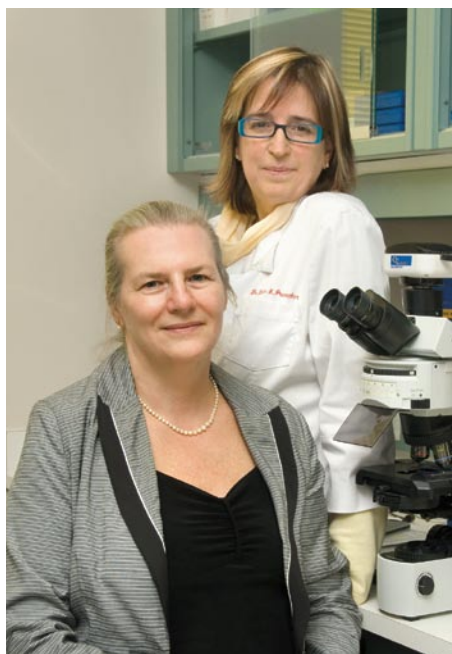


A dynamic duo fighting ovarian cancer

One half of the duo is a basic researcher, the other a clinical researcher. They decided to form a team 20 years ago to defeat ovarian cancer. This type of cancer is one of the deadliest — 70% of its victims die within five years of being diagnosed. In light of this stark statistic, the CRCHUM'S Anne-Marie Mes-Masson and Diane Provencher adopted a team approach characterized by innovation, dynamism and exemplary complicity.

➔ By Marie-Josée Richard



Anne-Marie Mes-Masson
and Diane Provencher

PIONEERS OF TRANSLATIONAL RESEARCH

Anne-Marie Mes-Masson, Director of the CRCHUM'S cancer research theme and Director of the FRSQ'S Cancer Research network, and Diane Provencher, gynaecologist and Director of the CHUM'S Oncological Gynaecology Service, are indeed a dynamic duo.

They are pioneers in the development of translational research, a research model in which basic laboratory research and more clinically-oriented research are unified in an integrated continuum. As Mes-Masson points out: "Diane let me know that she had no interest in curing mice with cancer. At our very first meeting, she told me that she had "patients to save." So our starting point has always been the needs expressed in clinical settings. The first step is to identify a problem, and then we move to the laboratory in the hope of resolving it. Once a solution has been found or tentatively identified, we test it with patients, which, in turn, raises new questions and sends us back to the laboratory."

In 1990, examples of this kind of collaboration were few and far between. Today, however, its success in delivering results has encouraged an increasing number of researchers to adopt it. For Mes-Masson and Provencher, two decades of hard work have begun to yield interesting results.

COMBINING EARLY DETECTION AND TREATMENT

Mes-Masson and Provencher head up the Ovarian Cancer Group, a laboratory with two major research foci: perfecting early detection tests and developing better treatments. Together, these two aspects are the key to defeating ovarian cancer. Early detection of this cancer is virtually non-existent. In its first phases, it is almost asymptomatic. Moreover, even though post-diagnosis life expectancy has risen from one to five years, the survival rate still remains at 30%.

Hunting for biomarkers

"To detect the presence of ovarian cancer in the blood, you have to take the time to understand what the tumour expresses," notes Mes-Masson, "Our lab has already identified ten promising biomarkers [molecules in the blood that signal the presence of a tumour]. We are currently testing them with blood samples from 700 women." Quebec's Ministry of Economic Development, Innovation and Exports (MEDIE) and a number of private-sector partners have expressed considerable interest in this research. In 2003, Mes-Masson and Provencher undertook a collaborative research project with Alethia BioTherapeutics' Mario Filion. This project

➔ Continued on page 6

From molecules to humans

Osteoarthritis is a debilitating and slowing developing disease that affects 15% of the industrialized world's population. More particularly, it affects 65% of people aged 60 years and older. Johanne Martel-Pelletier, a member of the CRCHUM's musculoskeletal research program and Director of the Osteoarthritis Research Unit, has made many significant and innovative contributions to the understanding of the causes of this disease and to its treatment.

➔ By Dalila Benhaberou-Brun

A DISEASE THAT HAS GROWN IN IMPORTANCE

It is anticipated that the number of people suffering from osteoarthritis will double by 2030. "It's worrisome," says Martel-Pelletier, "because by the time it's diagnosed, the disease has already caused severe damage." Osteoarthritis develops over several years before becoming symptomatic and inciting people to consult a physician. People with osteoarthritis experience pain in their joints. Despite the existence of so-called dormant phases and our understanding of certain risk factors, such as age and obesity, we are still in the dark about the cause of the resurgence of the disease symptoms. Current treatments range from analgesics to relieve the symptoms to surgical replacement of the affected joint because of the extent of tissue degeneration. The disease can also affect younger people following injuries. For example, it is not unusual for professional athletes to be forced to have hip or knee replacements.

STARING FROM SCRATCH

"At a very young age, I discovered the term *physiology* and its implications," says Martel-Pelletier, "and I decided to study in this field without knowing where it would lead me." She obtained a Bachelor's degree in molecular biology and completed her graduate degrees in physiology. Following a postdoctoral fellowship in biophysics, she embarked on a second one in rheumatology.

For the last 30 years, Martel-Pelletier has worked in the CRCHUM's Osteoarthritis Research Unit, which she co-founded with Dr Jean-Pierre Pelletier. "The idea was to create an environment in which my work could encompass everything from molecules to humans," notes Martel-Pelletier. And with her background in both physiology and molecular biology, she has been able to carry out novel work on the inflammatory component of osteoarthritis.

"In the early 80s, little was known about osteoarthritis," recalls Martel-Pelletier. She began with limited technological resources, but had "an analytic approach with an open mind." She and her research team attempted to explain the mechanisms of osteoarthritis by studying the main joint tissues: the cartilage, synovial membrane

and subchondral bone. They have made major breakthroughs in the pathophysiology of the disease, as is illustrated by their impressive number of publications and abstracts in peer-reviewed journals and guest speaker appearances, not to mention their international reputation and active participation in various scientific societies devoted to rheumatology and other disciplines.



Johanne Martel-Pelletier

INTERNATIONAL RECOGNITION

In recognition of their scientific accomplishments, Martel-Pelletier and her husband and colleague, Dr Jean-Pierre Pelletier, were recently awarded the 2010 King Faisal International Prize for Medicine. This annual competition draws nominations from around the world and has only been won by two other Canadians since its creation in 1976. Martel-Pelletier is also the recipient of three other distinguished scientific awards honouring her excellence in osteoarthritis research.

LEADERSHIP AND ORGANIZATION

In her day-to-day activities, Martel-Pelletier oversees the management of the Osteoarthritis Research Unit, its research activities and the organisation of national and international meetings.

Her collaborations with engineers and specialists in radiology and biophysics have led to the development of imaging systems to quantify the volume and thickness of certain joint tissues.

She insists on collaborative activities with rheumatologists: "researchers tend to work alone, but it is important to bring physicians and researchers together through exchange venues such as reading clubs and scientific meetings." She likes to surround herself with experts in complementary fields. In this regard, her collaborations with engineers and specialists in radiology and biophysics have led to

the development of imaging systems to quantify the volume and thickness of certain joint tissues. As she notes, "this project seeks to develop objective tools for reliable and accurate diagnosis of diseases and for testing the effects of new drugs aimed at halting the disease at an early stage."

In light of this impressive career, when asked how she manages to get everything done, she replies with a smile "I try to be organized and to demonstrate leadership. I try to anticipate potential problems and to have a plan B as well as a plan C."

WOMEN IN SCIENCE

When asked about the place of women in research, she simply says, "When I began my career, the medical research field was somewhat of an old boys club with the men at centre stage and limited access to women. Today, fortunately, this is no longer the case. In our research unit, people are selected because of their expertise; being male or female is of no importance at all." ■

When the infinitely small leads to big discoveries!

For the past 25 years, the CRCHUM's Johanne Tremblay has followed her passion for molecular biology. Her area of expertise? The genetics of hypertension and type 2 diabetes, two extremely common diseases. 25% of the world's population suffers from arterial hypertension. In 15 years, this number could well increase by 60% and affect 1.5 billion people. ⁽¹⁾ Moreover, 50% of diabetics also suffer from hypertension. In women over 60, this proportion jumps to 90%!

➔ By Marie-Josée Richard

This deadly tandem is a cause for alarm since it is often accompanied by other complications such as heart problems, amputations, blindness and kidney failure, and we have yet to understand the causes. Johanne Tremblay's recent discoveries could lead to an end to this Russian roulette.

SHERLOCK HOLMES IN THE LABORATORY

Tremblay, who heads up the CRCHUM's cardio-metabolic diseases research theme, studies the genomic signatures that signal the onset of cardiovascular complications in patients with type 2 diabetes. Whereas genetics targets specific genes, genomics looks at the entire genome sequence, that is, all of a person's genetic material. As Tremblay puts it, "we try to understand why certain diabetics develop complications while others in the same environment, even those using the same drugs, appear to be exempt." Not surprisingly, this is a very complex undertaking. A single human cell contains no less than 30,000 genes and 2 million possible markers. "Not only do we have to grasp the function of each of these genes, we also have to reconstitute the entire sequence," Tremblay notes.

EUREKA!

Tremblay nevertheless recently succeeded in identifying two genes that play an important role in the onset of hypertension. This discovery is the latest in a series contained in some 200 published articles and numerous patents. Building on these discoveries, her team is currently at work on the development of preventive and diagnostic tests which will become powerful tools in identifying patients at risk of hypertension and/or type 2 diabetes, not mention those who could develop complications affecting their kidneys, vision, heart, brain or vascular system. It should soon become possible to provide preventive treatments for patients carrying the defective gene — that is, intensified medical monitoring and prescribing a healthier diet and lifestyle. "Our goal," she says, "is not to heal people who have the disease, but to delay its onset as well as that of its complications."

Sources

(1) The Lancet, 2005: www.ncbi.nlm.nih.gov/pubmed/15652604

(2) Vers une médecine personnalisée: www.cyberpresse.ca/sciences/genetique/200904/07/01-844221-vers-une-medecine-personnalisee.php

NO SHORTAGE OF LABORATORY WORK

Thanks to samples provided by the ADVANCE project — a cohort of 11,000 Caucasians with type 2 diabetes, her laboratory was able to pro-



Johanne Tremblay

file the genotype (all of an individual's genetic characteristics) of 3,000 candidates. The data collected made it possible to make genetic correlations and to distinguish between true ones and those which come about by chance. Tremblay has her sights set on extending this research to other races, with cohorts of people of Chinese, Indian and African origin.

TAKING A STEP IN THE DIRECTION OF PERSONALIZED MEDICINE

Tremblay believes that the future will be the age of personalized medicine, recently defined by the American Congress as "the application of genomic and molecular data to better target the

delivery of health care, facilitate the discovery and clinical testing of new products, and help determine a person's predisposition to a particular disease or condition." In other words, it is an approach tailor made to each individual that takes into account his or her genetic baggage. It should not come as a surprise that interest in this approach is very widespread. It holds the promise of a numerous benefits.

As Tremblay points out, "all drugs are effective in only about half the population. Our research expertise seeks to make it possible to identify patients who are likely to respond better to a given drug because of their genetic makeup." She is referring here to pharmacogenomics, a research field that

Tremblay nevertheless recently succeeded in identifying two genes that play an important role in the onset of hypertension. This discovery is the latest in a series contained in some 200 published articles and numerous patents.

looks into the impact of drugs as a function of individual genetic profiles. Not to be forgotten is the fact that drug side effects are among the top six causes of death and hospitalization in North America.⁽²⁾ This approach will be of great benefit to these people as well.

There is another striking example of the benefits of this approach. Removing drugs from the market costs pharmaceutical companies millions of dollars. However, as Tremblay notes, "some of the drugs taken off the market could have a second life if we are able to identify the patients who might experience undesirable side effects when ingesting them." As might be imagined, pharmaceutical companies are following the development of personalized medicine, not to mention the expertise developed by Johanne Tremblay and her team, with considerable interest. Thanks to her work as well as that by many other researchers, the coming decade holds considerable promise. ■

Piercing the mystery of multiple sclerosis

Described for the first time in 1868 by the French neurologist Jean-Martin Charcot, multiple sclerosis has yet to reveal all its secrets. Indeed, its cause is still unknown. Nathalie Arbour, a researcher with the CRCHUM, has devoted her work to understanding and treating this disease.

➔ By Dalila Benhaberou-Brun

MULTIPLE SCLEROSIS IN CANADA

Multiple sclerosis (MS) is a degenerative disease that affects young adults. It destroys the sheath that protects the cells of the central nervous system. This sheath, called the myelin, is crucial for the transmission of nerve information throughout the body. Sclerosis takes the form of lesions or plaques and leads to the paralysis of limbs, tingling sensations, visual problems or problems of coordination and balance. MS affects between 55,000 and 75,000 Canadians, three-quarters of whom are women. Its progression, which varies from one person to the next, is unpredictable and has a debilitating impact on quality of life.

DIALOGUE BETWEEN THE CENTRAL NERVOUS SYSTEM AND THE IMMUNE SYSTEM

Arbour joined the CRCHUM in 2006 and is a member of its neuroscience research theme. Funded by the Multiple Sclerosis Society of Canada, the Fonds de la recherche en santé du Québec, the National Science and Engineering Research Council of Canada, the Canadian Institutes for Health Research and the Canada Foundation for Innovation, her work focuses on attempting to understand the dialogue between the central nervous system (CNS) and the immune system. In particular, she studies CD8 T cells, white blood cells able to kill other cells and which play a key role in viral diseases and in MS. These T cells have been found in the brains of deceased MS patients.

By studying the brain cells retrieved from deceased patients as well as samples of blood and cerebrospinal fluid – or the cerebrospinal fluid protecting the brain and the spinal cord –, she hopes to be able to explain how CD8 cells

infiltrate and destroy part of the brain and the way in which the CNS reacts to this attack. Current medication for MS only serves to reduce inflammation and the frequency of MS episodes. Arbour's ultimate goal is "to find the key that will allow us to develop new treatments."

KEEPING IN TOUCH WITH PATIENTS

Even though she is a basic scientist who works with animal and human cells in a laboratory en-



Nathalie Arbour

vironment, she maintains frequent contacts with multiple sclerosis patients. In addition to presenting her research findings at scientific conferences, she and her team participate each year in the march organized by the Multiple Sclerosis Society of Canada.

A WOMAN WITH A PASSION

"As a little girl, I liked to explain things to my classmates," recalls Arbour. Although her mother was an artist and her father worked in construction, her interests turned to science: "My parents always encouraged me even though they had no idea where it would lead."

In addition to presenting her research findings at scientific conferences, she and her team participate each year in the march organized by the Multiple Sclerosis Society of Canada.

Drawn by intellectual challenges, she undertook an undergraduate degree in microbiology and immunology, followed by a Master's degree in virology and immunology. For her doctoral studies, her research focused on the potential involvement of viruses in the onset of multiple sclerosis. Her postdoctoral research was conducted at the Scripps Research

Institute in California, which was where her desire to become a researcher took hold. She learned all about the exigencies of data collection, how to write scientific articles and to collaborate with neurologists specialized in MS. Upon her return to Montreal, she worked at the Montreal Neurological Institute and was subsequently recruited by the CRCHUM in 2006.

WOMEN IN THE RESEARCH COMMUNITY

When asked about her views on the place of women in the research community, she replies that while women are in the minority on scientific committees, "they sit as equals with men." And although they are well represented in university programs, not all women necessarily undertake a research career. She adds that "in the research hierarchy, very few women hold positions of responsibility, such as department head or director of a research centre. However, their numbers are growing and stand as examples for future generations of young women." ■

When Mommy has diabetes

Gestational diabetes induces kidney malformations in children. When they reach adulthood, they typically have health problems such as hypertension or kidney diseases. For the last five years, Shao-Ling Zhang has been working to understand the mechanisms underlying these problems in the CRCHUM's Paediatric Molecular Nephrology Laboratory.

➔ By Dalila Benhaberou-Brun

A UNIQUE APPROACH

With funding from the CIHR, the Kidney Foundation and Canada, the FRSQ and the Canada Foundation for Innovation, Zhang has developed a unique research program: *Gestational diabetes and perinatal programming of kidney and cardiovascular diseases*. She has observed that mice with untreated diabetes during pregnancy give birth to underweight babies whose kidneys display serious malformations. As adults, some of these babies will suffer from hypertension, obesity and diabetes. "They are victims of what is known as perinatal programming," notes Zhang, "a complex and mysterious condition that affects embryos and adults alike." It is Zhang's goal to help prevent diseases in children whose mothers suffer from gestational diabetes. "I have a daughter and I feel touched by the subject," she adds.

Zhang has published several articles in this field which elucidate the mechanisms related to this phenomenon. This work has earned her several awards. Although she is a basic research who only works with animal models, she regularly communicates the results of her research to paediatricians and nephrologists. With funding from the Canada Foundation for Innovation, she is currently developing tools for preventing hypertension and kidney complications related to diabetes. This program will enable her to further our understanding of the factors that predispose offspring to kidney and cardiovascular diseases.

FROM LAB TECHNICIAN TO LAB DIRECTOR

After eight years as a lab technician, Zhang decided to return to university to complete her graduate studies in Montreal. In one respect, the step was not a big one: "because of my experience in nephrology, I had a good

grasp of the technical aspects. So, for me, it was like going from my lab to work in a colleague's lab." With one small difference – her supervisor was in Montreal and she was in China.

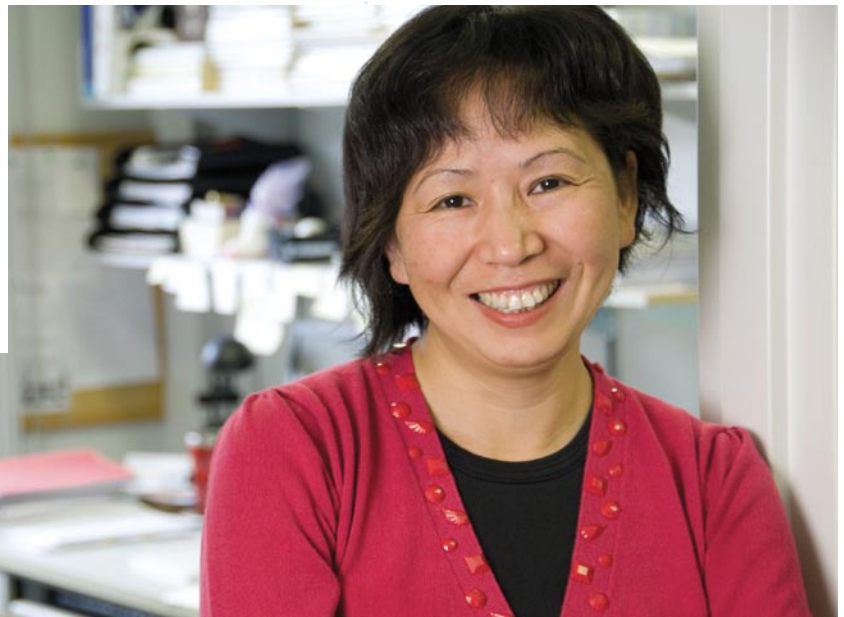
The adaptation was not easy because of the language difference: "Since I only spoke Chinese at the time, it was a quite a challenge for me to learn French and English at the same time." With support from friends and colleagues, Zhang got

health problem, asking the right questions and drawing simple conclusions. She recalls trying to explain an idea to her director: "With two words, she summed up what it was I wanted to say."

Shao-Ling Zhang is proud of the road she has taken and of her perseverance. In her view, success in research has everything to do with team spirit and the passion of each of its members, not to mention a touch of fantasy.

With funding from the Canada Foundation for Innovation, she is currently developing tools for preventing hypertension and kidney complications related to diabetes.

Zhang has published several articles in this field which elucidate the mechanisms related to this phenomenon. This work has earned her several awards.



Shao-Ling Zhang

through the linguistic and cultural transition, completed her doctorate and earned several awards along the way.

Armed with her determination and a CIHR fellowship, Zhang went on to do postdoctoral studies at the Harvard Medical School. "Had someone told me that I would work there one day, I wouldn't have believed them," says Zhang. This work enabled her to acquire the techniques of her trade: focusing on an important

A DIFFERENT WAY OF LOOKING AT THINGS

"Women ask different kinds of questions," muses Zhang, "Men are more rational, less emotional and focus their attention on different objectives." While not wishing to turn this into a value judgement, Zhang feels that women bring a unique and interesting dimension to basic research and that interactions between men and women in the laboratory yield interesting results. ■

Ovaries and lungs: an alarming correlation

Women who have undergone an ovariectomy (surgical removal of the ovaries) may run a twofold higher risk of lung cancer.

This alarming correlation is the result of a study conducted by Anita Koushik, a CRCHUM epidemiologist.

Her study echoes a similar epidemiological study conducted by a team at Harvard University at roughly the same time. "It just goes to show that it is important to conduct more research before rapidly jumping to conclusions," stresses Koushik.

Her research team studied 422 lung cancer patients in 18 Montreal-area hospitals as well as 577 healthy control subjects. In particular, the research team gathered information pertaining to medical history, socio-demographic status, professional activities and lifestyle (e.g.: whether they smoked or not). Among women who have had their ovaries surgically removed (either a bilateral ovariectomy or an ovariectomy and concomitant hysterectomy), a twofold increase in

the incidence of cancer was observed. This surgical procedure induces premature menopause, which leads to a decrease in the production of oestrogen. For many years, this decrease has been routinely treated through systematic use of hormone therapy.

The question is: do the ovaries or oestrogen levels play a protective role for the lung? Is long-term hormone therapy the culprit here? "These questions have to be examined more thoroughly by repeating and refining studies of larger samples of people before we can affirm correlations with certitude," notes Koushik, who hopes to share her research findings and information with other major international research teams. ■



Anita Koushik

→ Continued from page 1

received \$8 million in funding from Genome Quebec and Genome Canada. Since then, with support from various funding sources, including the Canadian Institutes of Health and the MEDIE, the two researchers have been able to develop antibodies to fight ovarian cancer cells, and this approach is now being used for breast cancer.

Towards better treatments

Over the past 20 years, Masson and Provencher have built an impressive database called the Tissue and Data Bank (TDB). This bank contains 3,000 samples taken from both malignant and benign ovarian tumours. This approach has enabled the TBD to develop its own cell lines. In contrast to using cell lines from outside laboratories, Masson and Provencher now have access to a wide range of information: type of cancer, age of the patient, treatments received, family medical history, response to treatments, etc. The availability of this information has an enormous beneficial impact on the quality and precision of their research activities.

These cell lines are used for conducting various tests on animals in vivo, that is, in a living milieu that resembles what happens with patients. In this way, it is possible to observe the evolution of tumours in response to various treatments and drugs and to conduct various genetic tests. "If we feel that a particular gene plays an important role in the development of cancer, we can extract it from our cell line and see whether or not a tumour forms in a mouse," says Mes-Masson.

The two researchers are also involved in Cancer Ovary Experimental Unified Resources, a pan-Canadian project bringing together affiliated research centres from every Canadian province. It will allow for the creation of a vast, shared data bank related to ovarian cancer.

RECONCILING FAMILY OBLIGATIONS AND CAREER IMPERATIVES

In Provencher's view, her career has not been slowed down because of her seven pregnancies or because she is a woman: "I feel that I have accomplished what I set out to do."

Nevertheless, the road is not always easy for researchers who are also mothers. Mes-Masson and Provencher feel that women should receive some kind of recognition when they give birth. At present, women who take time off to take care of a newborn have nothing to show for it

in their academic record. Researchers are rated in good measure as a function of the number of yearly publications. If she does not publish for several months because of maternity leave, there is a huge hole in her record. Provencher has never taken more than three months off following childbirth: "Once, I even had to be back within 30 days of giving birth to honour a research contract, and wasn't given any choice in the matter."

Mes-Masson and Provencher are optimistic about the improvement of working conditions in hospital settings, as much for mothers as for fathers. They are particularly happy about the creation of in-house daycare services, which has made life much easier for them. As Provencher points out: "Mentalities are changing. A few years ago, there was no such thing as paternal leave. We just have to be patient." ■

EXCELLENCE ■ INNOVATION ■ TRANSFER

Research CRCHUM is published three times a year by the CRCHUM — University of Montreal Hospital Centre's Research Centre.

Editor: Richard Ashby ■ Design: Production multimédia CHUM ■ Photographs: Production multimédia CHUM

Contributors: Dalila Benhabrou-Brun, Liliane Besner, Francine Cartier, Mireille Chalifour, Marie-Josée Richard

Free subscription (paper and/or PDF copy): info.crchum@ssss.gouv.qc.ca

Correspondence Research CRCHUM, Bureau d'aide à la recherche, Centre hospitalier de l'Université de Montréal Hôtel-Dieu, Masson Pavilion, 8-113, 3850 St. Urbain St., Montreal, Quebec, Canada H2W 1T7

Legal deposit 2009 ■ Bibliothèque nationale du Québec ■ National Library of Canada ■ ISSN 1918-5936
Reproduction authorized with mention of the source.

www.crchum.qc.ca