reports claimed that this strategy produced better outcomes than the traditional laboratory results-guided approach. These improvements were largely attributed to patients receiving a higher dose of plasma earlier in the equal ratio protocol.

"There was a problem with those studies," says Callum at our rescheduled meeting five days later. "It wasn't randomized. They had many patients who died before they had the opportunity to get plasma." Without proper

randomization, the sickest patients—those who succumbed within the hour it takes to prepare the plasma—were over-represented in the control group, thus skewing the results in favour of the 1:1:1 approach.

To address the controversy, Callum and the Sunnybrook team took part in the Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial, the first multicentre, randomized controlled trial (RCT) to examine the safety and effectiveness of the 1:1:1 protocol. The trial included 680 severely injured patients treated at 12 level I trauma centres in North America. The patients were randomly assigned to receive either a 1:1:1 mixture of plasma, platelets and red blood cells; or a 1:1:2 mixture, which is representative of what laboratory results typically recommend. There was no difference in the rate of death from all causes between the two groups at 24 hours and at 30 days after treatment. When the researchers drilled down into specific causes, however, they

found that significantly fewer patients in the 1:1:1 group died from blood loss at 24 hours. Further, the balanced protocol stemmed the flow of blood in more patients compared with the 1:1:2 strategy. The results were published in the *Journal of the American Medical Association* in 2015.

At hospitals and blood banks, the higher ratio of plasma given in the 1:1:1 protocol raised concerns about safety and resource utilization. "There's growing evidence of the severe complications of transfusing plasma," says Nascimento, who is an assistant professor in the department of surgery at U of T. These adverse effects include transfusion-related acute lung injury, a rare but dangerous condition where patients go into respiratory distress after receiving blood products.

Using a fixed 1:1:1 strategy also means that thawed, ready-to-go plasma needs to be available all the time. Patients arriving at the hospital in need of a transfusion are initially given universal group O blood and type AB plasma until lab results confirm their blood type. As Nascimento notes, however, only 4% of blood donors are type AB, which means that blood banks experience a chronic shortage of AB plasma. Thawed plasma that is not used within five days must be thrown out, raising the possibility that the 1:1:1 approach could drain an already precious resource. The PROPPR trial allayed both fears—it found no difference in the number of transfusion-related complications between the two groups at 30 days, and a secondary analysis showed that the 1:1:1 protocol could be implemented without excessive wastage of AB plasma.

Pumping patients full of blood can buy physicians more time but does not address the root causes of bleeding—damage to blood vessels and clotting factor deficiencies. The former can be remedied with surgery and time; the latter requires a recalibration of the so-called coagulation cascade, a chain of biological processes that is set off upon vascular injury. An essential player in these events is fibrinogen, a clotting factor protein that works with platelets to plug leaky vessels. "Nowadays, we believe that fibrinogen is key for clotting," says Nascimento. "Even if you don't have a lot of platelets, if you have enough fibrinogen, you can clot." In a patient that is hemorrhaging, though, it is the first

clotting factor to drop to dangerous levels, making its supplementation a critical part of the resuscitation strategy.

In Europe, patients who are bleeding out receive fibrinogen concentrate, a dried and purified form of the protein that is dissolved in water before being infused into the patient. Here in North America, patients with low levels of the clotting factor receive cryoprecipitate, a frozen blood product derived from donated plasma. Unlike fibrinogen concentrate, the golden honey-coloured cryoprecipitate contains a mixture of fibrinogen and other clotting factors. More concerning, however, is that cryoprecipitate is not treated to kill any viruses that might be present in the original donor plasma.

“European governments decided that cryoprecipitate was not safe because it’s not virally inactivated,” says Callum, who is also an assistant professor in the department of laboratory medicine and pathobiology at U of T. “That obviously makes physicians in North America, the U.K. and Australia uncomfortable, because we’re still using cryoprecipitate when other countries have switched to blood products that have been deemed safer.”

For fibrinogen concentrate to become the standard of care in North America, evidence is needed to show that it can be administered quickly and that it is as safe and effective, if not more so, than cryoprecipitate. To that end, Nascimento and Callum led the first RCT to examine the feasibility and efficacy of using fibrinogen concentrate in trauma resuscitation.

“We were able to demonstrate that we could deliver this intervention very quickly at the bedside of trauma patients,” says Nascimento. Almost all—96%—of patients randomized to the fibrinogen concentrate group received the product within an hour of admittance to the hospital. For each patient, eligibility determination and randomization took 30 minutes, while the preparation and administration of fibrinogen concentrate took 30 minutes or less—far shorter than the time required to thaw, mix and deliver a dose of cryoprecipitate. The results were published in the *British Journal of Anaesthesia* in December 2016.

While it’s too early to say if the study will change practice, Nascimento is optimistic. “The coagulation system behaves



A Code Omega activates Sunnybrook’s massive hemorrhage protocol when a patient is experiencing life-threatening blood loss.

Developed by Drs. Jeannie Callum and Barto Nascimento, the protocol ensures that consistent and evidence-based care is provided to all patients in need of large blood transfusions.



Code Omega is called when a patient needs at least 10 units of blood.

The blood bank starts making cases of blood to ensure that the mobile blood bank at the patient’s bedside is always one case ahead.



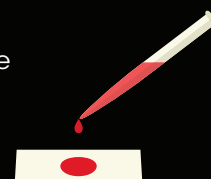
A special blanket called a Bair Hugger is used to keep the patient at 37°C. For every degree that body temperature drops, blood loss increases by 20%.

A pro-clotting drug called tranexamic acid is given to reduce the risk of death from blood loss.



A dedicated porter keeps track of where the patient is and runs blood products and test samples back and forth from the lab to the bedside.

Hourly blood testing is done to monitor the patient’s status. These tests are given the highest priority by the technicians in the blood lab.



The protocol is deactivated when the patient has stopped bleeding and no longer needs blood transfusions.

better and patients are able to clot faster and stronger if fibrinogen is given early on," he says. "We believe that this is an intervention that should be used routinely in the trauma clinic for patients." The success of the trial has pushed him to run a large, multicentre RCT with Canadian trauma centres to determine whether fibrinogen concentrate can improve coagulation in patients and therefore decrease the need for blood transfusions. Then there is the economic upside. "We believe fibrinogen concentrate is also a blood conservation strategy that can be used to save money," he says. He hopes that the data from this trial and similar studies being planned in Australia and the U.K. will persuade Canadian policymakers to license fibrinogen concentrate for use in trauma and shift practice toward a safer and more cost-effective product.

The blood transfusions and clotting factor supplementations that trauma patients receive prevent them from bleeding out; however, these life-saving measures also change the makeup of blood, such that it clots more easily. This trauma-induced hypercoagulopathy, along with vascular injury and abnormal blood flow due to immobility, put trauma patients squarely in the middle of Virchow's triad, a set of three risk factors that contribute to the formation of blood clots. "Every single trauma patient is at high risk for developing a blood clot," says Dr. James Byrne, a surgeon-scientist completing his PhD with Nathens. "Their prevention is a very important thing to address."

Venous thromboembolism occurs when a blood clot forms in the vein. When the blockage is in a deep vein, such as those in the leg, the condition is called deep vein thrombosis (DVT). Occasionally, clots can break loose from other sites in the body and travel to the lungs, leading to a pulmonary embolism. While DVT occurs more commonly in trauma patients, pulmonary embolisms pose a greater risk of death because they can block some or all of the blood flow to the lungs and deprive the body of oxygen.

In the mid 1990s, Sunnybrook physician Dr. William Geerts became one of the first to describe the incidence of DVT in patients with trauma. He later conducted the first large RCT comparing the effectiveness of two types of the blood-thinning drug heparin in preventing DVT. "His was really a pivotal trial," says Byrne. "He showed that low molecular weight heparin was associated with lower rates of DVT compared to unfractionated heparin." Geerts' seminal work led many hospitals, including Sunnybrook, to adopt low molecular weight heparin as the agent of choice for DVT prevention in trauma patients.

Despite the wealth of studies on how to avoid DVT, less is known about the best agent to thwart blockages in the lung, a more fatal complication. To address that gap, Byrne, Geerts and Nathens combed through data on more than 150,000 patients treated at 217 trauma centres enrolled in the American College of Surgeons Trauma Quality Improvement Program. "We wanted to

compare the rate of pulmonary embolism between patients who received low molecular weight versus unfractionated heparin," says Byrne. Unfractionated heparin is a blend of differently sized heparin molecules—some heavy, some light. In contrast, the low molecular weight agent is a purer concoction of lighter weight heparin molecules with greater potency and less risk of complications.

In their data set, low molecular weight heparin was given in 74% of cases. After matching for patient and hospital traits, the researchers found that the lower weight agent was associated with a significantly reduced rate of lung clots compared with unfractionated heparin. This pattern held true even when they compared patients who were given different prophylactic agents within the same hospital. "This study shows that the type of prophylaxis we use really does influence risk of pulmonary embolism," says Byrne. These results, published in the *Journal of Trauma and Acute Care Surgery* in November 2016, were the first to show a relationship between the type of prevention agent and rate of lung embolism in patients with major trauma.

"There's no question low molecular weight heparin is a better agent. All the RCTs have shown this," says Nathens, who is also a professor of surgery at U of T. Despite data supporting use of low molecular weight heparin in preventing DVT and now pulmonary embolism, roughly one-third of American hospitals still use unfractionated heparin because of its lower cost. The same is not true in

DR. WILLIAM GEERTS is a pioneer in the study of thromboembolism, or blood clots, and how to prevent them. His research challenged how blood clot risk was perceived and managed in trauma patients, which led to practice changes worldwide. Here, he reflects on how his research has helped shape trauma care.

What was the state of blood clot prevention in trauma when you started your work?

The idea was these patients have a high risk of bleeding, and that risk stays high over time. If this were the case, then you would be reluctant to give an anticoagulant to someone whose risk of a

blood clot was also high. Our hypothesis was that bleeding risk drops off. We thought that once the surgeon fixes the bleeding or it stops on its own, these patients should not be at high risk for bleeding. If we wait a little bit before we start anticoagulant prophylaxis in trauma patients, then we can prevent clots and not cause bleeding.

Why is the thromboembolism program at Sunnybrook unique?

Ever since the early 1990s [when the program started], we've seen every trauma patient that comes here. We give a bit of individualized prophylaxis to these patients depending on their risk of thrombosis and their risk of bleeding. That doesn't happen at

other hospitals—no other trauma unit in the world has a thrombosis service that sees all their patients.

What has been the impact of your work?

Before we started, every year there was between one and six trauma patients who died of a pulmonary embolism (PE) at Sunnybrook. In the last 10 years, to the best of my knowledge, there's been one person who died of PE and that's with greatly increased numbers of trauma patients per year. I think what we do is the gold standard. Our experience here has had a huge impact on trauma care around the world. **BZ**



The trauma team leader—TTL—is the conductor of the trauma bay. A physician with expertise in resuscitation, he or she coordinates the actions of the doctors and other specialist health professionals caring for a trauma patient. A TTL can be an emergency medicine doctor, surgeon or anesthesiologist. Here, trauma surgeon **Dr. BARTO NASCIMENTO** works as TTL at Sunnybrook, which has nine such specialists.

Canada, where nearly all hospitals use the lower weight agent. “I think this study pushes the evidence a little bit more to further favour low molecular weight heparin. It probably will lead to more hospitals converting,” says Nathens.

Nathens and Byrne are also hoping that their work will persuade physicians to change the way they inhibit the formation of blood clots in another vulnerable patient population—those with traumatic brain injury. “One of the big dilemmas in venous thromboembolism prophylaxis in trauma patients is what to do with patients that have severe brain injuries with intracranial hemorrhage,” says Byrne. The neurosurgeons who treat these patients are often reluctant to prescribe blood thinners like heparin for fear that it will worsen bleeding in the brain. “Any potential to increase the

amount of blood in the brain is risky,” says Nathens. “In patients with head injury, probably 30% to 40% receive no prophylaxis whatsoever.”

Recognizing the need for more evidence, the researchers looked at data from over 3,600 patients compiled through the American College of Surgeons Trauma Quality Improvement Program. The patients all had a severe traumatic brain injury and were given venous thromboembolism prophylaxis with either low molecular weight or unfractionated heparin. Forty-three per cent of patients received heparin early within 72 hours of hospitalization. The rates of both pulmonary embolism and DVT were nearly twofold lower in the early prophylaxis group than in those who received heparin after 72 hours. There was also no difference in the rate of late neurosurgical interventions or

in-hospital mortality between the two groups, indicating that early administration of blood thinners did not worsen intracranial bleeding in these patients.

The results, published in the *Journal of the American College of Surgeons* in October 2016, were well received. “People welcomed this data because there’s so little out there,” says Nathens. By undertaking studies like this, he and his colleagues are helping to define best practices that can turn the crimson tide in the patient’s favour.

Research Funding

Byrne: Canadian Institutes of Health Research (CIHR). Callum: Canadian Forces Health Services, CSL Behring, Defense Research and Development Canada (DRDC) and National Lung, Health and Blood Institute. Nascimento: DRDC. Nathens: CIHR and the De Souza Chair in Trauma Research.

Putting Humpty Back Together

Orthopaedic trauma surgeons repair badly broken bodies and are changing practice through their work

By ALISA KIM

Some people thrive on routine, so much so that they seek jobs where they do the same work, day in and day out. Dr. Richard Jenkinson is not one of those people. A researcher in the Holland Musculoskeletal Research Program at Sunnybrook Research Institute (SRI) and the head of orthopaedic trauma at Sunnybrook, Jenkinson says he enjoys being challenged by the unexpected. “I like the variety,” he says. “Almost everybody has a slightly different version of the same kind of fractures. I like putting pieces of the ‘puzzle’ together.”

As part of the trauma care team at Sunnybrook, which has the largest regional trauma centre in Canada, Jenkinson looks after people who have fractures of the pelvis, hip, leg, or arm. These injuries are usually due to motor vehicle crashes or falls from heights, and can be in addition to grave conditions like punctured organs and internal bleeding. He, along with colleagues from six centres across Canada, is conducting a randomized controlled trial comparing

approaches to managing a chest wall injury called flail chest. This occurs when a section of ribs is broken in multiple places and doesn’t move in synch with the rest of the rib cage. “Instead of expanding as it’s supposed to, to help pull air into the chest, that segment will sink in, which is very painful because it’s moving broken bones inappropriately,” says Jenkinson. He notes that about a handful of patients with flail chest are admitted to Sunnybrook every month.

The way physicians tend to rib fractures varies widely, from surgery to stabilize the ribs so that the chest wall moves as a unit, to, well, nothing. “In the past, rib fractures were one of those things where we’d say, ‘there’s nothing much we can do. The rib fractures will heal on their own,’” says Dr. Hans Kreder, an orthopaedic trauma surgeon and a scientist in the Holland Musculoskeletal Research Program at SRI. He is a co-investigator on the flail chest trial, which will compare these two approaches. Kreder notes that in letting fractures heal naturally, which some doctors are wont to do, sometimes the pain is so great that people cannot

breathe properly, and therefore are put on ventilators. This solution is far from ideal, however, since healing can take weeks. “Over the years we’ve learned pretty conclusively the longer that people are on a ventilator, the worse it is for them. There’s a higher chance of problems or even death if they’re on a ventilator longer than they absolutely have to be,” says Jenkinson.

In the trial, one-half of the study’s 200 patients are randomly assigned to non-operative treatment, and the other half to surgery. Surgical fixation involves putting fractured bones back into position and securing them with plates and screws. Patient recruitment is almost done; enrolment will likely be finished by the end of 2017. The main outcome of interest is how many days patients are on a ventilator during the first 28 days after injury. The researchers will also follow patients over 12 months to determine whether they return to normal function and if they report having chronic pain in a survey on their well-being. If the results show that having surgery leads to fewer days on a ventilator, then the research will provide

much-needed evidence in favour of the intervention and could change clinical practice in Canada and globally. “[The data] haven’t been analyzed yet, but our sense is that these patients may well benefit in terms of being able to get off the ventilator sooner, being able to breathe on their own faster and having less deformity,” says Kreder.

Another area of orthopaedic trauma care where the literature does not provide clear direction is in treatment of open fractures. These are fractures in which there is an open wound near the site of the broken bone. Usually the wound is caused by a piece of bone tearing through skin at the moment of injury.

Going back to around the mid-1900s, doctors thought it best to wash out open fractures and leave the wound exposed. “There was a general idea that maybe it wasn’t safe to close the wound because patients might get this terrible infection if you didn’t allow things to drain out,” says Jenkinson. He says they now know that the outside world, particularly hospitals, is rife with germs, but in keeping with tradition, some surgeons do not seal open fractures right away. This method requires patients to have multiple surgeries to clean the limb. “Some of the smaller hospitals are still coming back for second or third looks,” says Kreder.

Also contributing to differences in practice is the nature of treating serious injuries itself. “Trauma is difficult to standardize. No two things are exactly alike,” says Kreder. That said, he notes that at most large trauma centres, including Sunnybrook, doctors treat open fractures by removing dead or damaged tissue, called debridement, and binding the wound immediately. “We’ve been very aggressive about doing one decent debridement, closing the wound and not taking the patient back for a second look,” he says.

Sunnybrook’s guidelines for treating these injuries were informed by a study led by Jenkinson and Kreder that analyzed rates of deep infection in people who had open fractures. A deep infection, where the injured bone and deep tissue are infected, is a serious complication that delays recovery significantly. “When someone gets a bad infection they need multiple more surgeries, they’re in the hospital a lot longer and need intravenous antibiotics, not to mention having worse function. No one wants to have

“There’s a higher chance of problems or even death if they’re on a ventilator longer than they absolutely have to be.”



DR. RICHARD JENKINSON (right), head of orthopaedic trauma at Sunnybrook, is studying whether surgical stabilization of rib fractures improves people’s ability to breathe on their own.

an infection that will lay them up for an extra several months,” says Jenkinson.

The researchers looked at 146 open fractures treated at Sunnybrook from 2003 to 2007. One-half of the wounds were closed immediately after debridement; the other one-half were closed about two days later, during a second procedure. Matching the treatment groups for sex, age and type of fracture, the researchers found that those patients whose wounds were closed immediately were four times less likely to have a deep infection than patients whose wounds were closed a few days later. “Covering a wound early leads to fewer infections than if you cover it later. It seems to be more important for certain fractures

where there’s worse blood supply than for others,” says Kreder.

Doing research that has clinical impact is gratifying, says Jenkinson. “We have the backing to say that closing the wound initially is what should be done when the wound is closeable. And that’s basically changed that practice [at Sunnybrook], which is a lot better for patients.”

Jenkinson and Kreder’s research was supported by the Canadian Institutes of Health Research, Canadian Orthopaedic Trauma Society, Marvin Tile Orthopaedic Surgery Research Chair and Orthopaedic Trauma Association.

Mild Brain Injury? That's a Misnomer

Yes, there are degrees of severity when the brain is hurt, but concussions can have life-altering repercussions

By ALISA KIM



DR. LEO DA COSTA (right) is studying imaging techniques that detect subtle changes in the brains of people who have had a concussion, or mild traumatic brain injury.

The lethal effects of concussions sustained by former NHL player Eric Lindros weren't understood when he played for the Philadelphia Flyers in the 1990s. Yet, the once-dominant power forward was a different person psychologically after repeated hits on the ice. In a 2011 *Maclean's* article Lindros said, "You want to wake up in the morning, and you want to look at yourself and say, 'I've got the perfect engine to accomplish what I need to in this game tonight.' You are not going to look in the mirror and say, 'Boy, I'm depressed.'"

A concussion, or mild traumatic brain injury (TBI), is a blow to the head or

whiplash that disrupts normal brain function for less than 30 minutes. About 100,000 to 150,000 Canadians have a concussion annually, a number that is hard to ascertain because of under-reporting. Also complicating identification is that when people who've had a concussion seek care, there is usually no damage to the brain that's visible on CT or MRI scans, which can be misleading, says Dr. Leodante da Costa, a clinician-scientist in the Hurvitz Brain Sciences Research Program at Sunnybrook Research Institute (SRI). "'Mild' TBI is probably a misnomer. There is a percentage of [these patients]—not all—that has ongoing problems. Some of [the problems] are quite disabling," says da Costa, who as a neurosurgeon at Sunnybrook treats people

who've had a brain injury, including concussion. Thinking and memory problems, anxiety and depression are some common symptoms of post-concussive syndrome.

The disconnect between patients' normal brain scans and their symptoms led him and his colleagues to use an imaging technique called magnetoencephalography to map the brain's electrical activity after a concussion. This technique combines MRI with a test that measures electrical signals in the brain. In a study published in *NeuroImage: Clinical*, the researchers scanned the brains of young men who'd recently had a concussion, and those who had never had one. They compared brain activity patterns during a mental task. The average overall IQ scores of the two groups were comparable, but

the images of the group who'd had a brain injury were different. "There was a lot of 'noise'—more brain areas being activated to cope with the same processes than a normal volunteer. [Their brain activity] seems to be more disorganized and inefficient," says da Costa.

That brains of concussed people appear to be more taxed during mental activity than those of their healthy peers might help explain their cognitive difficulties. He notes the findings may lead researchers to investigate why after a TBI the brain works harder to cope with a task, which could account for loss of concentration, for example.

What if one reason why the brain works differently after a concussion is due to a problem with its blood vessels? To answer this question, da Costa looked at cerebrovascular reactivity, which is how well blood vessels in the brain dilate in response to increased carbon dioxide (CO₂). He used a machine that raises CO₂ intake on men who'd recently had a concussion and on healthy men. He compared blood vessel dilation in the brain in both groups and found poorer reactivity correlated with the degree of mental impairment in men with mild TBI.

The technique may one day be used to spot complications from TBI and determine when people can resume playing sports or working, neither of which can be gleaned from standard imaging. His aim is to help people who often fall through the cracks. "When you see someone who looks perfect but who says they can't work or go to school, or are having trouble at home because they can't cope with stress, that makes it very difficult for them to adapt because they need some support, but it doesn't look like they do," says da Costa.

Dr. Anthony Feinstein, an associate scientist in the Hurvitz Brain Sciences Research Program at SRI, founded the TBI clinic at Sunnybrook in part to address this gap. The clinic, which had close to 800 visits in 2016, offers rehabilitation and neuropsychiatric services to every person treated at Sunnybrook for a mild-to-moderate TBI. Feinstein, who is a neuropsychiatrist, says about 90% of all TBIs are mild to moderate, and that people with these injuries generally don't receive follow-up because there are so many of them.

He led a study comparing two screening tools for cognitive impairment: the standard Montreal Cognitive Assessment,

a paper-and-pencil exam, and a computerized battery. Both evaluate working memory, information-processing speed, and how well the brain organizes and acts on information. The computerized test, however, which scores how fast one can add a series of numbers correctly, for example, was more sensitive in detecting problems. It identified deficits in more than one-half of participants with TBI who were deemed intact using the Montreal Cognitive Assessment. "You have to be quite impaired to do badly on the Montreal assessment. Here, we're looking at subtle impairments, and we're picking them up with the computerized battery," says Feinstein.

The research, published in the *Journal of Neuropsychiatry and Clinical Neuroscience*, has had significant impact. The American Psychiatric Association flagged the study and sent it to its leadership. Requests for the electronic assessment from international colleagues led Feinstein to create a web page where the program can be downloaded by mental health professionals.

Feinstein's commitment to mending the battered mind also led him to study how post-traumatic stress disorder (PTSD) can develop in spite of memory loss after a traumatic injury. "How can you have PTSD if you can't remember the event that gave it to you? We wanted to explore that," says Feinstein. He published a study in the *Journal of Head Trauma Rehabilitation* that showed people who had amnesia for less than one hour following a TBI experienced flashbacks of the incident and avoided thinking about the trauma—symptoms of PTSD. Feinstein also found physical injuries from the event were associated with increased risk of PTSD because they served as reminders.

He hopes the research will help practitioners anticipate the needs of people who've had a TBI, especially so-called "mild" TBI. "I think trauma surgeons need to know that physical symptoms in the context of a traumatic event raises the likelihood of developing PTSD. If they understand that, they'd be more open to referring people to psychiatry or psychology. It's part of an education process."

Da Costa's research is supported by the GE-NFL Head Health Challenge. Feinstein's research is supported by the Canadian Institutes of Health Research, Multiple Sclerosis Society of Canada and Progressive MS Alliance.

Future Coma Care

A coma, from the Greek "koma," meaning "deep sleep," can be caused by a stroke, head trauma, diabetes, brain tumour or infection. People in a coma are given supportive care, but there are no treatments for recovery of consciousness, says Dr. Nir Lipsman, a scientist in the Hurvitz Brain Sciences Research Program at Sunnybrook Research Institute and a neurosurgeon at Sunnybrook. "It is such a complex illness," he says. "Many structures and circuits in the brain are implicated. Where does one target?"

He hopes to answer this question as he establishes a functional neurosurgery program at Sunnybrook, where he will study the use of technologies like focused ultrasound and deep brain stimulation. "Functional neurosurgeons deal with problems that can't necessarily be seen on an MRI or CT scan. The problem is dysfunction within different circuits in the brain," says Lipsman.

Unlike other brain operations where surgeons remove large parts of the skull to access the brain, functional neurosurgical techniques are less invasive. "By comparison, deep brain stimulation is minimally invasive. It involves two holes in the skull and insertion of an electrode. Focused ultrasound is entirely noninvasive," says Lipsman. These methods lend themselves to treatment of psychiatric and movement disorders precisely because doctors know which area of the brain is driving symptoms.

That's not so in a coma, which is why Lipsman is working with experts in traumatic brain injury and neuromodulation to design clinical studies using these technologies to revive those who are minimally conscious. This is a state in which a patient exhibits signs of awareness, like responding yes or no to a question. He will first need to determine where in the brain treatment should be targeted, and says there must be a sound rationale for any procedure. There is much work to be done, but he is optimistic: "It's not science fiction. It's going to happen, but it's critical it happens in a proper way."

Inside Trauma at Sunnybrook

We partnered with the dedicated trauma staff at Sunnybrook and the base hospital program to capture scenes from the front lines of care during many shifts, day and night, over several months. While they do not tell the full story, these photos do capture the remarkable effort that goes into treating a trauma patient at Sunnybrook, a legacy that has been built on excellence in care and excellence in research.

Photography by NATION WONG

Text by STEPHANIE ROBERTS





Facing page: 1. At the scene of a car crash, EMS assesses injuries. 2. In the land ambulance, the patient is monitored constantly. 3. On a different shift, EMS picks up a trauma patient transported via air ambulance to Sunnybrook. The Regional Base Hospital, part of Sunnybrook's Centre for Prehospital Medicine, is the largest in Canada. It leads globally in innovative practice and research.

This page: 1. Contact between EMS and the hospital ensures the team is prepared. 2. EMS uses a land ambulance to transport the patient from the hospital's airfield to the emergency department where the trauma bay is located. 3. As the team works on the patient in the trauma bay, EMS (right) gives an overview of the situation. 4. Trauma team leader (TTL) Dr. Luis da Luz, a surgeon, directs the team. 5. A caring moment.





This page: 1. The trauma team activates. At minimum, there is a TTL; two emergency department nurses; a respiratory therapist; an X-ray technician; and medical residents from anesthesia, general surgery and orthopaedic surgery, but there can be many more depending on the injuries. 2. Blood is needed for a transfusion. 3. Clothes are cut away for access. 4. Dr. Barto Nascimento (left), TTL and a trauma hospitalist, views a penetrating injury.

Facing page: 1. Fluids are given. 2. The team tries to resuscitate a patient. 3. Almost 75% of Sunnybrook's trauma patients are male, and 47% are aged 14 to 44 years. The average age is increasing. Today, 25% of patients are aged over 65 years. 4. Each team member has a dedicated function. 5. Medical imaging is integral; here, a chest X-ray.







This page: 1. While the trauma bay is pervaded by a sense of urgency, it is rarely chaotic. Everyone's movements are coordinated. 2. Some patients are relatively aware; others are unconscious. 3. Road traffic injuries, including motor vehicles, pedestrians, RVs and bicycles, account for 50% of all traumas. This is followed by falls at 31%; and stabbings, shootings and assaults at 17%. 4. TTL Dr. Avery Nathens, surgeon-in-chief and a trauma surgeon, oversees the care of a man with badly broken bones.

Facing page: 1. Giving fluids is a skilled task. The balance must be right. 2. Dr. Doreen Yee, an anesthesiologist and TTL, works to stabilize a patient. 3. Moments of levity are essential. 4. So, too, are empathy and compassion. It's clear that the staff in the trauma bay have an abundance of both.



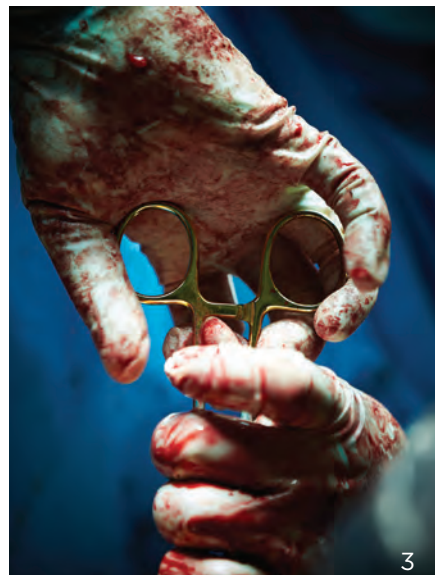




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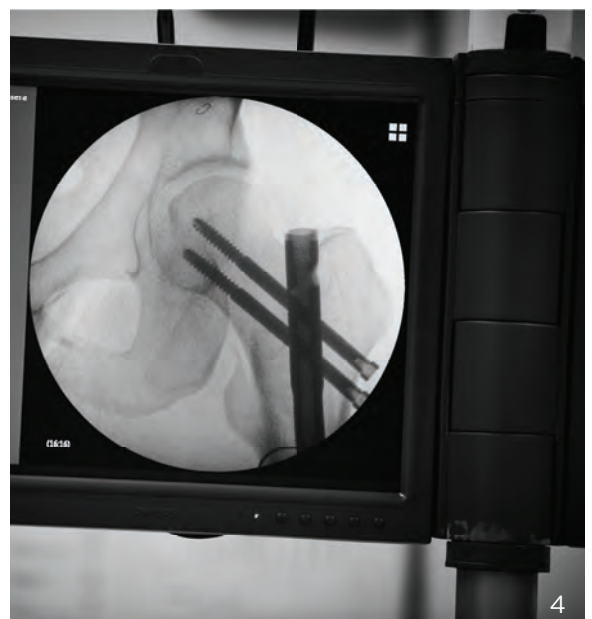
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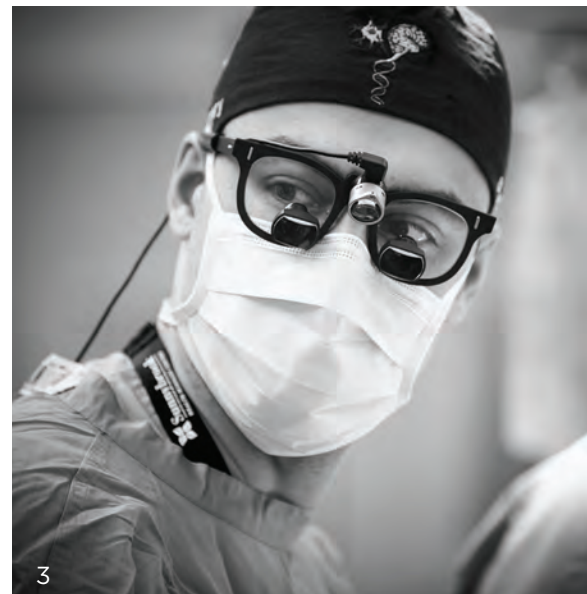
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Facing page: 1. It takes a team to position a patient for MRI. 2. Almost 20% of trauma patients go directly from the ER to the OR. 3. Many surgical specialties may care for a patient, including orthopaedic, plastic, neurosurgical, trauma, urologic and vascular, among others. The most common surgeries are for the pelvis and extremities. 4 & 5: Orthopaedic surgeons fix a complex fracture.

This page: 1. An orthopaedic trauma surgeon operates on a patient with grave leg injuries. 2. Nathens operates on a man with a stomach injury. 3. Neurosurgeons operate when there are brain or spine injuries. 4. Trauma patients often are moved to the trauma ward, where an interprofessional team provides expert care. Long term, the aim is to help patients regain as much physical and mental function as possible.



A FINE BALANCE

For patients vulnerable to developing sepsis while in hospital, how to balance the need for antibiotics against prudence in the face of increasing microbial resistance? Two docs take up the challenge

By ELENI KANAVAS

Bloodstream infections are a common and serious problem that affects 15% of critically ill patients and an estimated 50,000 Canadians per year. Bloodstream infections arise when bacteria leaks into the blood, arising from an infection elsewhere in the body. They can lead to sepsis, a life-threatening condition. For trauma patients, whose wounds and injuries leave them susceptible to infection, avoiding sepsis becomes yet another hurdle to clear. Invasive life-support devices commonly used in the intensive care unit (ICU), like mechanical ventilators to help with breathing, central venous lines to deliver medicine or nutrients, and urinary catheters also increase the risk of infection.

Sepsis occurs when chemicals released into the bloodstream to fight infection trigger an inflammatory response. This in turn can damage internal

know much about what to do after that, including how long to treat them,” says Dr. Nick Daneman, a scientist in the Trauma, Emergency & Critical Care (TECC) Research Program at Sunnybrook Research Institute (SRI) and an infectious disease specialist.

Over the past decade, clinical trials have found that shorter durations of antibiotic treatment are as effective as longer courses for syndromes caused by intra-abdominal infections, and those of the lung, skin, soft tissue and urinary tract. In one case, a landmark trial involving critically ill patients with ventilator-associated pneumonia found no differences in death and relapse rates among 402 patients who received antibiotics for eight versus 15 days.

Yet there are no studies that examine what duration of antibiotics is required for bloodstream infections. To address this void, Daneman and Dr. Rob Fowler, a senior scientist in the TECC Research Program at SRI and critical care doctor

says the drugs can cause 5% to 10% of patients to experience side effects that include rash, gastrointestinal upset and diarrhea, kidney failure, hearing loss, dizziness and other adverse reactions. A more serious complication is *C. difficile*. The rate of this infection, which can cause diarrhea and life-threatening inflammation of the colon, has doubled in the past decade. About 5% of ICU patients with *C. difficile* will die.

“There is a global public health threat from antimicrobial resistance driven by antibiotic overuse and misuse in the context of a lack of new drug development,” says Daneman, who is a co-principal investigator of the BALANCE research program. “We need to work out how to best use available drugs to maximize benefits for patients, while minimizing harms for the patients themselves, neighbouring patients and future patients.”

Before launching the BALANCE trial, the researchers had to confirm the gaps

Audits show that 30% to 50% of antibiotic use in the ICU is inappropriate.

organs, leading to multiorgan failure and critical illness or death. It’s therefore essential that doctors tending to trauma patients who have been moved into the ICU after initial resuscitation find ways to prevent, diagnose and treat the onset of bloodstream infections. Although antibiotic therapy is crucial for survival, it does not come without risks. A fundamental and unanswered question for many infections is that no one knows how long is best to treat.

“For patients who have sepsis, especially septic shock from infection, getting them on the right antibiotic early improves their outcomes. But we don’t

at Sunnybrook, established a research program called BALANCE, which stands for Bacteremia Antibiotic Length Actually Needed for Clinical Effectiveness. The BALANCE program was developed to ask whether seven days of antibiotic therapy is as good as 14 days for preventing death among critically ill patients with bloodstream infections.

There’s another issue that is top of mind for Daneman and Fowler in doing this research. Audits show that 30% to 50% of antibiotic use in the ICU is inappropriate, says Daneman. Excessive antimicrobial use has led to rapidly rising antibiotic resistance rates. Daneman

in evidence and validate the urgent need to compare the length of antibiotic therapy for clinical effectiveness in patients with sepsis. The research team led five studies over five years leading to the current one. They did a systematic review of the medical literature, a national survey of Canadian infectious disease and critical care physicians, a single-centre retrospective study, a multicentre observational study and the BALANCE pilot randomized controlled trial. Findings from these studies laid the foundation for the BALANCE trial, a five-year, \$2-million trial funded by the Canadian Institutes of Health Research. The analy-



PATIENTS in the intensive care or critical care unit receive around-the-clock specialized care. Even so, they are at higher risk of bloodstream infections, which in turn can lead to sepsis. Researchers are striving to make sure they get the decision about how long to treat patients with antibiotics just right.

ses were done with support from the Canadian Critical Care Trials Group (CCCTG), an organization comprised of more than 350 clinicians and researchers who work in ICUs across the country.

“We were able to determine the BALANCE pilot study was feasible in terms of protocol adherence, site participation and interest,” says Asgar Rishu, project manager of the BALANCE research program. Patients in the BALANCE pilot study were from 15 hospital ICUs admitted for reasons deemed medical, surgical, traumatic, neurological or relating to burns. Sixty per cent of the infections were acquired in the community.

All 115 patients from the pilot study are enrolled in the current trial, which will recruit 3,600 patients. The BALANCE trial is randomizing critically ill patients with a bloodstream infection into two treatment arms—seven versus 14 days of antibiotics. The survival rate for each group will be measured at 90 days from the date bacteria is first detected in the bloodstream. Sunnybrook is leading the trial with 58 patients, and 206 patients are enrolled across all sites. Canada-wide, another 20 sites in Alberta, British Columbia, Manitoba, Nova Scotia, Ontario and Quebec are partici-

pating. The team has also engaged collaborators from Australia, New Zealand, Saudi Arabia, Switzerland, Brazil, France, Israel and the United Kingdom.

“More and more people are realizing these large paradigm-setting trials need to be conducted across multiple countries,” says Daneman. “One, it helps with speed of recruitment to get to your target sample size. Two, it improves the generalizability of your findings when you can see if they are robust across different health care systems with different micro-organisms, different treatment practices.”

Fowler agrees. He says determining the differences among patients in a variety of countries might show a change in resistance patterns and rates of *C. difficile*. “We see certain antibiotic resistance patterns here that are worrisome, but then you go to other parts of the world and you realize this is an enormous problem. There are lots of places that are already in pretty tough shape with respect to not having drugs to treat infections.”

Knowledge gained from the BALANCE trial could lead to benefits for hospitalized patients and the health care system, as well as broad global reductions in antimicrobial use. “If shorter du-

ration is as effective as longer duration therapy for these severe infections in the critically ill, findings may also reasonably be generalizable to non-bacteremic and non-critically ill populations, and hence could generate large reductions in hospital-wide antimicrobial consumption and complications,” says Rishu. As Daneman notes, uptake could be quick, “because it doesn’t require any new technology, doesn’t require any new expensive drugs, just a different way of deploying medications that we’re already using.”

“This research matters because it’s so fundamental to what we do as infectious disease specialists and antibiotic prescribers,” says Daneman. “We have to choose a drug and decide how long to use it for. We need to learn how to get those simple treatment decisions right, so we can maximize outcomes for the patients we are treating.”

In addition to changing practice and informing guidelines, the results could promote savings. “We anticipate that the costs associated just with the drugs would by definition be halved if you’re treating for seven versus 14 days,” says Fowler. “Then the associated side effects of *C. difficile* resistance or other organ in-

jury that you might occasionally deal with antibiotics should favour fewer costs for the short-treatment arm." He explains that unnecessarily prolonged antibiotic therapy contributes to an increase in ICU hospital stay by two to three weeks and excess costs to the health care system that range from \$25,000 to \$40,000.

Antibiotic resistance doesn't happen overnight, Fowler says. "It's the kind of thing that happens somewhat slowly, and like boiling water, you're never really sure that you're in trouble until you get beyond a certain point, and this is sort of one that has been boiling for quite a while."

The BALANCE Research Program is funded by the AFP Innovation Fund at Sunnybrook through the Ontario Ministry of Health and Long-Term Care, Canadian Institutes of Health Research, Heart and Stroke Foundation, and the Physicians' Services Foundation Incorporated.



DR. ROB FOWLER (left) and DR. NICK DANEMAN are leading studies to identify the right duration of antibiotics for patients in the ICU, who are at increased risk of getting sepsis.

Intensive Care Needs Intensive Interaction

Clear and effective communication among health care professionals is paramount. New research shows there is a constant need to improve how medical teams interact and talk to each other to ensure quality care.

Few studies have looked at ways to improve communication between surgeons and critical care teams working in the intensive care unit (ICU) of a trauma centre. That prompted researchers at Sunnybrook Research Institute (SRI) to examine the factors that lead to crossed wires between these teams day to day or when tough decisions need to be made.

"Understanding communication between clinicians is about understanding the relationships between clinicians, and their critical impact on the function of teams and on patient safety," says Dr. Barbara Haas, a trauma surgeon, intensivist and health services researcher at SRI. "Without understanding the social context in which people work, we can't help them improve how they do it."

Haas works with Dr. Lesley Gotlib Conn, a medical anthropologist at SRI. They led a study to probe the social and cultural context of surgical ICU work, and its implications for how

surgery and intensive care teams interact to deliver care. Their findings highlight the challenges physicians face when it comes to delimiting their expertise, negotiating patient ownership and sharing decisional authority.

"We used anthropological research methods to explore communication as a proxy for team relationships and the culture of interspecialty care," says Gotlib Conn. She conducted 50 hours of observations on routine patient care activity and 43 interviews with hospital staff.

Results showed that ensuring quality team-to-team communication is complex and, although it can be difficult, it can be improved. The researchers found surgeons and intensivists were eager to communicate more, but there were few facilitating structures. For example, the most valued form of communication was face-to-face conversation, but there were no routines to ensure this happened daily.

Although checklists and pagers are often used to facilitate communication, these tools can also impede it. "We have a pager system that should help people keep in touch. In reality, it often seems to lead to delays, 'broken telephone' and a lot of frustration,"

says Haas. They also found that leaving notes by the bedside and changing the way staff record information did not help solve the challenges.

Surgeons, intensivists and nurses described episodes of poor communication, such as disputes over feeding or keeping a patient on a ventilator, as distressing—not only to them, but also to patients and the whole care team. Good communication was related to feelings of respect, trust and being valued. These findings reflect the need to foster an interspecialty team culture characterized by collaboration, equalized power relationships and mutual goals, says Gotlib Conn.

"It's critical that all doctors be on the same page," agrees Haas. As the trauma education lead, she encourages physicians, residents and interdisciplinary specialists to learn together and engage socially. "That way, when you're meeting at three o'clock in the morning at the side of a patient's bed, you know each other's name, strengths and weaknesses," says Haas. "We need to explore interventions that focus on building relationships and trust between teams that collaborate in taking care of complex patients." **EK**

Identifying Sepsis

Dr. Gordon Rubenfeld says when people die after major trauma they usually do so in the first 48 hours. For those people who die from trauma outside that window, however, their deaths often are not from the trauma itself but from complications such as sepsis or the acute respiratory distress syndrome (ARDS). In some cases, a combination of both illnesses presents in patients.

Rubenfeld, senior scientist in the Evaluative Clinical Sciences platform at Sunnybrook Research Institute and chief of the Trauma, Emergency & Critical Care Program at Sunnybrook, calls sepsis a “silent killer.” He defines it as “the body’s response to an infection” and says it occurs when the immune system engaged to fight off the infection becomes harmful. The complications can range in severity from a mild fever to multiple organ failure, also called multiple organ dysfunction, a life-threatening condition that affects at least two organs.

Occurring independently or in association with sepsis, ARDS is inflammation of the lungs. It is commonly caused by infection—usually pneumonia—but can also occur from trauma. Rubenfeld says when ARDS is a result of trauma it’s particularly problematic because patients are often put on ventilators, which places them at greater risk of infection.

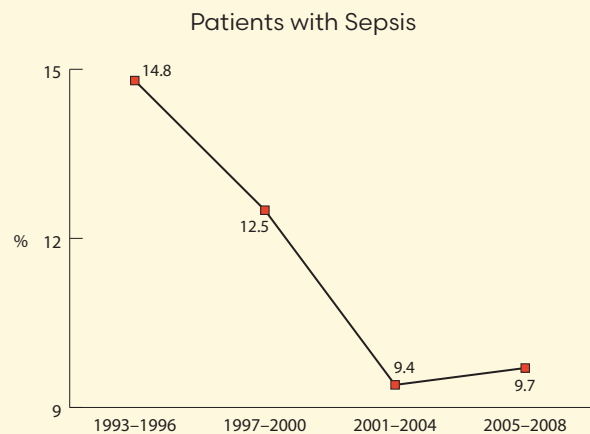
Treating these potentially fatal complications is a matter of recognition and early management. For sepsis, rapidly administering antibiotics and intravenous fluids to offset dehydration is crucial, Rubenfeld says. If this seems straightforward, it’s because it is. Recognition and early management “were the mainstays of therapy 30 years ago, and they’re still the mainstays of therapy,” he says. Although the mortality rate associated with sepsis is declining, the challenge of accurately identifying the illness in a timely manner remains.

To tackle the obstacle, Rubenfeld, who is helping to write evidence-based guidelines for how to manage patients with sepsis, worked with a dozen other scientists to create qSOFA (quick sepsis related organ failure assessment). The tool is essentially a calculator that enables doctors and nurses to recognize patients with sepsis, or those soon to develop it, at an early stage. Low blood pressure, fast respiratory rate and altered mental status are three criteria that are evaluated to produce a score. This result is used to determine which patients need further testing and extra attention.

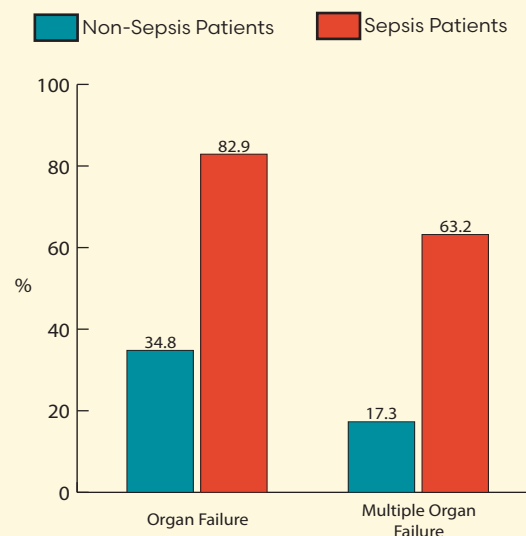
Rubenfeld says when treating ARDS the approach is, as with many aspects of modern trauma care, “less is more.” He adds that turning the dial down on ventilators and focusing on bedside teamwork and skill rather than high-tech treatments has been a significant advance. “Instead of taking a great big breath and putting it into an inflamed lung, we’ve learned to ventilate the lung gently,” he says. This change in therapy, paired with the idea of laying patients on their fronts and not their backs to open the base of the lung, has led to a decline in mortality rates.

While lower mortality rates among sepsis and ARDS patients is positive, Rubenfeld points to the aging population as a reason to increase awareness around the illnesses. An older population translates to an older trauma patient population, and aged trauma patients are at a greater risk of developing sepsis and ARDS complications. “The older population has made everything we’ve talked about in terms of sepsis and ARDS that much more important,” Rubenfeld says. **MP**

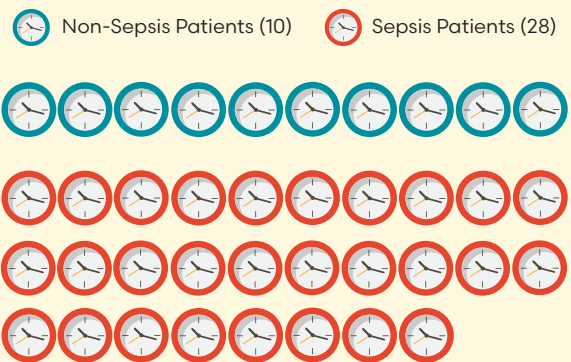
Sepsis After Multiple Trauma*



Patients With Organ Failure and Multiple Organ Failure



Mean Intensive Care Unit Length of Stay (Days)



*Wafaisade et al. *Crit Care Med.* 2011;39(4):621-628.

All POCUS, No HOCUS

Bedside imaging, also known as point-of-care ultrasound (POCUS), is emerging as a powerful, evidence-based tool in the ER

By ALISA KIM



DR. JORDAN CHENKIN (far right) and his colleagues in Sunnybrook's trauma bay use point-of-care ultrasound to help expedite diagnoses.

The case is one of the more memorable ones of Dr. Jordan Chenkin's career: a 38-year-old woman who seemed well walked into Sunnybrook's emergency department (ED), where Chenkin is a staff physician, complaining of blurry vision.

Her breathing was normal, and there were no problems with her brain or heart. She was triaged to the "purple zone," designated for minor conditions. The only abnormality was high blood pressure, common in anxious patients. Chenkin tried examining her eyes with a

lens that shines light into the back of the eye, but couldn't get a good view. Determined to get to the bottom of her troubles, he pulled out one of the department's portable ultrasound units. Gliding the probe gently over each closed eye, he had his answer: retinal detachment.

It is rare for both retinas to detach simultaneously. A common cause of the condition is preeclampsia, a complication of pregnancy that's characterized by high blood pressure. Chenkin ordered a blood test, which, to the patient's utter shock, revealed she was pregnant. He knew that to relieve her high blood

pressure she would need to give birth immediately; delaying it would increase her risk of stroke, seizure or coma. But first he had to determine how far along in the pregnancy she was. With the same ultrasound unit, he measured the fetus' head circumference, which is used to calculate gestational age. At 26 weeks, the baby, if delivered, had a relatively good chance of survival.

"She went from walking into the minor area of the ED to going to the operating room for an emergency C-section within a few hours," says Chenkin, a researcher in the Trauma, Emergency & Critical Care Research Program at Sunnybrook

Research Institute (SRI). Following up, Chenkin learned that his patient's vision had returned to normal after delivery and she and her baby were well.

The case, which he reported in the *Canadian Journal of Emergency Medicine*, highlights the utility of point-of-care ultrasound, sometimes abbreviated as POCUS. This is imaging done by doctors on their patients, which is why it is also called bedside ultrasound. The technology is gaining traction in the ED; as Chenkin notes, there is a difference between bedside ultrasound and that done by radiologists. Emergency doctors use ultrasound during physical exams to troubleshoot ailments efficiently, whereas radiologists use it to perform comprehensive exams. "This is a tool that can help you make better decisions more quickly. It helps free up some of that burden of the long differential diagnosis we face with a lot of patients. You can cross a lot of things off that list and make it a little bit easier to manage high volumes of patients," says Chenkin.

Trauma care was the catalyst for bedside ultrasound in the ED, says Chenkin, because it can immediately show life-threatening conditions like fluid around the heart and internal bleeding. "The core applications are designed for the sickest of the sick patients. You have a patient who's dying in front of you, and before ultrasound you had to go with your best guess as to what was going on, but now you can actually rule things in and out pretty quickly," he says. Point-of-care ultrasound also expedites diagnosis of other grave conditions like abdominal aortic aneurysm, which is a bulge in the main vessel that carries blood from the heart to the rest of the body, and ectopic pregnancy, where the fetus grows outside the uterus.

The popularity of bedside ultrasound is growing, but there are two issues: a knowledge gap regarding best use of the technology, and challenges in training doctors in how to use it. Chenkin is addressing these concerns through research and his role as a clinician-educator. In addition to teaching emergency doctors across Canada how to do ultrasound imaging, he is also director of point-of-care ultrasound for the division of emergency medicine at the University of Toronto.

He led a study showing web-based learning is effective in teaching doctors to use ultrasound to check for proper placement of a breathing tube. This

work, which was published in *Critical Ultrasound Journal* in 2015, found that emergency physicians could learn this skill by watching a web tutorial and studying sample cases online. After just two practice attempts, all 66 doctors in the study could consistently identify when a breathing tube was placed correctly in the trachea, as opposed to the esophagus, an error that can cause brain damage due to lack of oxygen.

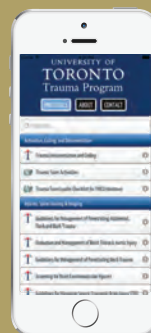
He is also looking at bedside ultrasound to screen people in the ED who've had a "mini stroke," which is a temporary obstruction of blood flow to the brain. He will study how well ultrasound detects blockages in the carotid arteries, major blood vessels that supply blood to the brain, neck and face, to identify people at high risk of stroke.

Chenkin says that because Sunnybrook is a teaching hospital, he is able to consult with experts from every specialty. The hospital is building on the strength of its human resources by creating state-of-the-art infrastructure to optimize care of complex patients who might benefit from point-of-care imaging technologies. Plans are underway to construct a hybrid operating room (OR) equipped with advanced imaging and surgical devices. The facility will have the standard features of an OR, along with a CT scanner and angiography equipment used in cardiac procedures. Having diagnostic and surgical tools in one space will save time and reduce the risk of further injury to patients by not having to move them to different parts of the hospital. Expediting treatment could make all the difference, as it did for Chenkin's patient whose pregnancy had caused potentially fatally high blood pressure. Moreover, specialists of different stripes will be able to work side by side; a trauma surgeon could work on stopping abdominal bleeding while a neurosurgeon operates on the brain.

"It will be a game changer," says Dr. Avery Nathens, director of the Trauma, Emergency & Critical Care Research Program at SRI and surgeon-in-chief at Sunnybrook. "Surgeons will be able to perform complex image-guided procedures with the ability to switch to open surgery, if needed; similarly, surgical procedures will be more precise with the availability of imaging. A hybrid OR means we will never have to compromise in our approach."

NOT SURE HOW TO TREAT A TRAUMA PATIENT?

Naturally there's an app for that.



The University of Toronto Trauma Protocols app was created by Dr. Avery Nathens and U of T trauma residents.

The app provides best practice guidelines on how to treat traumatic injuries.

The guidelines were developed with input from trauma team leaders at U of T and are updated regularly.



22,095

downloads since 2013

Before the app, "residents would not necessarily do the right thing," says Nathens. This would often lead to extra procedures and tests, which would in turn cause delays in treatment. "The app puts everybody on the same page," he says.

150+

number of countries where the app has been downloaded

five countries with the most downloads:



This was just going to be a U of T thing, but now I go to meetings and people are talking about this app. I'm amazed at how popular it is.

Dr. Avery Nathens

Chenkin's research was supported by the Canadian Association of Emergency Physicians, Canadian Institutes of Health Research, Sunnybrook and the University of Toronto.



UNDAUNTED: JOURNEY THROUGH TRAUMA

One man's story of survival and healing

By BETTY ZOU

NAMIR MOHAMMED HUSSAIN was severely hurt in a motorcycle crash. He was rushed to Sunnybrook, where his injuries sparked a massive activation of the trauma team.

Photo: Nation Wong

Don't move, don't move. They're collecting parts of your leg."

Sitting in his bed at Sunnybrook's trauma ward, Namir Mohammed Hussain thinks back and laughs at the absurdity of those words etched forever in his mind. It is Oct. 13, 2016, nearly one month after the crash that almost claimed his leg. "I don't remember anything [about the crash]," says Mohammed Hussain. "As soon as I hit the tire, I went completely blank." What he does remember are the events leading up to the crash and being brought to Sunnybrook's Tory Regional Trauma Centre. Despite the gaps in his memory, Mohammed Hussain says he is sure of one thing: had he been taken to another hospital that day, his outcome would have been very different.

On Sept. 16, 2016, Mohammed Hussain was riding his motorcycle on the highway when another driver merged into his lane and pushed him into the path of the eight-wheeler truck next to him. The 30-year-old father of two was travelling back from a meeting at the Loblaws office in Brampton to the Weston Foods headquarters in Etobicoke, where he worked as a software engineer. "When I woke up, I saw that I was on the road and lying down," he says. "There was a guy standing next to me, and I asked him if he could help me take my leg out." The passerby told him not to move and that they were collecting pieces of his leg. "That was so scary. I was awake, but I

couldn't feel the left side of my body." His left leg had been run over by the truck and was pinned underneath it. Paramedics rushed to free Mohammed Hussain and bring him to Sunnybrook, one of only two Level 1 adult trauma centres in the Greater Toronto Area. He arrived with chest injuries, broken ribs, a fractured shoulder and a mangled left leg. "The primary focus was his leg, which was almost amputated," says Dr. Avery Nathens, director of the Trauma, Emergency & Critical Care Research Program at Sunnybrook Research Institute (SRI) and the trauma surgeon who oversaw Mohammed Hussain's care. "Sometimes the easiest thing to do is to amputate, but our surgeons felt they should use all the tools in their armamentarium to try to save it."

That decision fell to Dr. Diane Nam, the orthopaedic surgeon on call when Mohammed Hussain was brought in. "I was concerned about the blood supply at first because the left foot was cold and white," she says. As she and her team stabilized the leg by carefully realigning the limb and removing dead tissue, warmth and colour returned to the foot—encouraging signs that the limb could be saved. As Nathens pointed out, however, retaining an arm or a leg can be harder for the patient than amputating one. Orthopaedic surgeons like Nam can repair bone,

but for the limb to survive and be functional, they rely on the expertise of vascular surgeons to fix damaged blood vessels and plastic surgeons to mend nerves and obtain soft tissue coverage. "Limb salvage of a mangled extremity is our primary goal whenever possible," says Nam, who is also an associate scientist in the Holland Musculoskeletal Research Program at SRI. "But we can't reattach a limb if there's no blood supply, and the timing to restore this after injury is critical."

The injuries he sustained to his chest and lungs meant that Mohammed Hussain had to be sedated and put on a ventilator to breathe for him for two days. During that time, an orthopaedic team led by Dr. Hans Kreder spent six hours trying to find a live nerve in his damaged leg before piecing the broken bits of bone back together. Soon after, a plastic surgery team led by Dr. Joan Lipa grafted skin from his right leg into the wound defects on his left leg. "When I woke up, I saw that my leg was pretty much tied with big rods and big screws on top," says Mohammed Hussain. All told, he had three operations on his leg and one to fix his fractured shoulder.

Speaking from his hospital bed, Mohammed Hussain reflects on how lucky he is that he did not sustain any injuries to his head or internal organs, and how fortunate he is to have been brought to



DR. LARRY ROBINSON wrote the book on trauma rehabilitation.

Sunnybrook. He is grateful for the care he received here, but cannot wait to be home with his four-year-old daughter and 18-month-old son. “I miss my kids,” he says. “My daughter came, and she was like, ‘why are you not coming home? Why

are you in the hospital?’”

“He has his leg, which is a big positive,” says Nathens. “He may not have had his leg if he had been at a community hospital. Saving an extremity requires a team of experts in orthopaedic trauma, plastic

surgery and vascular surgery. There is good evidence to suggest that teams like we have at Sunnybrook have a tremendous impact on restoring function after injury.”

Improving function in trauma patients is also the focus of Dr. Larry Robinson’s work. Robinson is the director of the St. John’s Rehab Research Program at SRI and program chief for rehabilitation services at Sunnybrook. He is leading a project looking at whether early consultations with physical medicine and rehabilitation (PM&R) specialists—also known as physiatrists—can shorten hospital stay and improve outcomes for trauma patients. The idea is based on a model of care in many U.S. trauma centres where such patients are seen by a physiatrist within days of admission. Early and regular care by a physiatrist helps identify potential complications and develop plans for discharge.

“Patients tend to fall between the cracks as they transition from the acute care hospital to rehab, and from inpatient to outpatient rehab,” says Robinson, who is himself a physiatrist. “This project is a way to overcome that. It will enhance the continuity of care and improve the patient experience as they traverse the continuum of care from injury to rehab.” The study will also contribute to the sparse literature on the impact of early PM&R

PAIN in the Trauma Bay

As an emergency department nurse for 11 years Thao Sindall has seen firsthand how inadequate early pain management can affect patients’ outcomes and perception of care in the trauma room. “Pain not being managed initially does lead to difficulties managing it later,” she says. Those challenges include longer hospital stays and chronic pain after discharge. Patients reported less satisfaction with their care because their pain wasn’t managed well while in the trauma room.

Sindall wanted to address the issues she saw through a quality improvement project of trauma patients during their initial stages of care. To carry out this work, she received the Sunnybrook Trauma Health Professions Innovation Fellowship, a partnership between the hospital’s Trauma, Emergency & Critical Care program and Practice-Based Research and Innovation.

“Because [Sunnybrook] is a teaching

hospital and we have a lot of team members rotating through our doors, there isn’t a lot of consistency when it comes to the way we manage pain,” she says. “I really wanted to work on standardization so we can provide the best care to our patients.”

Patients arriving in the trauma bay do so in physical discomfort. “They’ve been hit by a car; they’ve fallen off a balcony. Oftentimes when we assess them, there are severe levels of pain,” says Sindall. Often, more urgent concerns—an obstructed airway or uncontrollable bleeding—push pain management to the bottom of the list of priorities. Sindall’s preliminary research found that the average time between arrival in the trauma room and first administration of pain medication was 19 minutes. “I’m looking to improve the time that we provide the first dose of analgesics,” she says. Her goal is to reduce that time by 30%. She believes

that this would not only improve outcomes, but also patients’ satisfaction with their care.

In the first part of her project, Sindall interviewed nurses and trauma team members who work in the emergency department to understand their perception of pain management practices and to identify gaps in care. “Nobody thinks it’s their role to ask about pain,” she says. “So either everybody does it or nobody does it.” For the second part of her project, she is using the data she collected to develop and implement a strategy to enhance pain management in the trauma bay.

Specifically, Sindall is exploring the use of visual cues to prompt nurses to include pain in their routine assessments. She hopes that by empowering her nursing colleagues to assume responsibility for the initial assessment of pain, patients’ suffering will be alleviated earlier and more effectively. **BZ**

The Trauma Journey at Sunnybrook*

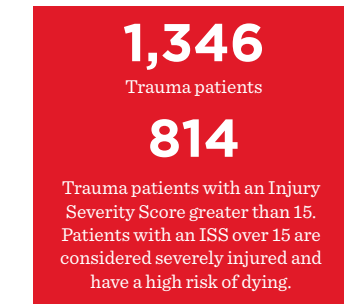
Sunnybrook has the largest trauma centre in Canada. (It was also the first.) The Tory Regional Trauma Centre is a Level 1 Centre—it cares for the most severely injured patients from across Ontario. The journey of a trauma patient like Namir Mohammed Hussain only begins upon arrival in the trauma bay. It is a long path to functional recovery.



consultations on acute care and rehabilitation outcomes. In a review of papers published between 1946 and 2015, Robinson and PM&R resident Dr. Alan Tam found only four that described the effects of a PM&R intervention on how patients fared. Although limited in number, these studies show benefits for patients receiving an early physiatry consult in areas such as post-injury pain and return-to-work rate. If successful, then Robinson's study will strengthen the case for including physiatrists as part of the acute care team, and underscore their role in helping patients make the fullest recovery possible.

To that end, the researchers have started collecting data on trauma patients who were seen by a physiatrist within three days of admission and those who were not. The researchers will be following these patients for one year. Preliminary results suggest that involvement by a physiatrist significantly reduces a patient's stay in acute care from 25 days to 16 days. Fewer days in acute care means these patients begin rehab sooner, although it is too early to tell what effect, if any, this will have on a patient's ability to return to his pre-injury life. "Acute care has done a really good job of saving people's lives," says Robinson, who is also a professor of medicine at the University of Toronto. "Our goal is to do a better job of giving patients their lives back."

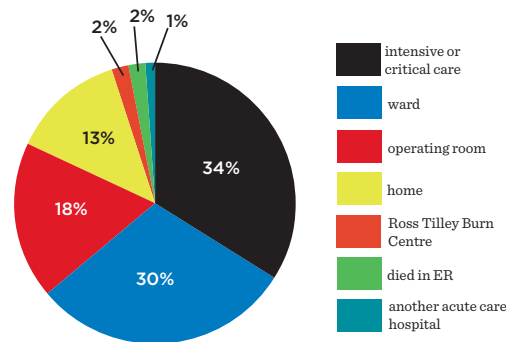
After seven-and-a-half weeks recovering in Sunnybrook's trauma ward—his discharge was delayed when he developed a rash in response to the antibiotics he was taking—Mohammed Hussain began the next stage of his journey toward getting his life back. He arrived at Sunny-



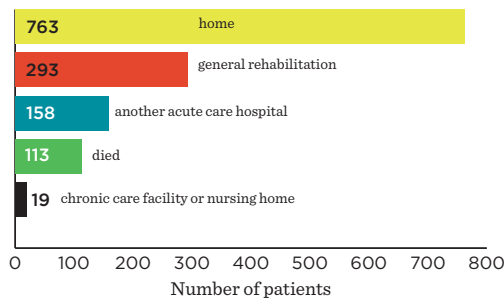
How did patients get here?



Destination of patients after assessment in the ER



Outcome after discharge



*Source: Data are from 2013–2014, as noted in the Sunnybrook Trauma Strategic Plan.

OR Visits by Patients

at least 1: 618
2: 172
more than 2: 80
16: 1

15.4 days

Average length of stay

46%

Trauma patients who stayed in hospital seven or fewer days

13%

Trauma patients who stayed in hospital 29 or more days

brook's St. John's Rehab Hospital in a wheelchair and left 15 days later walking on his own with a cane.

Today, he is back at home with his family and trying to return to his old life. He goes to physiotherapy three days a week for his shoulder, which is now strong enough to lift a bag and has enough range of motion to swing his arm. Months after his surgeries, Mohammed Hussain continues to experience pain in his leg. "There's always pain but I believe that I have to live with it," he says. "It's not going to end in a day or two." While the medications his doctors prescribed help to alleviate his discomfort, they can also interfere with the bone-healing process

and could delay his recovery. Despite the setbacks—his first skin graft did not take so he underwent a second procedure in early January 2017—and the sometimes frustratingly slow progress, Mohammed Hussain remains optimistic and grateful. "I'm really thankful that I'm alive and that I'm getting back to my normal life," he says. "It's a long journey, but I'm lucky that I have my family and glad that I made it to here."

Robinson's research is funded by an AFP Innovation Fund from the Ontario Ministry of Health and Long-Term Care. He holds the John and Sally Eaton Chair in Rehabilitation Science.



A Matter of Perspective

Study illuminates surprising source of collisions

By ELENI KANAVAS

Safe driving relies on good eyesight and an accurate visual sense of your surroundings. Weather conditions also affect our judgment in measuring distance and speed. Despite drivers knowing to take extra caution in inclement weather, they may be unaware of the potential danger while driving on a sunny day.

Researchers at Sunnybrook Research Institute (SRI) recently led a study that shows bright sunlight may create an optical illusion that can lead to driver error. A visual phenomenon known as aerial perspective can cause drivers to misjudge the distance of objects on the road, which in turn can result in a serious collision. Aerial perspective renders the depth or distance of close objects as crisp and clear, and farther objects as faded, hazy or dim. An example of this illusion can be seen in Leonardo da Vinci's portrait of the Mona Lisa. He was one of the first painters to use the technique of aerial perspective. The Mona Lisa's face

is painted in crisp, clear light to appear close, and the mountains in the background are shown in dim, dusky light to appear distant. The same artistic methods are used for rendering 3-D effects in modern movies.

"Bright sunlight is a natural factor in aerial perspective because it increases the contrast, resolution and luminosity of surrounding landscapes," says Dr. Don Redelmeier, director of Evaluative Clinical Sciences at SRI and a clinician-scientist in the Trauma, Emergency & Critical Care Research Program. He holds the Canada Research Chair in Medical Decision Sciences, a field that explores how people formulate judgments and make decisions, and has applied much of his expertise to studies that aim to prevent road traffic crashes.

"What we think goes on under bright sunlight, under the most benign conditions possible, is that all of the terrain in the distance seems unduly close," he says about travel velocity. "The approach and speed of surrounding landscapes seems unduly slow [for drivers]. For example,

the mountain in the distance appears crisp, so the driver thinks he or she can get to it in about five seconds. As a consequence of that, people adjust by accelerating faster. That is why we think the underlying 'optical illusion' can lead to a higher risk of a life-threatening motor vehicle incident under bright sunny conditions."

Motor vehicle collisions are a major cause of disability and death in people of all ages. An estimated 1.3 million people die per year from a car crash—an amount that is on par with worldwide deaths from lung cancer. Injuries from motor vehicle crashes can range from mild to severe. They include concussion, bleeding in the brain, broken bones, pelvic fractures, obstructed airway, spinal cord compression and abdominal organ damage. Often, they lead to long-term complications. Most life-threatening crashes are caused by too much speed, says Redelmeier, who is also a scientist at the Institute for Clinical Evaluative Sciences and a professor of medicine at the University of Toronto. "With modern

"It can be entirely avoidable."

automobiles, you can't tell the difference between going 60 miles per hour versus 60 kilometres per hour, even though your risk of a life-threatening crash has gone up by more than 100%," he says. "[The drive] is just so comfortable and smooth that unless you deliberately look at the speedometer your eyes will trick you every time, especially under bright sunny conditions."

Redelmeier and colleagues collected data on car crashes involving patients hospitalized at Sunnybrook, Canada's largest trauma centre, from Jan. 1, 1995 to Dec. 31, 2014. The study aimed to evaluate the prevailing weather conditions at the time and place of the crash compared to weather at the same hour and location on days that served as "controls" one week earlier and one week later.

Researchers found bright sunlight was present in about one-third of daytime

collisions. Most patients were injured during daylight hours, and bright sunlight was the most common weather condition at the time and place of the crash. A total of 11,539 patients were injured during the study period through 11,095 separate life-threatening crashes. The average patient was a middle-aged male driver with no major illness in whom alcohol was not detected. The results, published in *Medicine*, showed the risk of a life-threatening collision was 16% higher during bright sunlight than during "normal" weather such as a cloudy or overcast day, and excluding rainy, snowy or stormy conditions. "Sixteen per cent is a very big number," says Redelmeier. "For perspective, your air bag is only going to make a 10% difference in the chance of a life-threatening injury, or snow tires in the winter make only about a 5% difference."

Although the weather and traffic conditions cannot be changed, driving behaviour can reduce the risk of a crash. "It can be entirely avoidable. You just have to adjust your attitude slightly and slow down. Be a little bit more aware," says Redelmeier. Public education and traffic enforcement can also help reinforce standard safety practices, like respecting speed limits, minimizing distractions, using a seatbelt, and not drinking and driving. His take home message: "Drive carefully so you don't ruin a beautiful day with an ugly crash."

Redelmeier's research was supported by the BrightFocus Foundation, Canadian Institutes of Health Research and Comprehensive Research Experience for Medical Students at the University of Toronto.

Road Safety in Ontario By the Numbers*



licensed drivers

9.6 million



reported collisions

188,999

people killed in motor vehicle collisions

518

Seatbelt safety



One in every six vehicle occupants killed was not wearing a seatbelt

Senior drivers and young drivers

100%

Increase in deaths among senior drivers aged 80 and older from 2012 to 2013

72%

Decrease in average fatality rate for drivers aged 16 to 19 years since introduction of graduated licensing

Situations with the highest fatalities



drinking and driving: **110**



inattentive driving: **81**



high-speed driving: **72**

Vulnerable road users



pedestrian deaths: **100**



bicycling deaths: **25**

*Source: Ontario Road Safety Annual Report 2013

Restraining Natural Killer Cells

Landmark discovery brings researchers closer to vanquishing virus

By ALISA KIM

Photography by NATION WONG

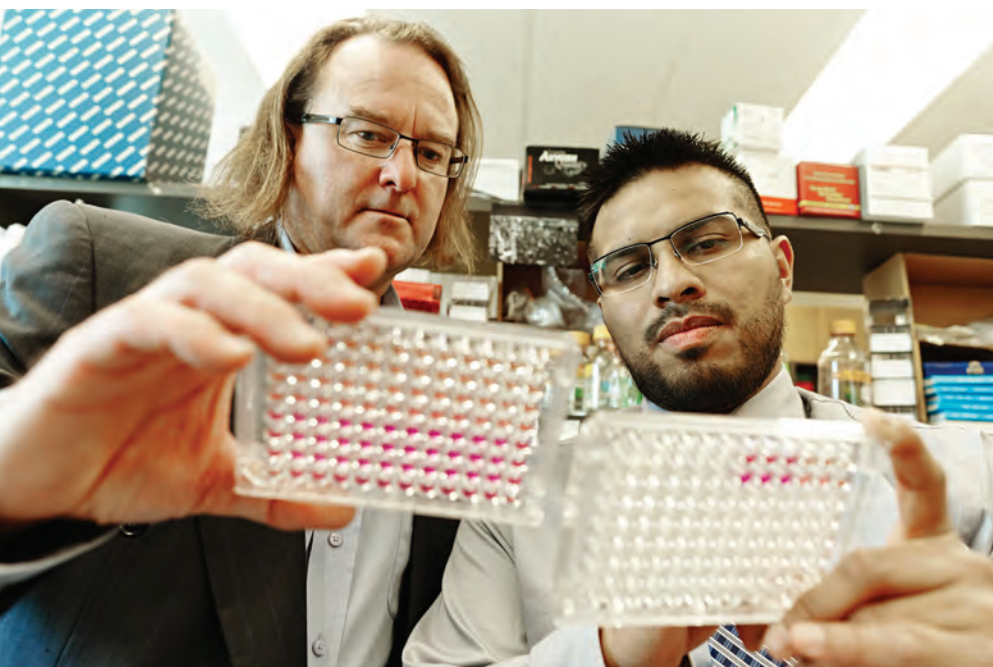
A GROUP OF doctors published a report in 1982 in the *Journal of Pediatrics* about a family ravaged by disease. The parents were healthy, but three of their four children had severe infections from the Epstein-Barr virus, a common virus that is part of the herpesvirus family. Many people carry it, but do not get sick; those who do typically have flu-like symptoms that resolve on their own. In this family, however, three siblings suffered dire bouts of mononucleosis, which was caused by the virus and required them to be hospitalized. Two of them died. Curiously, the fourth sibling had a mild case of mononucleosis but recovered fully. Blood tests enabled doctors to pinpoint the cause of devastation in the family's sickest members: natural killer cell deficiency.

Natural killer (NK) cells are a type of white blood cell that fights cancer and infection. Their job is to patrol the body and help protect it from disease. To prevent an attack on healthy cells, however, NK cells are normally restrained. When needed, they spring into action by two mechanisms. One occurs when stimulatory receptors on NK cells bind to stimulatory molecules on tumour cells or cells infected with a virus. This interaction, called "induced-self" recognition, tells the NK cell to release a lethal protein that tells diseased cells to die. The other, which leads to the same outcome, is called "missing-self" recognition: NK cells sense a loss of self-recognition proteins on their surface that is caused by pathogens. The loss of these proteins acts as a signal that something foreign has invaded and unleashes the NK cells' offensive, which is how the body fights infection.

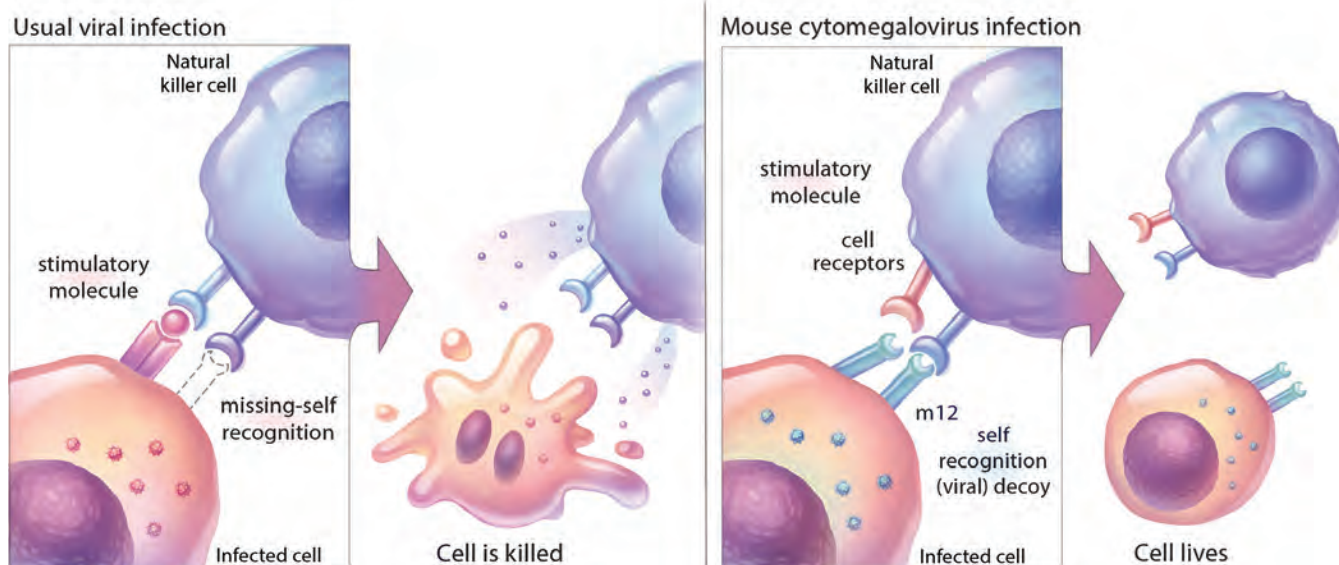
Over time, viruses have found ways to

bypass the body's defences. This phenomenon has captured the attention of Dr. James Carlyle, a senior scientist at Sunnybrook Research Institute (SRI), whose study of mouse cytomegalovirus (CMV), a herpesvirus, highlights this struggle between host and pathogen. "We're using the virus as a tool to tell us what's important about the immune system. Since the virus has co-evolved with the host over millennia to find a way to get around the immune system, it's telling us aspects about immunity we previously didn't understand," says Carlyle, who is also an associate professor of immunology at the University of Toronto.

He and Dr. Oscar Aguilar, who did his PhD training in Carlyle's lab, have discovered a viral molecule that inhibits NK cells. This molecule, aptly called an immunoevasin, is also the first protein known to bind to the NK1.1 receptor, which belongs to the NKR-P1 family of



Dr. JAMES CARLYLE (left), a senior scientist at Sunnybrook Research Institute, and his former PhD student, Dr. OSCAR AGUILAR, discovered a viral molecule that inhibits natural killer cells.



Left to right: A natural killer (NK) cell identifies a virally infected cell as “foreign” and kills it. Scientists at Sunnybrook Research Institute have discovered, however, that cells infected with a mouse herpesvirus evade death by making a protein (m12) that restrains the NK cell.

NK cell receptors. The NK1.1 receptor was first discovered 40 years ago as the prototypical NK cell marker. Since then, researchers have tried to find any molecule that interacts with NK1.1, but have come up empty—until now. “We’ve identified a number of other receptor-ligand interactions, but this is the first ligand identified for the very first NK cell receptor discovered,” says Aguilar.

They published a study in *Cell* that shows m12, a viral protein identified in mouse CMV, binds to NK1.1 and other NKR-P1 receptors. This family of NK cell receptors has three stimulatory receptors that activate NK cells (including NK1.1) and two inhibitory receptors, which bind to inhibitory “self” molecules on target cells and shut down NK cells.

When the researchers studied cells infected with mouse CMV, they observed decreases in a self-recognition protein called Clr-b—a “missing-self” response that is akin to triggering an alarm. Interestingly, they also saw a strong signal from one of the inhibitory receptors, NKR-P1B, which rapidly shuts the alarm off.

By using different strains of the virus and analyzing interactions between molecules, Aguilar was able to identify m12 as the “decoy” molecule that was blocking NK cells by binding to the NKR-P1B inhibitory receptor. He and Carlyle could appreciate the strength of this interaction thanks to the work of collaborators

in Australia, who generated an X-ray crystal structure showing the binding of the two molecules. “It’s a very neat interaction,” says Aguilar, making a fist and wrapping his other hand around it. “The m12 [protein] binds like my hand on top, with a palm and polar-charged fingers that tightly bind to the NKR-P1B receptor. That is why our collaborators coined this a ‘polar claw’ mechanism.”

Aguilar, the study’s first author, notes the m12 protein is an example of how herpesviruses are suited to sidestepping the immune system, owing in part to their large genomes. “Some other viruses like HIV have much smaller [genomes] and don’t have the luxury of encoding a molecule like this,” he says.

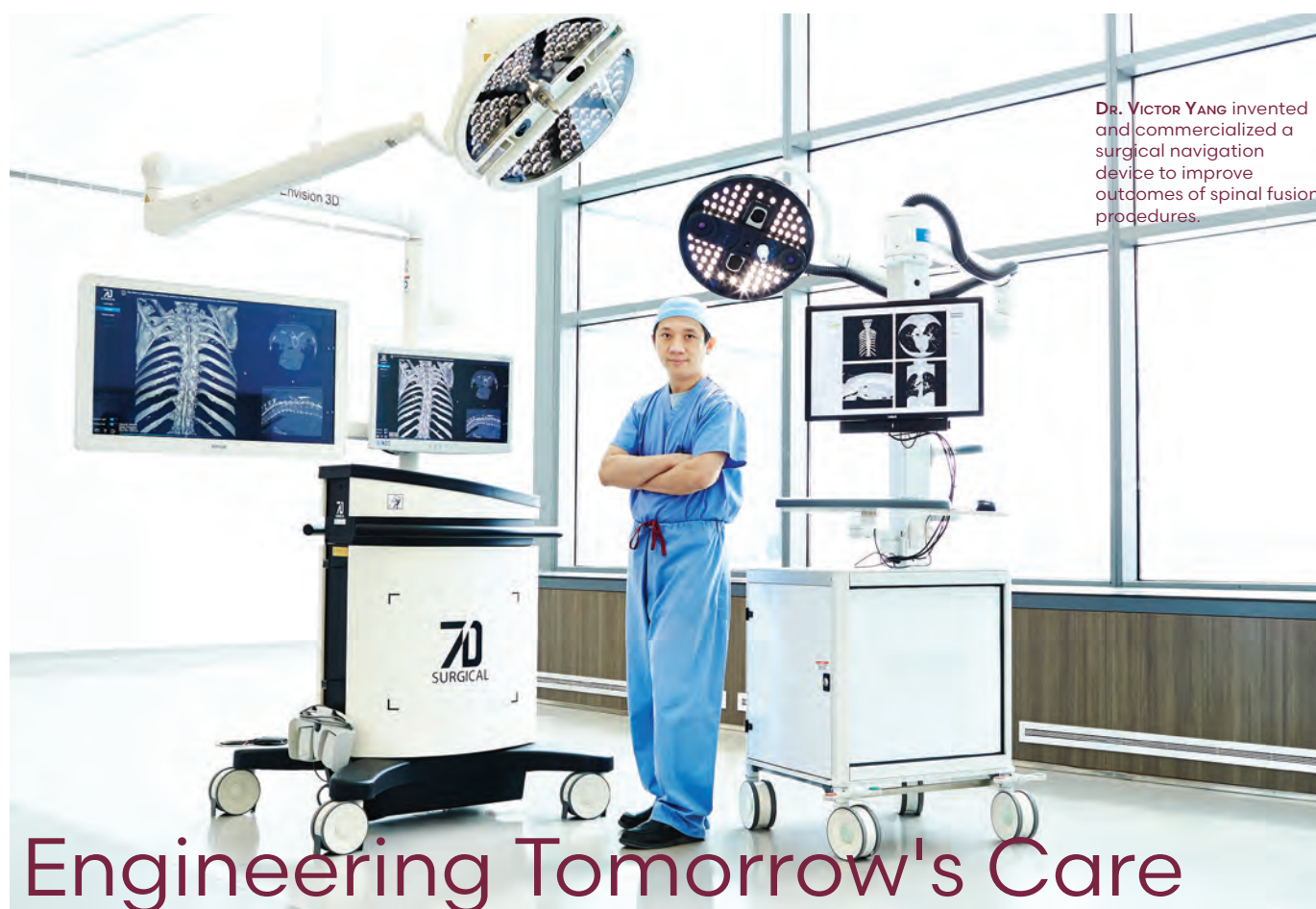
What also surprised the researchers is that the m12 protein weakly interacted with two stimulatory receptors, called NKR-P1A and NKR-P1C (NK1.1). The results suggest an unfolding struggle, one where each organism is adapting to the other’s devices. “The weak stimulatory interaction really demonstrates the host and pathogen evolution,” says Aguilar. “The reason why the inhibitory interaction is the stronger response is because the virus is evolving to make sure it inhibits NK cells, whereas the host is trying to evolve mechanisms that also recognize this decoy—but I think the virus is winning, at least with respect to this [study].”

The next step is to study CMV and the

NKR-P1A receptor in humans to see if there is a corresponding human viral decoy protein. About 70% of adults carry CMV, but most show no symptoms because a healthy immune system prevents the virus from causing illness. In people whose immune systems are compromised, however, like newborns, those with AIDS, or people who are undergoing chemotherapy or organ transplantation, CMV can cause serious damage, for example, to the liver, lung, eyes and nervous system.

If such a decoy is found in human CMV, then it could serve as a therapeutic target. Researchers could develop an antibody to the protein, which would give people with an immune deficiency like the one in the family profiled above, a fighting chance. “Using the monoclonal antibody to the viral protein [would] turn the immune response against the virus. Where [the virus] is trying to evade immunity, now it’s expressing a ‘flag’ that tells the immune system that the cell is infected and would result in more rapid clearance,” says Carlyle.

Aguilar was funded by the Natural Sciences and Engineering Research Council of Canada. Carlyle was funded by the Burroughs Wellcome Fund, Canada Foundation for Innovation, Canadian Institutes of Health Research, and Ontario Ministry of Research, Innovation and Science.



DR. VICTOR YANG invented and commercialized a surgical navigation device to improve outcomes of spinal fusion procedures.

Engineering Tomorrow's Care

Two architects of medicine are reconstructing how surgery is done

By ALISA KIM

Photography by NATION WONG

IN EARLY 2015, a 30-year-old woman came to see Dr. Oleh Antonyshyn, a craniofacial surgeon at Sunnybrook, because of a skull tumour. To take it out, Antonyshyn and neurosurgeon colleague Dr. Mahmood Fazl would have to remove the front of her skull, leaving a huge structural void that would be nearly impossible to fix.

They were not worried. Antonyshyn, who is a scientist at Sunnybrook Research Institute (SRI), and his partners, Dr. James Mainprize and Glenn Edwards, have developed and commercialized technology that shapes clinically approved materials into a custom-fitting implant for skull and facial

reconstruction. In June of that year, Antonyshyn and Fazl operated on the young woman, who was otherwise healthy. While Fazl removed the tumour, Antonyshyn used the system to craft implants to rebuild the bony ridge of her eyebrow and restore her forehead right there in the operating room.

So, how is she now? “Excellent,” he says, happily.

In 2009, Antonyshyn, Mainprize and Edwards filed a patent for the system and formed a startup called Calavera Surgical Design. Using MRI or CT scans Mainprize makes a computer model of the patient’s skull; Edwards exports the model to a 3-D printer in the plastic surgery department, which churns out a cast of the patient’s skull. In the operating

room, the surgeon presses material like titanium or polyethylene into the cast to form the implant. He then places the implant into the defect—which could be bone that has eroded from cancer or a broken eye socket, for example—and presto, a perfect fit.

“Surgeons are pretty specific about the material they like to use to reconstruct certain things,” says Antonyshyn, during a meeting in his cozy, taupe-coloured office in Sunnybrook’s plastic surgery department. On his computer, he pulls up a model of a skull that had a chunk removed to relieve swelling in the brain. “The forming tool can press whichever type of implant material [surgeons] have. We give them the ability to develop that three-dimensional shape specific for that

patient that is perfect restoration of anatomy,” he says. The technology is a boon to Dr. Victor Yang, a neurosurgeon at Sunnybrook and a senior scientist at SRI, who recalls having to shape implants by hand while a patient is lying on the operating table. “That’s not the right thing to be doing in the 21st century,” says Yang.

A manually sculpted implant, because it’s not a perfect match, can be disfiguring and in rare cases lead to more surgery. Antonyshyn once had to fix a deformity resulting from inaccurately shaped eye socket implants that caused a patient to have double vision. The labour-intensive practice also increases operative time, adding cost and risking complications. With Calavera’s technology, meanwhile, one can fashion a bespoke prosthetic in minutes.

If a surgeon decides instead to buy a prefabricated custom craniofacial implant, then the bill can be a whopping \$10,000 to \$20,000, depending on its size and complexity. Such costs can be prohibitive, which drove Antonyshyn to create a workaround. Most people with facial fractures in Ontario are referred to Sunnybrook as a leading trauma centre. Due to budget constraints that face every hospital in the province, he was told he’d need to get approval before ordering a preformed implant. “We get about 20 cases per year, and the high cost of prefabricated implants restricted the number of cases which could be completed to two to four per year. We couldn’t keep up,” Antonyshyn says. Now, instead of purchasing a premade implant, he and colleagues like Yang can make a custom one for a fraction of the cost—about \$3,500.

The system has been used in 57 cases at Sunnybrook since 2013; 17 more have been ordered and are pending. “It’s the go-to technology. If there’s a defect, [the surgeons] don’t even look anywhere else. They just ask us to provide the implant,” says Antonyshyn. He also has used the system on humanitarian missions to the Ukraine, where he has performed reconstructive surgery on people who have suffered horrific injuries due to that country’s civil war. To facilitate this, Calavera created a library of average skulls for situations in which an implant must be made at the point of care.

The next step is to send the technology for beta testing to other hospitals, including St. Michael’s and Toronto Western.

Based on the feedback, the team will make refinements before taking the system to market.

Like Antonyshyn, Yang was also inspired to develop a device to improve outcomes and make the job of surgeons easier. He has engineered a computer-assisted navigation system that efficiently guides spinal fusion, where surgeons insert screws and rods to stabilize the backbone and encourage bones to fuse. The procedure is done for spinal fractures, herniated discs, spinal tumours and scoliosis.

The technology consists of hardware that takes intraoperative pictures of the patient’s exposed spine and software that matches the current position of a

patient’s spine to a preoperative CT scan. It does this in only a few seconds, without emitting harmful radiation. The navigation system helps surgeons to place implants correctly and avoid critical errors like hitting the spinal cord. The device blends seamlessly into an operating room because the unit that scans the patient’s anatomy looks and functions like a standard operating light, a feature that appeals to Sunnybrook orthopaedic surgeon Dr. Albert Yee. “The benefit of bright surgical light illuminating the field makes this navigation unit multipurpose and compact,” he says.

Dr. Todd Mainprize, another neurosurgeon, has used Yang’s device during spinal fusion. He says he was impressed with how fast it matched preoperative CT scans and images of the patient’s spine that were generated in the OR. “Instead of taking the usual, frustrating 20 minutes to register the images to the patient’s spine, this system accomplished that within seconds,” he says.

Yang is commercializing the system through 7D Surgical, an early-stage company. The firm has more than 30 employees and continues to hire talent. The system is manufactured locally, in Brampton, Ont., to guaranteed quality standards. 7D Surgical plans to roll out new applications for brain, orthopaedic and plastic surgery.

In early 2017, the company achieved a milestone: approval from the U.S. Food and Drug Administration and Health Canada to use the device clinically, the latter ahead of schedule. “We’ve been focused on U.S. hospitals because we thought it would be a few more months until we received Canadian clearance,” says Yang, who notes neurosurgeons at Sunnybrook are using the system during spinal procedures to assess its effectiveness in a clinical trial. “Now, if any Canadian hospitals want it, we’ll say, ‘we’ll add your order.’”



Top: a Ukrainian man prior to reconstruction surgery by **Dr. OLEH ANTONYSHYN** during a humanitarian mission. Antonyshyn has developed a system to craft custom craniofacial implants. **Below:** after surgery.



Antonyshyn’s research was supported by the Federal Economic Development Agency for Southern Ontario, Health Technology Exchange and Ontario Centres of Excellence. Yang’s research was funded by Brain Canada, Canada Foundation for Innovation, Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and the Ontario Ministry of Research, Innovation and Science. He holds the Canada Research Chair in Bioengineering and Biophotonics.



No Cure

And few—or no—treatments for these devastating brain diseases: **Why not?**

By **BETTY ZOU**
Photography by **NATION WONG**

Dr. LORNE ZINMAN (left) and Dr. AGESSANDRO ABRAHAO say a deeper understanding of ALS is needed to stop it, and for that, biomarkers are needed.

M

EDICAL ADVANCES HAVE drastically changed the health landscape. Vaccines and antibiotics have wiped from memory once deadly and debilitating diseases like smallpox and polio. Antiretroviral therapies and insulin have transformed AIDS and diabetes from a death sentence to manageable chronic conditions. Despite these leaps, there remain diseases for which a cure—and indeed, effective treatment—remains elusive. Many of these originate in and affect the brain, the body's most complex and enigmatic organ. Why are we not further ahead? The answers are as complicated as the diseases themselves.

Take amyotrophic lateral sclerosis (ALS), a rapidly progressing neurodegenerative disease in which the nerve cells that control muscles, known as motor neurons, die. “ALS is arguably one of the worst diseases humans have known because you are witness to your body's decay,” says Dr. Lorne Zinman, a neurologist who directs the ALS clinic at Sunnybrook and is an associate scientist in the Hurvitz Brain Sciences Research Program at Sunnybrook Research Institute (SRI). “You become trapped inside your own body. In most cases, your mind is relatively intact, but you get progressively weaker.” Most patients succumb to the disease two to five years after diagnosis. “Why is this happening?” asks Zinman. “The main gap is an incomplete understanding of the disease pathophysiology. How can you fix a disease if you don't really understand why it starts and how it progresses?”

Significant progress, including by Zinman, has been made in uncovering the genes responsible for the hereditary type of ALS. Researchers can now identify between 60% and 70% of the genetic alterations that lead to familial ALS. They are studying these mutations in preclinical models to elucidate how they contribute to motor neuron death. The familial variant, however, only accounts for 10% of

ALS patients—the remaining 90% develop the condition sporadically, often without any of the previously described genetic aberrations.

“The disease is incredibly heterogeneous,” says Zinman, speaking to its diverse biological origins. This variation represents one of the biggest obstacles to finding an effective treatment. Drug trials tend to lump all patients together—familial cases with sporadic ones. As he notes, it would be simplistic to expect that a single drug would benefit all these patients irrespective of the underlying disease mechanism. The inherent diversity of ALS explains, in part, why human drug trials have failed despite promising results at earlier stages, where testing is typically done in a single, uniform, pre-clinical model. Without biomarkers of drug activity, however—a characteristic of one's biology that can be quantified, like the presence of a gene or a protein—it is difficult to pinpoint why a drug was unsuccessful.

In 2014, Zinman and collaborators published the results of a Phase 3 randomized controlled trial examining the safety and efficacy of the antibiotic ceftriaxone for ALS. The drug seemed to slow the progression of symptoms in earlier studies, but had no benefit in the

University of Toronto. “When you're playing without a blindfold, you know how far you are from the target and can recalibrate. With a blindfold, you can't correct your errors. That's the biggest problem in proceeding without a biomarker in an ALS trial.”

He is partnering with researchers across Canada to look for and validate MRI biomarkers in patients with ALS. These features, which would be visible on an MRI scan, would enable objective and accurate measurements of brain degeneration. A reliable biomarker would also allow researchers like Zinman to observe directly what effects, if any, a treatment has on neurological function in clinical trials. He is leading two such trials to determine whether the herbal remedy ashwagandha and the antipsychotic drug pimozide can slow disease progression as they did in ALS preclinical models. A third study poised to start will examine the safety of using low-intensity focused ultrasound to open the blood-brain barrier of the motor cortex safely—a world first. The motor cortex controls voluntary movements; it is the brain region affected by ALS. The ultimate goal of the study, led by Zinman and his neurology fellow Dr. Agessandro Abrahao, is to deliver stem cells or viral vectors car-

"IT'S KIND OF LIKE PLAYING DARTS WITH A BLINDFOLD ON."

Phase 3 trial. “Over a decade of development, the drug demonstrated safety in Phase 1, showed promise in Phase 2, and sadly, it failed in a large Phase 3 trial.” A trial can fail for many reasons. The medication may not have engaged the target of interest, or perhaps the drug only works in a subset of patients, say, those with a specific mutation; in a mixed-patient population any benefit would be masked. Without a reliable biomarker in ALS, the researchers were unable to determine which of these reasons contributed to their failed study.

“It's kind of like playing darts with a blindfold on,” says Zinman, who is also an associate professor of medicine at the

rying neurotrophic factors to the targeted area where they might protect damaged motor neurons and prevent further deterioration.

As founder and head of the Canadian ALS Research Network, Zinman points out that collaboration is the best hope for progress. “This disease is so complicated, it's not going to be untangled by one person,” he says.

Dr. Richard Aviv, an affiliate scientist in the Hurvitz Brain Sciences Research Program at SRI and a neuroradiologist at Sunnybrook, feels similarly about his field. He is combining his expertise in MRI and computed tomography (CT) with the knowledge of his neurology col-

leagues to tackle intracerebral hemorrhage (ICH), a catastrophic event that accounts for 15% of all strokes, but 30% of all stroke deaths. An ICH occurs when a blood vessel ruptures in the brain and blood pools to form a hematoma. If the bleed is not stopped, then the hematoma continues to expand and exert pressure on surrounding tissues, killing brain cells. Roughly one-half of patients who

Gladstone and Aviv recently reported the findings of joint research between their Canadian SPOTLIGHT study, of which they are co-principal investigators, and the American STOP-IT study. Both studies tested whether a blood-clotting drug called recombinant activated coagulation factor VII (rVIIa) could reduce hemorrhage expansion and improve outcomes in patients with ICH. “Up to

matomas were actively expanding, and were assigned to receive emergency treatment with either rVIIa or a placebo. Despite promising results from earlier studies, the results from this trial were disappointing. Patients in both groups saw their bleeds increase in volume over 24 hours. There was no significant difference in final hematoma size between the groups. Nor did they differ in clinical out-

“ALZHEIMER’S DISEASE SHOULD BE RECOGNIZED AS A CAUSE OF STROKE.”

suffer an ICH do not survive. Depending on the location of the hematoma and the extent of the damage, those lucky enough to pull through can face long-lasting consequences, such as paralysis, vision loss and personality changes. “It is the deadliest, most disabling and least treatable type of stroke,” says Dr. David Gladstone, a scientist in the Hurvitz Brain Sciences Research Program at SRI and stroke neurologist at Sunnybrook. “We desperately need to develop effective and safe treatments that can stop bleeding in its tracks and prevent brain hemorrhages from enlarging to a critical, life-threatening size.”

30% of patients undergo expansion, which is a major determinant of bad outcome,” says Aviv. “We can’t do anything about the initial bleed, but if we can prevent hematoma expansion, that would significantly improve outcomes.”

The initiative involving 26 hospitals, led by Gladstone and Aviv with colleagues in Calgary and Cincinnati, built upon Aviv’s discovery of the spot sign, a bright white spot visible on a CT scan of the blood vessels that predicts hematoma growth. All of the patients enrolled in the SPOTLIGHT and STOP-IT studies had the spot sign, meaning that their he-

comes at three months. “It underscores how very difficult this condition is to treat,” says Gladstone. More positively, the researchers also tracked a cohort of ICH patients who were spot sign-negative and found that they had a better prognosis than those with the spot sign. “The optimistic side of the results is that they confirmed the spot sign as a potent predictor of hematoma expansion,” says Aviv, who is also a full professor in the department of medical imaging at U of T.

They believe the treatment didn’t work because patients got the drug on average three hours after stroke onset. “By that time, most of the hemorrhage expansion in our patients had occurred,” says Gladstone, who is also an associate professor of medicine at U of T. “This research will push future trials to find ways to deliver this type of treatment to patients earlier,” he says. With emerging technologies, including ambulances equipped with CT scanners, the researchers foresee patients being diagnosed and treated before they get to hospital, for example.

Aviv notes that these studies also helped him to appreciate the spot sign isn’t just a binary indicator of whether or not a bleed will expand; it can also represent different rates of bleeding. He is testing this hypothesis in preclinical models he developed to determine if certain drugs work better against slow- versus fast-growing hematomas. “If you’re gushing blood rapidly, a drug is never going to get in fast enough to work,” he says. “But if you’re bleeding slower, maybe there’s a threshold that we can measure clinically that will determine if you can be treated with these drugs.”

The most common cause of ICH is high blood pressure. “We have made huge progress in [preventing] ICH that are related to hypertension,” says Dr. Sandra Black, director of the Hurvitz Brain Sci-



DR. RICHARD AVIV (left) and DR. DAVID GLADSTONE say time is of the essence when it comes to treating intracerebral hemorrhage, and trials need to figure out how to get treatment to patients sooner.

ences Research Program at SRI. As a neurologist who specializes in cognitive impairment and dementias like Alzheimer's disease (AD), she studies how amyloid contributes to disease pathology. She is developing better strategies for detecting and targeting amyloid in the brain. Amyloids are protein fragments that clump together to form plaques in the brain. They are most often associated with AD, where they are believed to have a causal role, and can be detected with positron emission tomography (PET).

Less well known is amyloid's involvement in strokes like ICH. Amyloid angiopathy develops when the toxic protein is deposited along blood vessels in the brain. While this build-up typically increases with age, it is also considered a hallmark of AD, where patients produce too much amyloid or have trouble clearing it from the brain. Unlike hypertension-related ICH, brain bleeds caused by amyloid angiopathy are subtle. They often start out as asymptomatic microbleeds caused when amyloid doesn't clear properly from the brain but instead accumulates and penetrates the arterial wall, causing tiny breaches and blood cells to leak out into the brain, where they show up as small black spots or streaks on an MRI scan. Sometimes, however, such bleeding can gradually or quickly get larger and cause brain damage.

"Alzheimer's disease should be recognized as a cause of stroke," says Black. "Amyloid pathology along the vessels walls can cause hemorrhagic stroke, which can be the first manifestation of AD. That's totally off the radar, something that people are not aware of." She is developing strategies to detect and treat amyloid earlier, before devastating consequences—ICH and dementia—occur. In one study, her team is looking at whether amyloid in the retina of the eye or possibly the lens correlates with its presence in the brain and, if so, if it can be observed in the eye before it is detectable in the brain. "If this works out, then you could be checked at your ophthalmologist," she says. "It would be like having a routine mammogram or colonoscopy."

Black is also leading trials to slow the neurodegeneration associated with AD before it begins or reaches an untreatable stage. One trial in AD patients with hypertension is comparing the effectiveness of two anti-hypertensive medications in slowing brain atrophy, where



DR. SANDRA BLACK says amyloid protein in the brain can cause catastrophic stroke, a mechanism of which many people are unaware. She also notes that such strokes can be the first sign of dementia.

brain cells and tissues waste away. While these drugs are good at lowering blood pressure and protecting the heart, some might have an edge in the brain because they can stimulate uptake of glucose and breakdown of amyloid. Another, the A4 study, is recruiting people from sites across North America and Australia who have no outward signs of AD but detectable deposits of brain amyloid on a PET scan. These people receive either an anti-amyloid antibody or a placebo, with the aim of preventing memory loss.

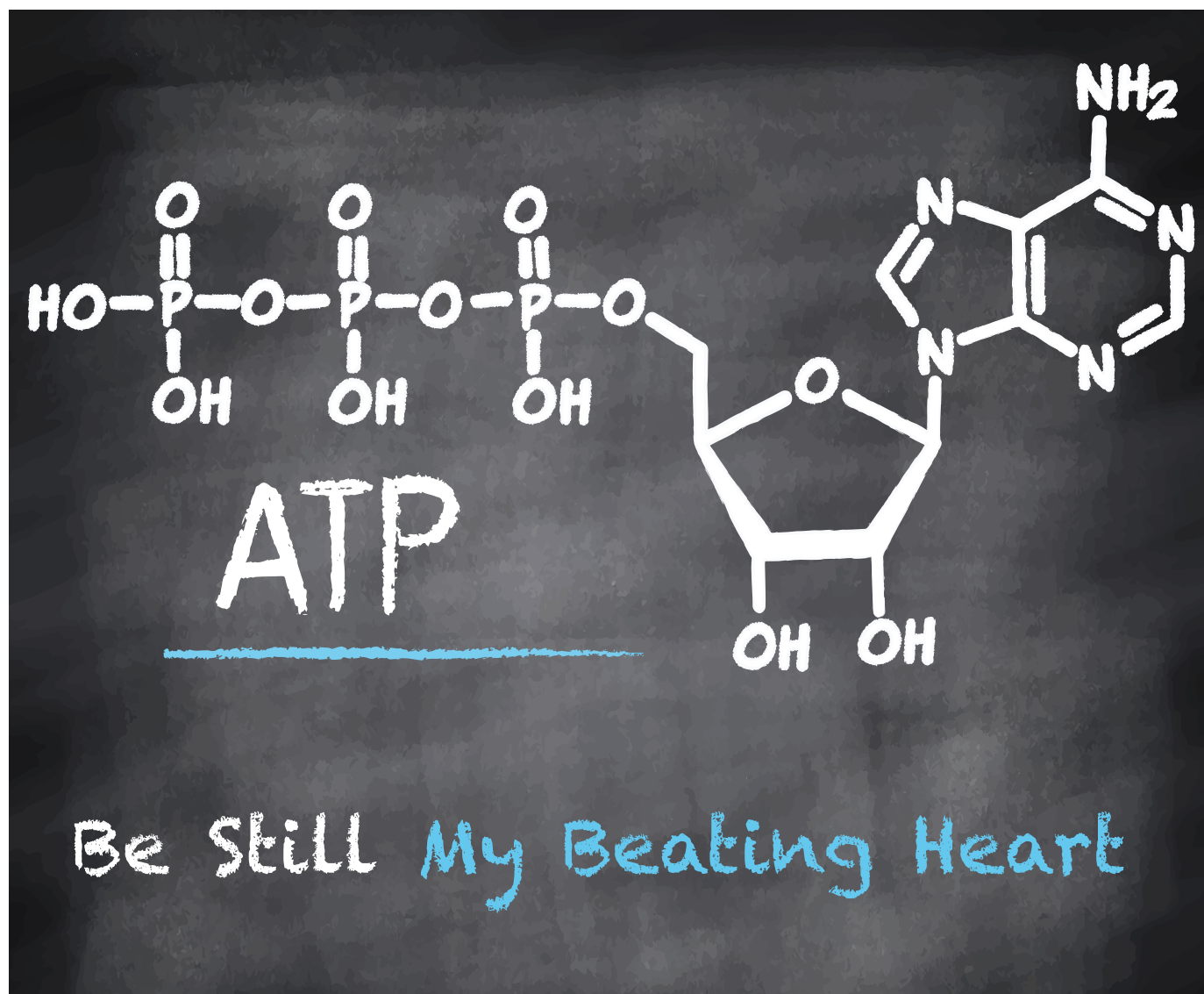
Given that recent attempts at slowing progression in AD have failed, Black suggests disease stage might be to blame. "It might be too little, too late," she says. When it comes to ICH, she notes that a history of microbleeds makes it even tougher. "We've seen people with over 100 microbleeds. Well, how are you going to deal with that?" One answer is a usual one: more research, especially studies over time to track how the disease progresses. Another is awareness—avoiding drugs or doing things that increase the odds of more bleeding. "It is a terrifying disease, because when you have a brain hemorrhage from amyloid angiopathy, you are at high risk of having another

one," she says. "It's one of those diseases where there's a continual worry, and you feel badly for people affected because they know that, and there's nothing we can do—except to tell them to avoid the things that make you more likely to bleed."

Against this dark backdrop, seeking out effective therapies for such challenging diseases is not for the fainthearted. "You have to have patience, stamina and determination," says Black. Critically, even unsuccessful trials are, as Gladstone puts it, "one small step toward future treatment."

Research Funding

Aviv: Canadian Institutes of Health Research (CIHR). Black: Alzheimer's Drug Discovery Foundation, Avid Pharmaceutical, Brain Canada, CIHR, GE Healthcare, National Institutes of Health and Ontario Brain Institute. She holds the Deborah Ivy Christian Brill Chair in Neurology at U of T. Gladstone: Heart and Stroke Foundation of Canada. SPOTLIGHT trial (Aviv and Gladstone): CIHR, Ontario Ministry of Research, Innovation and Science, and Ontario Stroke Network. Zinman: ALS Society of Canada, Ontario Brain Institute and Temerty Family Foundation.



Study is the first to enable biochemical reactions in the heart to be seen with MRI using a novel contrast agent

By ALISA KIM

ABOUT SIX WEEKS into a pregnancy, the steady heartbeat of a fetus can be detected via ultrasound. From the earliest moments of life until death, the heart toils unceasingly to pump life-giving blood around the body. Perhaps

unsurprisingly, this fist-sized workhorse has the greatest energy demands of all the body's organs.

To do its job of beating 100,000 times daily, our hearts need to make a chemical fuel called adenosine triphosphate (ATP)—and lots of it. (An adult heart makes about six kilograms of ATP—35 times its weight—daily.)

Until relatively recently, doctors weren't able to measure how much of an energy source, such as fatty acids and glucose, was consumed by the human heart. In the early 2000s they began using positron emission tomography (PET) to study glucose metabolism in cardiac patients. This technique relies on radiotracers to show uptake of

glucose or fatty acids that are used to make ATP. A missing link remained, however: what happens to those substrates once they enter the heart's cells? Pioneering work in medical imaging led by Dr. Charles Cunningham, a senior scientist at Sunnybrook Research Institute (SRI), is unraveling this mystery. Cunningham and colleagues are the first in the world to demonstrate noninvasive metabolic MRI of the human heart using a contrast agent called hyperpolarized carbon-13-labelled pyruvate. Put simply, this contrast agent is a byproduct of glucose that is prepared in a strong magnetic field and injected into a person undergoing MRI. A process called dynamic nuclear polarization increases the signal from the pyruvate 10,000-fold. A higher intensity signal increases image brightness, enabling biochemical reactions occurring within the heart to be seen. The study was published in *Circulation Research*; images from the paper landed the team the cover of the journal's November 2016 issue.

The contrast agent may prove useful in heart failure, where the heart is unable to meet the body's pumping needs. It could help establish metabolism as a biomarker of heart failure, opening the door to earlier diagnosis and care that is specific to each patient. "The progression of heart failure is very likely preceded by metabolic changes, so if you could image those and tell which people are going down that path, you could treat them more aggressively or tailor the treatment," says Cunningham, who is also an associate professor of medical biophysics at the University of Toronto.

Researchers do not fully understand the metabolic shifts that occur in heart failure, but they do know that there are abnormalities in how the heart makes ATP. Normally, pyruvate, which is made from glucose, goes into the TCA (tricarboxylic acid) cycle, the metabolic cycle that creates ATP within cells. When the heart starts to fail, however, it relies more on fat as the main fuel, says Dr. Kim Connelly, a co-author of the study and a cardiologist at St. Michael's Hospital in Toronto, Canada. At a later stage of heart failure, the heart reverts to using more glucose. "It's not a static process. [Metabolism] changes depending on how bad your heart failure is and what the cause of the heart failure is. Before this, we never had a good technique that could

It could help establish metabolism as a biomarker of heart failure, opening the door to earlier diagnosis and care that is specific to each patient.

help tease out exactly what's going on in terms of the heart taking up glucose and taking up fats, and what happens to them once they enter the cells in the heart and get broken down," says Connelly.

Hyperpolarized carbon-13 MRI could elucidate those changes, as well as the mechanisms behind them. Early on in heart failure, when the heart stops using glucose properly, seeing how much pyruvate is used to make ATP could be quite telling. "Bicarbonate is produced when pyruvate is converted into acetyl coenzyme A, which enters the TCA cycle. So high bicarbonate means lots of carbs going in, and low bicarbonate means that flux is downregulated. When it's decreased that could be the marker that we're after," says Cunningham.

The technique offers advantages over PET, which images metabolism to show differences between healthy and diseased tissue. First, PET only shows the uptake of a molecule, whereas hyperpolarized carbon-13 MRI shows what happens after the heart takes up glucose. "The big thing with this is you see the conversion of one thing into another," says Cunningham. Second, the contrast agent is safe, making possible long-term studies in patients. The use of ionizing radiation in PET however, restricts the number of scans people can have.

Moreover, carbon-13 metabolic MRI could easily be integrated with regular cardiac MRI, which assesses the heart's size and function, and analyzes scarring. It would only add 10 minutes to the procedure. "It's done at the same time as the MRI, so it's perfectly spatially coregistered to the MRI; [this means] on a pixel-by-pixel basis, you could compare metabolism to other parameters," says Cunningham.

He plans to study metabolic imaging in

people with enlarged hearts, a condition that puts them at increased risk of heart failure. By following them and looking at outcomes he hopes to learn whether glucose metabolism can be used as a biomarker to predict disease. "I think that will answer the question as to whether it'll be useful clinically," he says.

The current focus is on cardiac applications, but Connelly says metabolic imaging would be useful in other clinical domains. "There's no reason why we can't measure [metabolism] in the liver or kidneys, and use it to gain really valuable insight into what happens to people with kidney diseases or liver diseases, and also to tailor-make drugs. This is potentially much, much broader," he says.

It has been more than a decade since Cunningham began working on this technique. His lab had to engineer hardware to pick up the signal, and create software to switch the MR scanner to do metabolic imaging while retaining the capacity to see anatomy in the same frame of reference. He says most of their efforts were aimed at making the contrast agent safe. To ensure sterility, it was prepared with pharmacist oversight in SRI's good manufacturing practice facility, which guarantees quality control for patients.

So, how did it feel to finally see it work clinically after so many years of research and development?

"It was a good day," Cunningham says, smiling. "It was a huge step forward. I was happy."

Cunningham's research was supported by the Canada Foundation for Innovation, Canadian Institutes of Health Research, Heart and Stroke Foundation, and Ontario Institute for Cancer Research.

No Doubt

Doctoral student knows that the life he has fashioned—doing science, mentoring young people and preparing for a career in medicine—is his calling, but it wasn't always that way

"If you're lucky enough to do well, send the elevator down." So says Abdikarim Abdullahi in describing the motto he tries to live by.

A third-year PhD student in the Institute of Medical Science at the University of Toronto, Abdullahi is training in the lab of Sunnybrook Research Institute senior scientist Dr. Marc Jeschke.

He's usually at Sunnybrook until 11 p.m. on weeknights—"I'm more of a night person," Abdullahi says—yet he finds time to tutor elementary school kids. On Saturdays, he works at a learning centre in the city's west end instructing young kids in public speaking and science. Along with others, Abdullahi helped lead a team from the centre to national prominence in the First Lego League, a competition that encourages youth to get involved in science, technology, engineering and math (STEM). He also mentors black university students pursuing graduate studies in research, where they are strikingly underrepresented. He founded a group where he and his colleagues help students of colour navigate graduate research programs. Offering guidance on matters like choosing a thesis advisory committee and applying for awards, Abdullahi gives the kind of support he wishes he'd had when he began his PhD. "I felt like I was the only one [in the program] who looked like this," he says, recalling his first week of orientation. "I was kind of intimidated."

Any doubts he had about whether he belonged in academia have dissipated.

The 29-year-old, who is more than half-way through his doctoral studies, is flourishing. In 2016 he was awarded a Vanier Canada Graduate Scholarship through the Canadian Institutes of Health Research, one of the country's most prestigious awards. The accolade, worth \$150,000 over three years, recognizes academic excellence and leadership. Abdullahi, who has done extensive youth outreach for the city's Somali community, was ranked in the top 10th percentile of all applicants nation-wide.

He studies changes in metabolism in the liver and adipose (fat) tissue after a burn injury. His focus is on the biological

mechanisms driving browning, a process by which the body shifts from storing to burning fat. Different types of fat get their name from the colour of the tissue, Abdullahi notes. White fat stores fat, whereas brown fat burns fat. He has found that the immune system plays a role in the metabolic changes that accompany browning. In preclinical models, Abdullahi showed that immune cells called macrophages secrete a protein called interleukin-6, which activates browning. On the other hand, "when you get rid of the ability of macrophages to get to the adipose tissue, [the mice] don't brown," says Abdullahi. In studies of mice that are engineered not to express the interleukin-6 gene, he has found that browning does not occur.

The topic is popular because controlling browning could benefit people who are obese or have diabetes. Abdullahi, however, is studying the dangers of this process in people who have burn injuries and cancer. In both conditions the body tailspins into a hypermetabolic state where it begins to waste away. As the body burns fat stores, it begins to ravage muscle tissue. He catalogued the harmful effects of browning ensuing from burns and cancer in a paper published in *Trends in Endocrinology and Metabolism*. The editors of the journal praised the research for its originality and featured the study



ABDIKARIM ABDULLAHI (left) tutors kids at the Academy for English and Mathematics in the city's west end.



ABDIKARIM ABDULLAHI is a PhD student training in the lab of Sunnybrook Research Institute senior scientist **DR. MARC JESCHKE**.

on the cover of the August 2016 issue. “I actually have this framed,” says Abdullahi, pulling up a screenshot of the journal cover on his laptop.

This fall, he will continue his research into browning at Johns Hopkins University, in Baltimore, Maryland, under the guidance of Dr. Sheng Bi, a leading scholar in diabetes research. The catalyst for the placement was a travel award that Abdullahi won called the Michael Smith Foreign Study Supplement, which encourages outstanding Canadian graduate students to do research abroad and build global linkages. “I thought this was a great opportunity to expand my horizons,” says Abdullahi, noting he has his supervisor’s blessing. “When I told Marc he was pretty happy, too.”

He is excited about going to Johns Hopkins, but says that even though he is a Canadian citizen, he is wary of travelling to the U.S because he was born in Somalia. The political climate and the immigration ban drafted by the U.S. administration, which barred entry of people from six countries, including Somalia, weigh heavily on Abdullahi,

even though the ban has been blocked by the courts. “I’m afraid especially now with Trump and ‘America First.’ They might think I’m going over there to work, even though I’m fully financed on a scholarship. I won’t be picking up jobs to finance myself. I’m going to make sure all that stuff is clear,” he says.

He is on track to graduate in two years. His plan is to attend medical school. His career goal is to become a clinician-scientist so that he can practise medicine and conduct discovery research that has clinical applications. “As a basic scientist you can get bogged down with the mice work and not understand how your data can be taken to the clinic, which is something I’m passionate about,” says Abdullahi. “You want that research to go somewhere.”

He is open about his aspirations now, but growing up in the Jane and Finch neighbourhood in Toronto, a diverse community that also has some of the highest rates of crime and gang violence in the city, he was reticent about his desire to pursue higher education. “I remember some of the guidance counselors weren’t supportive. They were more

supportive of trades. I kept [my goals] to myself—then no one can shoot down your dreams,” says Abdullahi.

The youngest of seven children, he is still considered the “baby” of the family, but Abdullahi is like an older brother to kids in the Jane and Finch community where he still lives. He goes back to his old schools to give young people a different message than the one he received and, perhaps, inspire them to pursue STEM. “It builds up their confidence,” he says of the visits. “They think, ‘maybe I can be like that one day.’”

Looking ahead, Abdullahi says that once he has his medical degree, he plans to live and work in Canada, and make regular trips to Somalia to provide pro bono health care. He says he often thinks about how different his life would have been had his parents not immigrated here. It is these thoughts that push him to excel academically and to pay his blessings forward. “Whenever I accomplish something, I want to give back. You have to take every opportunity you get and run with it.”

ALISA KIM

What is the biggest misconception about being a scientist?"

EDITED BY **STEPHANIE ROBERTS**



SANDER HITZIG

THE BIGGEST MISCONCEPTION is that doing research means being stuck in a lab and not having any direct ties towards improving patient care. In reality, issues that affect patients' health and wellbeing are what drive my research. I work with patients, clinicians and other key decision-makers on finding ways research can help describe problems patients are dealing with, and what can be done to solve those problems. For example, I have worked with patients to better understand what it means to live with pain, and have used that information to help clinicians develop guidelines and interventions to help people better manage their pain.

Being in research to me means getting good evidence into the right hands so that it can support new ways to help people recover and be able to return to their lives. So if you have a problem, talk to a scientist; they might be able to help.

Hitzig is a scientist in Evaluative Clinical Sciences and the St. John's Rehab Research Program at SRI. This year, he received a one-year patient-oriented rehabilitation research collaboration grant worth \$20,000 from the Canadian Institutes of Health Research. He will conduct focus groups with rehab patients on issues affecting their health and wellbeing to inform a list of patient priorities.



BRAD MACINTOSH

WHEN I BECAME an SRI scientist I read *Advice for a Young Investigator* by the famous neuroscientist Ramón y Cajal. The book had inspiring words on the beauty and romance of science. It also had a lot on the need for rigorous, precise measurements. It was as if Cajal was wagging his finger at me reminding me to be careful, do good work.

One of the biggest misconceptions about being a scientist is that we spend our time doing rote and monotonous work, hiding out in our lab. Science is creative and hard. Doing something wrong can have repercussions. Like a gardener tending to their seedlings, however, a scientist's thrill is watching how careful work starts to bear fruit. The work invites intrigue from onlookers. A scientist can create something that others take up and scrutinize with their own lens and bias. And the conversation continues.

MacIntosh is a scientist in Physical Sciences and the Hurvitz Brain Sciences Research Program at SRI. As a neuroimaging scientist, he uses vascular imaging techniques to study brain function and physiology. Last year, he was awarded \$140,000 over five years from the Natural Sciences and Engineering Research Council of Canada. He is studying the effects of exercise on the brain and people's ability to perform difficult mental tasks.



BEV ORSER

THE BIGGEST MISCONCEPTION about being a scientist relates to the "pebble in the shoe" effect. Most folks think that the big breakthroughs come from doggedly pursuing a favourite hypothesis and by amassing loads of data to show that your idea is correct.

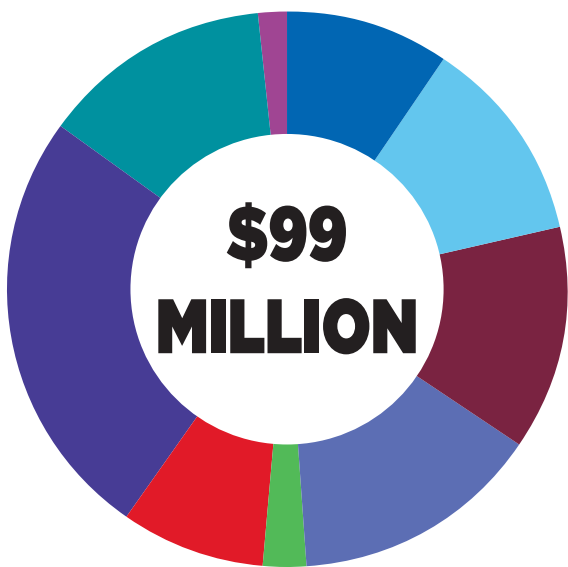
However, the big breakthroughs are more likely to come when you pay close attention to your data, watching for a signal or something that doesn't fit your hypothesis. Initially, these data are incredibly irritating, but such sentinel results are ignored at your peril. They should make you stop and re-examine the problem. Eventually, they may lead you in an entirely new, previously unimagined, but wonderfully fruitful direction.

Orser is an affiliate scientist in Biological Sciences and the Hurvitz Brain Sciences Research Program at SRI, and an anesthesiologist at Sunnybrook. She holds the Canada Research Chair in Anesthesia. This year, she was appointed chair of the department of anesthesia at the University of Toronto. Her five-year term begins July 1, 2017. She also was awarded the 2017 Gold Medal from the Canadian Anesthesiologists' Society. Her research seeks to understand how general anesthetics work at a fundamental level.

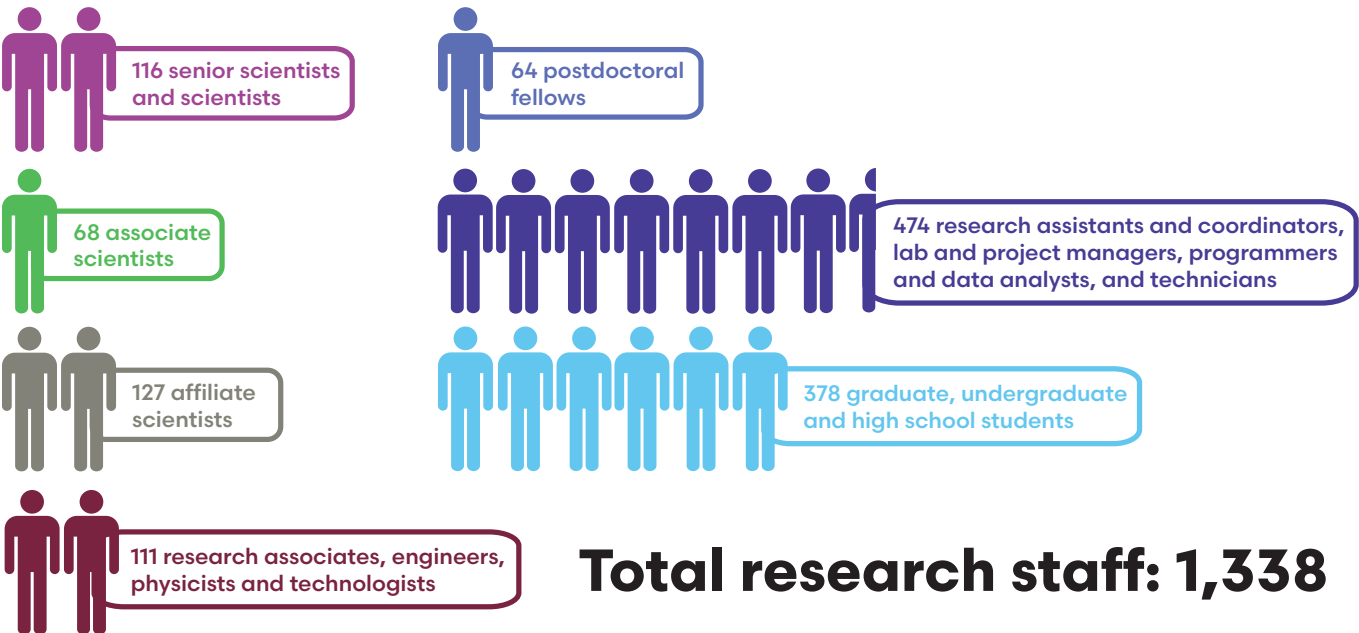
Quick Statistics

Each dollar we receive is invested in high-impact discovery and innovation

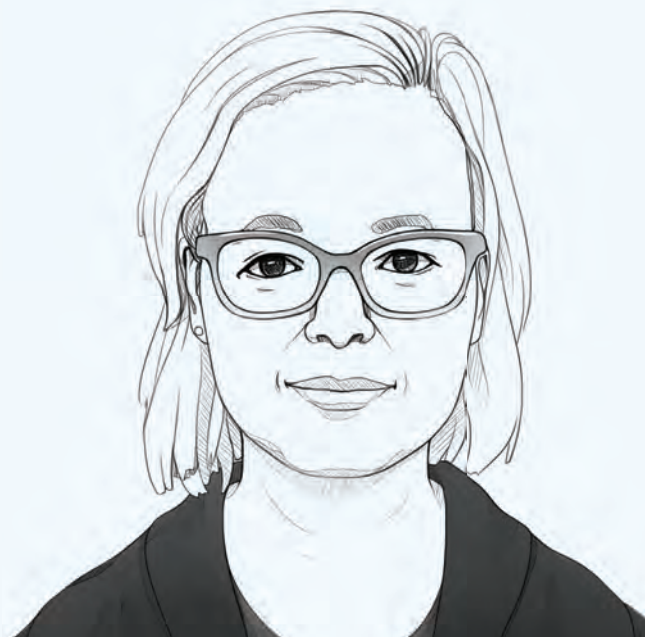
MAJOR SOURCES OF FUNDING 2015–2016



Sources	\$(M)	%
Canada Foundation for Innovation	9.5	9.6
Contracts With Other Private/Public Organizations	11.9	12
Industry	12.9	13.1
Internal Funding	14.1	14.3
Ontario Ministry of Research, Innovation and Science	2.7	2.7
Other Government Sources Within Canada	8	8
Private Sector Funding From Philanthropic Organizations	25	25.3
Tricouncil Funding: CIHR, NSERC and SSHRC; also includes Canada Research Chairs Program	13.3	13.4
U.S. Government	1.6	1.6
Total	99	100



Q&A



DR. CAROL SCHUURMANS joined the Biological Sciences platform and the Hurvitz Brain Sciences Research Program at Sunnybrook Research Institute (SRI) as a senior scientist in 2016. Additionally, she holds the Dixon Family Chair in Ophthalmology Research and is a professor in the department of biochemistry at the University of Toronto. She spoke with Matthew Pariselli about her work and moving to SRI.

What about the brain, particularly the neocortex and retina, fascinates you?

They're quite complementary. They're both layered structures in the central nervous system and there are similarities in how they're structured. The questions are, how are layers developed in these two independent parts of the central nervous system? How do the neurons go to the right layer? How are they born at the right time? I started working on the neocortex and then gradually shifted to the retina, and they both have advantages and disadvantages. The retina is more accessible for therapies—it's external, obviously—and the brain is harder to reach.

What excites you most about your work?

One project I'm excited about is a neocortical project. If you're making different cell types at different times in development, you have a stem cell pool that you have to retain. So if all the stem cells get used up at the beginning of development, you don't have enough left to make later-born cell types. We've found a new mechanism that controls and maintains this stem cell pool over developmental time. It's quite exciting because it's not well studied.

How would you rate your experience at SRI thus far?

I think I'm still in my honeymoon phase [laughs]. Nothing to complain about. I'm really happy here. I like my colleagues. There's JoAnne McLaurin and Isabelle Aubert, who are my neighbours on either side [of my office]. They both work on neuroscience. We're starting to do collaborative projects. I have a successful grant already with Isabelle, and I'm writing one now with JoAnne. It's a really good community.



QUICK FACTS

Neocortex

- It is the outermost layer of brain and accounts for about 76% of the brain's volume.
- It is involved in sensory perception, motor commands, conscious thought and spatial reasoning.

Retina

- It is located at the back of the eyeball and covers about 65% of the eye's interior surface.
- It converts images that come through the eye's lens to electric signals, which are sent to the brain via the optic nerve.

What are you working on with Isabelle?

It's a retina project. It looks at using focused ultrasound. So Kullervo Hynynen [director of Physical Sciences at SRI, who pioneered the technology] is also on that grant. We're using focused ultrasound to deliver cells into the retina to treat blindness, essentially, so to treat the loss of photoreceptors that occur in a lot of the animal and human models of blindness — retinitis pigmentosa, age-related macular degeneration, different diseases.

How do you feel about your role as mentor to the members of your lab?

Every student and trainee is different. They all need different things and different delivery methods. Some you can push; some you can't. Some need more handholding. It's interesting that way. I think their excitement is motivating for me, too. So when they get a result and they come in my office and they're all giddy because something worked, it's exciting for me to see how passionate they are about what they're doing.

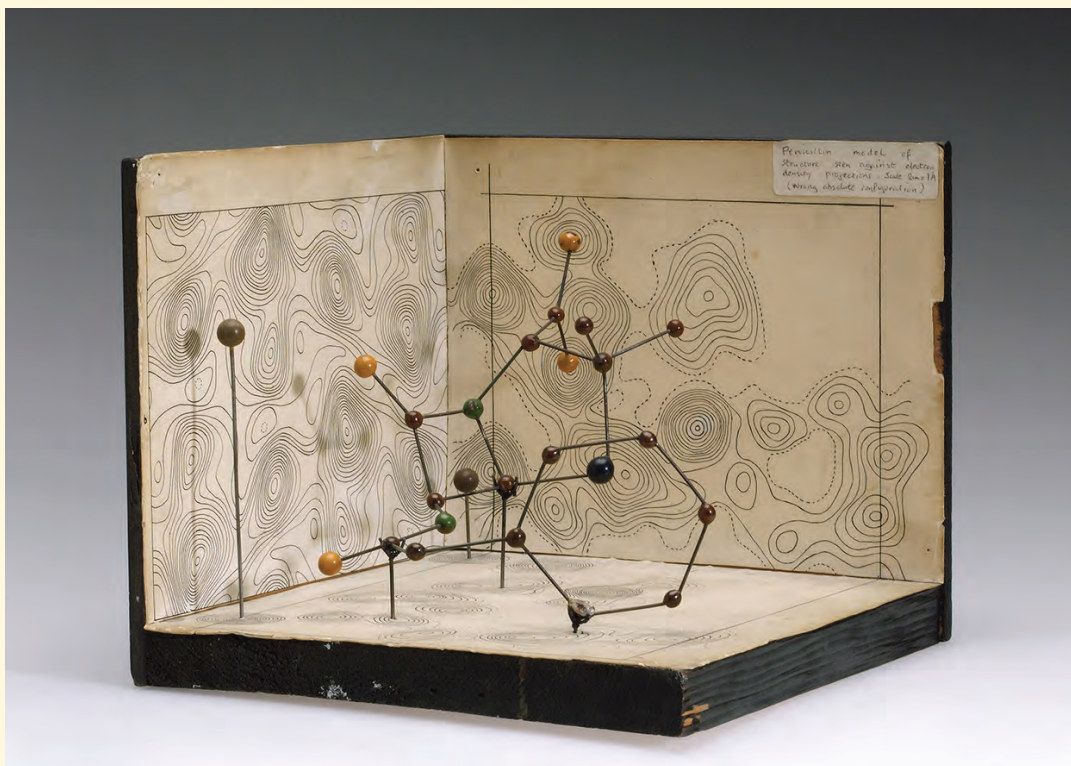
What words of wisdom would you offer aspiring neuroscientists?

I think right now the funding climate is really difficult, so I would suggest just trying to follow your dreams. If you're passionate about research and neuroscience in particular, don't give up. It's becoming harder and harder to be a scientist because of the way funding is but if you're passionate about it, keep exploring and don't give up.

Schuurmans' research is funded by the Canadian Institutes of Health Research and Medicine by Design. For more on her research, visit sunnybrook.ca/research.

Through the Wormhole

Journey into a different time in medical science



DOROTHY HODGKIN's molecular model of penicillin.

EGLISH BIOCHEMIST DOROTHY Hodgkin (1910–1994) made seminal discoveries in X-ray crystallography, a way of finding out the atomic structure of a molecule. The technique works by shining an X-ray through a crystalline material such as salt, and photographing the pattern of spots that is created. By analyzing the pattern, Hodgkin could create a 'map' of the electrons from which the positions of the atoms in a crystal could be derived. She pushed the limits of X-ray

analysis to determine the arrangement of atoms in complex molecules including drugs and proteins. She accomplished this almost always without computing technology—which didn't become available until near the end of her career—to do the painstaking calculations required to make pictures of the electrons within a crystal.

She used the technique to solve the makeup of penicillin, a discovery that continues to save countless lives by enabling chemical synthesis of antibiotics. Next, she unraveled the structure

of vitamin B-12, which led to mass production of the vitamin. Then, after more than 30 years studying insulin, Hodgkin and her colleagues decoded its complicated framework. This discovery was fundamental to helping researchers understand the biology of this vital hormone.

For her achievements, Hodgkin was awarded the Nobel Prize in Chemistry in 1964, which, at the time, a headline in Britain's *The Daily Mail* simply reported: "Oxford housewife wins Nobel." **AK**

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