Taking on healthcare’s sneaky killers

Chronic disease | Sepsis | Pressure sores
Almost every major news story or public-policy issue today has a scientific angle. How do non-scientists find their way through the debate?

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### Production Notes

Executive editor: Kathleen Thurber  
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Photography and Illustration: Trudie Lee  
Photography, Calgary; Laughing Dog Photography, Edmonton; Creative Services, University of Alberta; Hugo Dubon, Calgary; Julie McLaughlin, Calgary; Davey Thompson, Edmonton

AHFMR Research News is printed by Douglas Printing, Burke Group of Companies Ltd. on Pacesetter Matte Text 70 lb.

### Research News is an award winner!

In the past year, AHFMR’s Research News magazine has been recognized with the following awards:

- International Association of Business Communicators Capital Awards, Award of Excellence
- International Association of Business Communicators Silver Leaf Awards, Award of Merit
- Canadian Public Relations Society Awards of Excellence, Bronze Award
- Western Magazine Awards, Best Illustration or Illustration Feature, Finalist Valéry Goulet, Off to a good start, spring 2008 (shown above).

Thanks to all of you for helping to make this magazine a success. Feedback from our readers has always been played a key role in the creation of Research News.
Taking on healthcare’s sneaky killers

Chronic disease | Sepsis | Pressure sores

STORY BY CONNIE BRYSON / ILLUSTRATIONS BY BRENNAN KELLY
Some diseases are deadlier and costlier to treat than we might imagine. While cancer, heart disease and infectious diseases lead in public awareness and media attention, other serious and difficult-to-treat diseases fly under the radar. They cause a great deal of suffering, and yet aren’t well known. Three AHFMR interdisciplinary teams are focusing on some of these “sneaky killers”.

**CHRONIC DISEASE**

The increasing incidence of diabetes, chronic kidney disease, high blood pressure, and vascular disease is a sign of what many health observers are calling a “quiet epidemic” of non-communicable chronic diseases in developed countries. These chronic diseases commonly occur together and predispose people to more serious cardiovascular conditions such as heart attack and stroke. Although chronic diseases don’t get the same attention as cardiovascular conditions and major infectious diseases, they are leading causes of death and disability worldwide, not to mention a huge drain on national economies and family incomes.

“This situation with chronic diseases isn’t new, and governments and healthcare organizations have put a lot of time and effort into trying to improve how they manage chronic diseases,” notes Dr. Braden Manns, who researches health economics at the University of Calgary. “However, it’s fair to say that progress has been slow.”

The Interdisciplinary Chronic Disease Collaboration plans to look at chronic diseases from a broader perspective. “Many researchers have investigated such underlying risk factors for chronic diseases as obesity, smoking, and lack of exercise. As a result, we have a lot of tools to manage people with chronic diseases—we should be doing a lot better than we actually do. We don’t necessarily need another discovery from basic research; rather we need to understand the barriers that prevent people from better managing their health. And that requires studies that address the root causes of these risk factors. For example, we need to look at economic factors, the social environment, geography, education, and more. This is what our group aims to do.”

New AHFMR interdisciplinary teams are taking on diseases and conditions that rarely make the headlines yet take a tremendous toll on the lives of Canadians: chronic disease, sepsis, and pressure sores.
The first phase of the research will involve analyzing existing administrative and laboratory data collected on all patients in Alberta. Working with this data, the team will gather information about the prevalence of various diseases in certain areas, for instance, or how different medications are prescribed in urban and rural regions. The main objective in this phase is to identify where changes in health or public policy could most improve the health of Albertans. In the second phase, the team will use surveys to get a more detailed picture of people with known chronic diseases. “The exciting thing here is that we will be able to look more closely at root causes,” says Dr. Manns. “For example, what is it about certain patients that makes their blood pressure difficult to control? Is the medication too expensive? Are their diets unhealthy? Are they unemployed? We’ll be able to look beyond medical factors.”

In the third phase, the researchers will test new ways to overcome the most significant barriers to better care of chronic diseases. One such study is already underway in rural Alberta. Patients with high blood pressure were assigned to one of two groups: one group is prescribed blood pressure medication by a pharmacist, the other group by a physician. The researchers want to find out whether having a pharmacist prescribe drugs—compared to having a physician prescribe the same drugs—makes a difference in controlling blood pressure. Although pharmacists in Alberta are now authorized to prescribe some drugs, Dr. Manns notes that few of them do. “And yet prescribing by pharmacists has the potential to address the gap in access to certain healthcare services in rural areas. We need to figure out how to make this service more successful.”

Dr. Manns, is one of the team’s three principal investigators; the others are AHFMR Population Health Investigator Dr. Brenda Hemmelgarn, from the University of Calgary, and AHFMR Health Scholar Dr. Marcello Tonelli, from the University of Alberta. All three are nephrologists (doctors who treat people with kidney problems) and collaborators in the Alberta Kidney Disease Network. As Dr. Manns says, “Moving beyond nephrology is a stretch for us but that’s the beauty of the team. We’ve assembled a group of experts that will allow us to make an impact beyond nephrology.” The team comprises 23 researchers, clinicians, and decision-makers from the University of Calgary, the University of Alberta, the University of Toronto, Queen’s University, the University of Aberdeen, Alberta Health Services, the Canadian Agency for Drugs and Technologies in Health, Statistics Canada, and the University of Alberta Hospital.

Including decision-makers in the team is vital to better translating research findings into health policy and planning. In the long term, Dr. Manns envisions the team as a resource for Alberta Health and Wellness. “I hope we can develop a two-way relationship with policy-makers, where they forecast to us the types of policy changes they are considering, and we provide data to inform policy. In this way, we can prevent situations where new programs are implemented without incorporating the best evidence, or where marginally effective programs continue for years without any evaluation of their impact on health outcomes or costs. By getting information to the policy-makers, better decisions can be made.”

Chronic disease is a “quiet epidemic”

Manns. “For example, what is it about certain patients that makes their blood pressure difficult to control? Is the medication too expensive? Are their diets unhealthy? Are they unemployed? We’ll be able to look beyond medical factors.”

Dr. Manns envisions the team as a resource for Alberta Health and Wellness
A four-year-old boy with a fever and complaining of a “sore tummy” is brought into the emergency department. His condition is not considered serious and, after waiting a couple of hours without seeing a doctor, his mother takes him home. Twelve hours later he is back—with a ruptured appendix and bacteria in his belly. His appendix is removed, and he is transferred to the pediatric critical-care unit. Approximately eight hours later he suffers a cardiac arrest and dies.

Although this case happened in Alberta, healthcare professionals around the world deal with similar cases and ask the same question: What went wrong?

The culprit is sepsis—a life-threatening inflammation caused by the body’s system-wide immune response to bacterial infection. It causes severe problems throughout the body, problems that can lead to failure of the lungs, kidneys, liver, and heart. Doctors don’t know why one patient develops this response and another doesn’t.

Only trauma kills more North American children than sepsis. In adults, sepsis is one of the top ten killers, affecting 18 million patients every year worldwide; specifically, 750,000 North Americans and 30,000 Canadians. Only 50% of adults survive one year after having sepsis, and only 60% of those survivors return to a normal lifestyle.

About the team leaders

Dr. Brenda Hemmelgarn is an AHFMR Population Health Investigator and an associate professor in the departments of Medicine and Community Health Sciences at the University of Calgary. She is the director of the Alberta Kidney Disease Network.

Dr. Braden Manns is an associate professor in the departments of Medicine and Community Health Sciences at the University of Calgary.

Dr. Marcello Tonelli is an AHFMR Health Scholar and an associate professor in the Department of Medicine at the University of Alberta.

Recommended website

Alberta Kidney Disease Network
http://www.akdn.info

Selected publication


Only trauma kills more North American children than sepsis
“Critical-care groups around the world have been looking at sepsis for decades—billions of dollars have been spent on research,” says Dr. Christopher Doig, a critical-care physician at Calgary’s Foothills Hospital. “And still we don’t have many answers. People keep getting sick and dying. Mortality associated with sepsis has not improved in adults over the last 40 years. A group of us in Alberta became convinced we needed to take a different approach to sepsis research.”

Enter the Alberta Sepsis Network, a team of 25 researchers from the universities of Calgary, Alberta, Lethbridge, and Toronto. The network includes both basic researchers—immune experts, microbiologists, and biochemists—and bedside physicians such as infectious-disease specialists and intensive-care doctors.

Rather than looking for a blockbuster drug to treat sepsis—the strategy that has been pursued for decades—the research team believes that understanding the complexity of sepsis will provide clues to more effective treatment. Sepsis can be caused by many different bacteria, and each of these can provoke a different immune response. This immune reaction causes inflammation throughout the body, which can lead to irreparable organ damage. The critical step, therefore, is to stop the inflammation as soon as possible: identify the infection early, and treat it quickly with the appropriate antibiotics, along with intravenous fluids and other therapies aimed at reducing inflammation and organ damage.

This is easier said than done, notes Dr. Doig. “Often it’s not immediately obvious that a patient has an infection, because they don’t have typical symptoms. And even when sepsis is diagnosed, we frequently don’t know the actual cause. Is that right-side pain from a bacterium in the urinary tract or from pneumonia? To complicate matters, microbiological tests for bacteria often come back negative, even though we know there is infection somewhere. We need to look more closely at the immune response in septic patients.”

The team plans to collect blood samples from children and adults with serious infections that lead to severe sepsis or septic shock (when the infection leads to life-threatening low blood pressure). The blood samples will be analyzed using the “new science” of metabolomics. It uses nuclear magnetic resonance (NMR) technology to rapidly identify metabolites (the waste products of chemical reactions in the cell). In this case, metabolomic analysis will look for the chemical fingerprints of the infection and the cell’s im-
mune response. All the information gained from metabolomic analysis will be placed in a province-wide database. Once enough data is collected, it should be possible to identify common features and patterns among groups of patients.

AHFMR Scientist Dr. Paul Kubes, a basic scientist who studies infection and inflammation, is convinced that this information will lead to better treatment of sepsis. “To date, clinical trials for sepsis drugs have been unsuccessful because, I believe, they are looking for a single drug for all septic patients. Think of cancer; we don’t use one drug for all kinds of cancer. We want to use a similar approach to sepsis. The good news is that we don’t need to find new drugs. I know from my laboratory work that there are already drugs that should work in certain types of patients. Our goal is to identify the main subgroups of patients. Then we can start clinical trials of drugs in specific subgroups of patients.”

For Dr. Ari Joffe, a pediatric intensive-care unit (ICU) physician at the University of Alberta Hospital, one advantage of the database is that it will provide information on both adults and children. “With greater numbers and greater diversity in the patients we enrol, we increase our chances of finding differences among patients that may be associated with how well they respond to treatment. From my perspective in the ICU, one key outcome would be the ability to quickly identify patients who are likely to have severe sepsis, so we can start treatment early. I can’t emphasize enough how important this is. In the case of the little boy with appendicitis, it could have been the difference between life and death.”

About the team leaders
Dr. Christopher Doig is a full professor in the Department of Critical Care Medicine in the Faculty of Medicine at the University of Calgary.

Dr. Paul Kubes is an AHFMR Scientist and a full professor in the Department of Physiology and Biophysics in the Faculty of Medicine at the University of Calgary.

Dr. Ari Joffe is a clinical associate professor in the Department of Pediatrics (divisions of Pediatric Critical Care Medicine and Infectious Diseases) in the Faculty of Medicine and Dentistry at the University of Alberta.

Selected publication
PRESSURE SORES

Pressure ulcers are a classic underestimated health problem that is devastating to both the individual and the healthcare system. Pressure ulcers are sores that develop in deep muscle tissue as a result of constant pressure and reduced mobility; typically, in people who are wheelchair-bound. The sores can worsen, causing severe pain; doing extensive damage to muscles, tendons, and bones; and leading to severe infection, in which case they can be fatal. The direct annual cost of treating pressure ulcers is high: in Canada alone, the cost is $3.5 billion per year.

The treatment and prevention of pressure ulcers is one of three interconnected projects being tackled by the AHFMR Interdisciplinary Team on smart neural prostheses. This 16-member team brings together neuroscientists, biomedical researchers, engineers who specialize in microelectronics and wireless communication, nanotechnology experts, physicians, nurses, and rehabilitation medicine professionals. They come from the University of Alberta and the University of Calgary, as well as clinical-partner centres, industrial partners, and patient groups.

Pressure ulcers form when dead tissue becomes infected

The goal of the pressure ulcer project is to design form-fitting garments that will stimulate muscles of wheelchair-bound and bedridden patients to prevent pressure ulcers from developing. When these patients stay in one position for a long time without shifting, blood flow to the muscles and skin is cut off, and the tissue dies because it lacks oxygen. Pressure ulcers form when this dead tissue becomes infected. The project is led by AHFMR Senior Scholar Dr. Vivian Mushahwar, a biomedical engineer at the University of Alberta and a co-leader of the AHFMR Interdisciplinary Team. Her team is working on a device that would detect increased pressure and lack of oxygen in the muscles of the buttocks and then stimulate nerves to clench those muscles in response. The idea is to incorporate the sensors and stimulators into a kind of “smart underwear” that would simulate the fidgeting movements that a person with sensation would normally make. Even such small movements are enough to keep the tissues supplied with blood and oxygen, and thus prevent pressure ulcers from forming.

The device could make a tremendous difference in the life of anyone who is confined to a wheelchair. “It would take me 20 years to get the results that this team will be able to achieve in five years,” says Dr. Mushahwar. “Our team is designing neural devices with input from the people who will use them, and from the doctors and rehabilitation specialists who know the risks, and themselves have dreamed of creative solutions.”

Quick Facts

Actor Christopher Reeve died at the age of 52 from complications that were reported to be related to an infected pressure sore. Reeve was paralyzed in 1995 in a horseback riding accident.

The sores can lead to severe infection and death

Alberta Health and Wellness
Alberta Health and Wellness provides funding to the AHFMR Interdisciplinary Team Grant program.
Neural prostheses

Smart underwear to prevent pressure sores is part of a bigger project this team is tackling; namely, the development of neural prostheses—devices that connect with the nervous system and restore functions lost because of nerve damage. One of the most highly regarded neural prostheses available today is the WalkAide, invented by Dr. Richard Stein, a physiologist at the University of Alberta and a principal investigator in the neural prostheses team. The WalkAide stimulates a nerve in the muscle that lifts the foot, helping people who cannot lift their foot properly to walk normally.

Building on the success of the WalkAide and the knowledge gained from the smart underwear, Dr. Stein and Dr. Mushahwar are developing devices that help people with spinal-cord injuries to stand and walk. But whereas the WalkAide stimulates only one nerve, a device to enable standing or walking requires carefully coordinating the stimulation of many nerves all at once.

Such a device will likely use the intraspinal microstimulation (ISMS) technology that Dr. Mushahwar pioneered—which uses hair-like microelectrodes implanted directly into the spinal cord. Moreover, Dr. Stein explains, the ISMS device would also record sensory feedback from the legs and hips to help the patient navigate. “It will allow the device to function in the real world, because when you’re walking you need to deal with obstacles in your way.”

Using the knowledge gained from ISMS, Calgary neurosurgeon and AHFMR Clinical Investigator Dr. Zelma Kiss leads a project aimed at restoring sensation to the arms and legs of people with spinal-cord injuries or neural diseases. “These patients often lose the ability to sense where their limbs are,” she says. “This is incredibly disabling.”

Dr. Kiss specializes in deep brain stimulation, a technique which involves surgically implanting an electronic device (similar to a pacemaker) into the patient’s brain. Dr. Kiss will apply patterns of electrical stimulation to specific parts of the brain, and test whether the brain can interpret these signals as sensation. “We want to see if we can evoke more natural feelings of sensation. This is incremental work. I hope by the end of five years we’ll have proven the principle that we...
Taking on Healthcare’s Sneaky Killers

Can take a damaged nervous system and reactivate it by stimulating the right places.”

“Some of the devices, like the pressure ulcer garment, are closer to commercialization, and others will take longer to develop,” Dr. Mushahwar explains. “In the end, we hope to achieve a repertoire of enabling technologies that could be applied to restore various functions and significantly improve quality of life.”

Dr. Stein notes that “the time is right to build on the success we’ve had in Alberta with neural prostheses; not just my research, but other labs in Edmonton and Calgary. What has been science fiction for so long—restoring movement and sensation in people whose nervous systems have been damaged—can now be turned into science fact.” Important advances in three key areas have been made over the last decade: Neuroscience has moved ahead—in fact, it has been estimated that 90% of what we know about the brain has been learned in the last 10 years. Microchips are now much smaller and far more powerful. And computing power has increased dramatically.

“We need all these advancements to make smart neural prostheses, and they are coming together now,” adds Dr. Stein. *
Chances are, you’re sitting down right now.
Pay attention to how many times you adjust your position while reading this article: you’ll probably be surprised by just how much you fidget. That’s a good thing. Unfortunately, people who are wheelchair-bound or bedridden cannot fidget; and this immobility can cause pressure ulcers—sores that develop if blood flow to deep muscle tissue is cut off during long periods of sitting or lying in one place. The tissue dies, forming an open wound that can also become infected, extremely painful, and life-threatening.

AHFMR Senior Scholar Dr. Vivian Mushahwar’s team at the University of Alberta is developing an innovative way to prevent these sores from forming. Their “smart underwear” uses brief, periodic jolts of electricity to stimulate the muscles of the buttocks. The resulting muscle contractions distribute pressure around bones, increase blood flow and bring oxygen into tissues—possibly more effectively than having a nurse turn the patient. The team has already developed sensors to monitor pressure and indicate when electrical stimulation is needed, as well as electrodes to deliver the electrical stimulation. Now they are turning their attention to designing a garment that can put this technology to work.

The team is working closely with health professionals and patients at Edmonton’s Allen Gray Continuing Care Centre, the Glenrose Rehabilitation Hospital, Home, and Continuing Care Centre in Edmonton, and the intensive-care unit at Calgary’s Foothills Hospital. “Although the technology will be the same, the actual garment will have to be different to meet the needs of various types of users,” says Dr. Mushahwar. “What will work for a person in a wheelchair will likely not be suitable for an individual who stays in bed all day, or a patient in the ICU. This is what we’re sorting out now.”

Smart underwear
STORY BY CONNIE BRYSON / PHOTO BY VEER

Immobility can cause pressure ulcers