FROM RISK FACTORS TO THERAPY: Unraveling the Genetics of Alzheimer's Disease

The research of Dr. Judes Poirier, Director of the McGill Centre for Studies in Aging, Professor of Psychiatry, McGill University, and Senior Scientist, Douglas Hospital Research Centre

by Jeff Boyczuk

In these times of shrinking government research budgets, scientists are increasingly pressured to demonstrate that their work will have direct and immediate benefits for the public. "Basic" research, which tends to be theoretically rather than practically oriented, suffers under this "cost-efficient" funding plan. One strong argument against such a policy may be found in the career of Dr. Judes Poirier, whose study of the neurobiology of the brain has evolved into therapeutic discoveries.

A Montreal native, Poirier completed his B.Sc. in biochemistry at the University of Montreal in 1982. Realizing that his primary interest lay in neuroscience and aging, he leapt at the offer of a summer research assistantship in the lab of Dr. André Barbeau. Barbeau, renowned for his pioneering work in Parkinson's disease, employed Poirier as a "test run" before admitting him to the lab as a graduate student. The relationship was a good one and the project for which Poirier had been hired -- a search for peripheral blood markers for Parkinson's disease -- grew into his M.Sc. thesis. Besides the invaluable research experience he gained, Poirier credits Barbeau's passion for science and discovery with his own commitment to a career as a scientist. "After my M.Sc. there was an (Continued on page 2)
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interest. After my M.Sc. there was conviction.”

Poirier stayed on with Barbeau for his Ph.D. at the Clinical Research Institute of Montreal (CRIM). Unfortunately, tragedy struck shortly before he completed his degree, when Barbeau suffered a series of heart attacks. With the chances for his recovery poor, all of Barbeau's graduate students left the lab, save Poirier. As expected, Barbeau died shortly thereafter, leaving Poirier in the final stretch of his dissertation with a back-up supervisor, who was unfamiliar with much of his project. Compounding this challenge was a request from the authorities of the CRIM that Poirier take on the responsibility of shutting down the lab, since he was the one most familiar with its day-to-day operations. "I embarked on a one year thesis-writing / lab-closing effort… I learned how to manage a lab while I was 24 years old. This was an exciting experience when I discovered not only that I liked science, but that I could handle the process of administrating, coordinating and planning a research lab program.”

After receiving his Doctorate, Poirier went on to work with Dr. Caleb Finch at the world-renowned Andrus Gerontology Center in California. Finch, known for his work on Alzheimer's, suggested to Poirier that the only way to go about understanding the disease was through a consideration of genetics and the use of molecular biology tools. The two decided to direct their efforts towards identifying genes that were activated during the active phase of brain regeneration. As Poirier notes, this line of investigation had particular relevance to Alzheimer's disease, which is characterized by progressive cell death: "The brain is not static. When cells are dying it reacts by building new pathways. It reacts by rewiring itself, essentially. That's typical of the adult as well as the young human brain.”

Employing rat models, over the next two years Poirier and Finch identified three genes that played a role in brain regeneration, the most important of which coded for the cholesterol-processing protein apolipoprotein E (ApoE). The job of ApoE is to transport lipids, particularly cholesterol, from one cell to another in the brain. Cholesterol and phospholipids are the building blocks of axon branches, and hence a critical ingredient in the process of forming new synapses. It was with this exciting discovery in mind that Poirier returned to Montreal in 1989 to become part of the newly established McGill Centre for Studies in Aging (MCSA).

Recruited by the first director of the MCSA, Dr. Serge Gauthier, Poirier's background in molecular biology and neurodegenerative disorders fit perfectly into the Centre's multidisciplinary research program that targeted normal and abnormal aspects of aging. Besides the appeal of being able to return to his hometown, Poirier was enticed to the MCSA by the opportunity of contributing to its establishment. "I'm a builder…to be there when the whole thing is just put into motion was what really appealed to me.”

Backed by startup grants from the Fonds de la recherche en santé du Québec and the Medical Research Council of Canada, Poirier got busy exploring the implications of the ApoE gene for the Alzheimer's brain. A surprising initial finding was particularly low levels of ApoE in the brains of some Alzheimer's patients. This was in fact the opposite result expected, since cell damage induced by the disease was expected to generate compensatory regeneration, with a corresponding increase in ApoE. Such a result had been seen in his earlier work with rats. "That left only two possibilities. There was something fundamentally wrong with these patients' ability to produce ApoE, or there was a glitch in their genetic makeup that prevented ApoE from being produced.”

The second explanation turned out to be correct. In 1993, Poirier's lab identified a genetic mutation in the ApoE gene that was strongly associated with common Alzheimer's, the form of the disease that has no identifiable family history. The publication of this finding came four weeks after a paper by Alan Roses from Duke University, showing that the same mutation had a similar association with familial Alzheimer's. Beyond identifying this gene, known as ApoE4, as a risk factor for Alzheimer's, Poirier also found that it had some predictive power regarding the age of onset of the disease, its rate of progression, and the extent of the pathology. These factors depended on whether carriers possessed one or two copies of the gene.

The story of ApoE gene and its role in Alzheimer's was still just unfolding. In 1995, Poirier found a link between the genetic makeup of Alzheimer's patients and their individual response to drug therapy. "We discovered that the same ApoE gene, depending on the type of genetic anomaly you carry, will directly influence whether or not a memory enhancing drug will work. This was the birth of what we now call pharmacogenomics -- the influence of genes on drug response.” While other researchers had suggested such a relationship, Poirier's study provided the first conclusive evidence for brain disorders.

The implications of this finding were far-reaching. Besides revealing the necessity of genetic testing for Alzheimer's patients prior to proceeding with costly drug therapy, it also raised the possibility that previous experimental
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drugs that had been found ineffective may have been tested on subjects who had some genetic predisposition against them. The importance of this discovery was certainly not lost on the Wall Street Journal, who interviewed Poirier a week after the results were made public, sensing the long-term impact that genetic testing would have for the pharmaceutical industry.

Poirier was also aware of what these results might mean to private interests, leading him to file for a patent on ApoE testing before publishing the finding. The sometimes complicated relationship between publicly-funded research and private industry is something that he had become aware of a year earlier when a friend at the McGill Office of Technology Transfer suggested protecting his work on the ApoE gene. "That's when I really understood and learned what it meant to protect your ideas and intellectual property… which is not something we learn to handle through regular training programs."

Industry interest in Poirier's work is likely to continue as he has embarked on what he describes as the most exciting aspect of the ApoE story -- a potential drug therapy for Alzheimer's sufferers. Realizing that ApoE levels in some Alzheimer's patients were unexpectedly low, Poirier's lab set out to find a drug that might increase ApoE production. Through animal studies, several drugs were identified that had the desired effect. The one that was the most exciting was a drug that had been previously on the market in North America, used for lowering cholesterol, and had been shown to have little or no side effects.

Poirier's next step was to test the drug in human patients. A study was commissioned in collaboration with MCSA neurologist Michel Panisset with 12 subjects suffering from common Alzheimer's. After a drug trial, only half of the subjects showed improvements in symptoms. As it turned out, the pattern of positive and negative outcomes was strongly associated with subjects' ApoE genetic profiles - further proof of the gene-drug response relationship. However, the extremely exciting finding in this study was that patients who did show an improvement in symptoms turned out to only be ones in which the drug had the desired effect of increasing ApoE levels in the brain.

While Poirier stresses that ApoE drug therapy is not a cure for Alzheimer's, it could have a positive impact not only on patients already afflicted, but also perhaps those who are already afflicted, but also perhaps those who are...

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PUBLIC LECTURE SERIES
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acetylsalicylic acid (ASA), which turned out to be much more tolerable. In 1898 the Bayer Company produced this compound in what we know today as Aspirin®. Interestingly, the action of ASA in the body was only discovered 75 years after its discovery. In 1974, a British chemist by the name of John Wayne found that ASA worked by inhibiting a natural enzyme in the body called cyclooxygenase (or COX). He subsequently won the Nobel Prize for his discovery.

The role of COX is to synthesize a family of molecules called prostaglandins (PG). These molecules have different roles in different parts of the body. In the stomach they help make mucus and other juices that protect the lining of the stomach. In the kidney they help make urine. In the platelets they help the coagulation process. Finally, in the joint, they induce inflammation and pain. The inhibition of these molecules in the stomach by ASA is the reason for the common side effect of stomach ulcers found in chronic users of ASA. However, by blocking PG synthesis in the joints, ASA reduces pain of arthritis.

In the early 1990's it was found that the COX molecules are of two distinct types, called COX1 and COX2. COX1 is responsible for stomach protection, and COX2 is dormant unless there is inflammation as occurs in the joints. It was also found that these two molecules have different structures. This finding started drug companies to produce specific drugs that could stop the action of COX2 selectively and allow COX1 to continue its function. The importance of medications that spare COX1 is important since gastric ulceration and bleeds are devastating side effects of ASA. Studies have shown that more elderly people die from these causes than from motor vehicle accidents. The quest to find specific COX2 inhibitors has been achieved only recently. Two medications have entered the marked, called Vioxx® (rofecoxib) and Celebrex® (cecloxicib). Even though these drugs do not have a bigger effect on joint pain, they do have much less side effects.

Dr. Tannenbaum also explained that there are other classes of medications available in the market. One class called DMARD (Disease Modifying Anti-Rheumatic Drugs) includes methotrexate, plaquenil, and imuran. Dr. Tannenbaum noted that these medications could be very toxic. Studies have shown that after one year, 50% of patients stop these medications because of their many side effects. This shows that even though these drugs work, we need alternatives.

The most recent class of medications to enter the market has taken advantage of our extensive knowledge about molecular mechanisms of inflammation. In order for inflammation to proceed, immune cells need to communicate with each other. Communication between cells is achieved via specific molecules called cytokines. These molecules are sent from one cell and they activate an adjacent cell by binding to their specific receptor. In the past few years we have been able to determine the structure of these molecules and thus design specific drugs that selectively bind to them. One such cytokine that promotes inflammation in arthritis is called TNF-a. Specific drug design has allowed pharmaceutical companies to build molecules that resemble the structure of TNF-a. These molecules bind to the TNF-a receptors and instead of activating them, they block these receptors. In other words, they interfere with the communication between cells, and thus disrupt inflammation. Since these drugs are specific, there should be little side effects. One such drug is called Embrel® (etanercept). Studies have shown that 70% of patients will have moderate improvement, and that 20% will have dramatic improvement in their pain. Unfortunately this medication is only available in the US at this point, and it costs $1500 per month. It has to be given via self-injections, which can also be inconvenient to some patients. Another medication that blocks the TNF-a receptor is infliximab. This is also available in the US only, and must be given via intravenous infusion twice per month. It costs $2000 per treatment. Both these medications have shown very little side effects but Dr. Tannenbaum warns that our experience with them is still premature.

In summary, Dr. Tannenbaum pointed out that we have reached a new era in medicine, called molecular medicine and specific drug design. This is achieved because of our extensive knowledge of diseases at the molecular level. Dr. Tannenbaum is optimistic that we can achieve more relief for this devastating disease in the future.

Dr. Hyman Tannenbaum is Director of the Rheumatic Disease Centre of Montreal.
The Canada Foundation for Innovation

The federal government founded the CFI in 1997 to encourage world-class scientific research and development in Canadian universities, colleges and hospitals.

Some of the key aims of the CFI are to strengthen the research training of young Canadians, to build capacity for innovation and to ensure the best possible use of research infrastructure.

The CFI has a capital investment budget of $1.9 billion, and since its founding, $839.3 million has been invested in research projects throughout the country. In the recent funding announcement this July, $61 million went to McGill University projects. This news is particularly good for McGill because Quebec government matching funds will bring that total to almost $150 million.

The CFI hopes that the creation of state-of-the-art research infrastructure will help Canadian institutions attract and retain world class researchers.

More information about CFI is available at http://www.innovation.ca


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at risk of developing the disease. Epidemiologists have noted that if the average age of onset of Alzheimer's were delayed by five years, 50 percent of the cases worldwide would disappear, due simply to mortality rates. If the age of onset were pushed ahead ten years, 95 percent of Alzheimer's cases would be eliminated. As Poirier excitedly remarks, "If this drug works well in patients who are at risk, but are not at the Alzheimer's stage yet, we would probably be able to push this average onset by five or ten years. Although it is not a cure, it could drastically affect the quality of life of these people."

So what is the next step in the ApoE story? Poirier has licensed his discovery to Nova Molecular Inc., a Montreal-based biotechnology firm that will conduct large scale testing of the ApoE-inducing drug in Alzheimer's patients. Nova was founded by Poirier himself in 1995.

If you think that between his prolific research career and industrial ventures Poirier is busy enough, add to the list all the administrative, organizational, and promotional duties that go with his current appointment as Director of the MCSA. Furthermore, he prides himself on being involved in community efforts to teach young students about careers in science. This past summer he served as an ambassador for a summer science camp sponsored by the Medical Research Council of Canada and directed towards underprivileged children. He also finds time every fall to speak to Montreal high school students about careers in biomedicine, and the role of scientists in academia and industry.

Reflecting on the beginnings of his career in the early 1980s, Poirier recalls that aging research was almost considered a "laughable" discipline in the scientific community. Two decades later, with a rapidly aging population, research into age-related disease has grown and continues to grow exponentially, making it one of the priority areas for public funding. With a long list of professional awards and dozens of publications to his name, Judes Poirier's impact in the health sciences and the neurobiology of Alzheimer's disease has already been felt. As Poirier progresses in his relatively young career, we'll be sure to hear more from him as he continues to reveal the relationship between genetics and the biological mechanisms of aging.

For more information on the work of Dr. Poirier see:

WHAT IS VASCULAR DEMENTIA?  
by Jeff Boyczuk

While the popular press has made Alzheimer's disease one of the most discussed afflictions of old age, less attention has been paid to vascular dementia (VaD), which accounts for more than 20 percent of all cases of dementia in the elderly.

The term "vascular dementia" refers to dementia that is the result of one or more cerebrovascular accidents (i.e. strokes). Its onset is sudden, and the effects on cognitive function vary with the site of the brain lesion. As with most forms of dementia, symptoms may include impairments in memory, language, judgment, and abstract thinking. Personality changes are also frequently seen.

Several different types of VaD have been identified, with multi-infarct dementia (MID) being the most common form. MID is caused by a series of small strokes that damage cortical regions of the brain. Sometimes the terms vascular dementia and multi-infarct dementia are used interchangeably, though MID is more commonly considered to be a subcategory of VaD. Those suffering from MID are sometimes not aware that they have suffered a stroke, until it has been confirmed through brain scans.

Typical symptoms of MID include difficulty in remembering recent events, difficulty in communicating or following a conversation, hallucinations, delusions, general confusion, and depression. The progression of MID may be in a step-wise fashion, with sharp deteriorations in mental abilities following each stroke.

Binswanger's disease is another form of VaD that is characterized by damage to subcortical white matter. Binswanger's usually occurs in people over 60, and patients typically have a history of high blood pressure or cardiovascular disease. The disease is slowly progressive, and many patients will die within 5 years of onset.

The risk factors for VaD, which are the same as those for stroke, include high blood pressure, high cholesterol, heart disease, diabetes, and narrowing of the arteries. Through treatment and lifestyle choices, most of these risk factors can be controlled. This distinguishes VaD from dementia of the Alzheimer's type, which has risk factors such as family history and genetic predisposition that are largely uncontrollable.

There is some controversy among researchers surrounding the concept of VaD. Since VaD is characterized by stroke, which may occur anywhere in the brain, VaD subtypes are not easily distinguishable from each other or from Alzheimer's disease. Furthermore, Alzheimer's and VaD may co-occur, what is termed "mixed dementia," often making diagnosis and choice of therapy difficult. Some researchers have suggested that "vascular depression" -- a mood disorder resulting from cerebrovascular changes -- also exists and may be a precursor to VaD. As it now stands, a definitive diagnosis of VaD may only be achieved post-mortem through autopsy.

CONNECTED SENIORS EXPERIENCE PSYCHOSOCIAL BENEFITS  
by Hannah Hoag

Aging is associated with changes in physical mobility, the onset of disabilities (visual impairment, hearing loss, or chronic pain), and life-cycle changes (retirement, death of peers and family), which alter social support networks, and may lead to social isolation.

Near the end of last year, Silvia M. Straka and Fiona Clark set out to improve the psychosocial well-being of frail seniors by providing them with Internet access and the skills they needed to use it. The study, called Connections, ran in 5 Montreal residential and day centres for seniors, and was supported by the Office of Learning Technologies (HRDC), the McGill Centre for Studies in Aging, and McGill University.

Connections attracted 84 participants, varying in age from 68 to 98, with broad ethnic, educational, and employment histories. By providing these seniors with Internet access to on-site computers for 6 months, the study explored and documented the computing interests of the participants, the psychosocial benefits experienced by the participants, and the feasibility of creating this type of resource in residential and day seniors' centres.

Participants were taught the basics of Word, the Internet, and e-mail by an experienced instructor in 9 one-hour teaching sessions, in a 2:1 student:teacher ratio. Following the 9-week instruction period, students continued to use the computers on their own time with the aid of a volunteer. Pre- and post-test interviews evaluated the goals of the study and the participants' experience.

While the Internet and e-mail created, or re-established some seniors' social contacts, other seniors used computers for entertainment (game playing), education and training, and occupational therapy. E-mail was used to write to families and relatives who lived within Montreal or in other countries. Websites that provided up-to-date Canadian news or online versions of newspapers from their home countries were popular, as were sites that provided health and financial information. Games, such as bridge, solitaire, and Wheel of Fortune were popular among participants for amusement and for improving control of the mouse.

Contrary to stereotypes, these seniors were eager and able to learn the intricacies of the computer. With the design and implementation of adaptive training approaches, many seniors learned how to use computers and the Internet, and reaped the benefits. Autonomy, cognitive improvement, mental stimulation, enhanced self-esteem and a sense of competence were identified in the Connections participants.
As a large segment of the Canadian population ages, media attention has been focused on research into aging-related disease, particularly Alzheimer's and Parkinson's diseases. For patients dealing with less common diseases however, information is often scarce. In this issue we present a list of websites that provide information about aging-related conditions that are rarely mentioned in the popular press. All of the sites listed below provide news about the latest research, support for patients and links to further resources.

POLYMYALGIA RHEUMATICA AND GIANT CELL ARTERITIS

http://www.arthritis.ca/pages/polymyalgia (English site)
Polymyalgia rheumatica is a rheumatic disorder that is associated with moderate to severe muscle pain and stiffness in the neck, shoulder and hip. The disease is almost never found in anyone under 50 years of age, and the average age of onset is 70. The cause is uncertain, but treatment leads to improvement of symptoms. About 15% of polymyalgia rheumatica patients also develop giant cell arteritis, a condition that results in swelling of arteries in the head.

SPINAL STENOSIS

http://www.nih.gov/niams/healthinfo/spinalstenosis/spinal_sten.htm (English site)
Spinal stenosis, the narrowing of the spinal canal, usually develops as the spinal discs start to shrink as a person ages. Minor injuries that result in disc inflammation can cause impingement on the nerve root and trigger pain. Spinal stenosis occurs mostly in elderly adults with degenerative osteoarthritis. Patients with spinal stenosis often have the impulse to flex the spine to relieve the stress on the sciatic nerve.

AMYOTROPHIC LATERAL SCLEROSIS

http://www.als.ca (English site)
http://info-sla.iquebec.com/info-sla/index.html (French site)
Amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease) is a neurodegenerative disease that attacks nerve cells in the brain and spinal cord. Although young adults occasionally develop ALS, the disease usually develops between the ages of 40 and 70. The disease is more common in men than in women, but with increasing age the incidence becomes about equal.

PROGRESSIVE SUPRANUCLEAR PALSY

http://www.psp.org (English site)
http://www.chu-rouen.fr/sf/pathol/paralysiesupranucleaireprogressive.html (French site)
Progressive supranuclear palsy (PSP) is a degenerative brain disorder that strikes middle-aged and elderly adults. Early symptoms are similar to Parkinson's disease and include visual disturbances. The cause of PSP remains uncertain and although there is currently no cure, some symptoms can be treated.