GERONTO-McGILL

BULLETIN OF THE McGILL CENTRE FOR STUDIES IN AGING

March - April 2003 ISSN 0838-2263 Volume 19, No. 2

CUT BACK ON THE CALORIES AND LIVE LONGER?

by Jeff Boyczuk

Animal studies have repeatedly shown that restricting the calories consumed by a free-feeding animal by 30 - 40% results in a similar percentage gain in life span. Strengthening the argument that humans might also benefit from cutting calories, a recent study conducted by the National Institute of Aging has found that three biomarkers consistently seen in calorically-restricted animals, are also associated with men who live longer[1].

Previous work has shown that mice, rats and monkeys who were put on restricted diets had lowered blood insulin levels and lower body temperatures. Additionally, calorie-restricted monkeys have also shown a slowing in the decline of DHEAS (dehydroepiandrosterone sulfate), a hormone whose levels in primates drop as a normal part of aging. In a study described in the August 2, 2002 issue of *Science*, NIA researchers compared these biomarkers in rhesus monkeys who were placed on a reduced-calorie diet, to male participants in the Baltimore Longitudinal Study of Aging (BLSA), who were categorized according to their measures on each of the three biomarkers as being either in the upper or

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PAYING ATTENTION TO STIMULI

An interview with Dr. Joseph Rochford, Co-Director of Research on Disorders of Mood, Anxiety and Impulse Regulation, Douglas Hospital

by Alison McTavish

Look at a list of Dr. Joseph Rochford's publications, and you'll see he's studied everything from rats on antidepressants to mice with missing genes. Although Rochford admits that his work may seem like an array of very different things, there is a common denominator. "I'm interested in trying to figure out what happens when an animal doesn't pay the right amount of attention to a stimulus, and then trying to fix it."

In addition to being Co-Director of Research on Disorders of Mood, Anxiety and Impulse Regulation at the Douglas Hospital, Rochford is the Director of Academic Affairs at the Douglas, and Associate Professor of Psychiatry at McGill University, and runs McGill's graduate program in Psychiatry. He is also a member of McGill's Centre for Studies in Aging.

Rochford's original interest wasn't aging. He had been focusing on the influence that different mechanisms of learning exerted on behavior. "When I did my PhD, I was looking at endogenous opiate substrates and habituation to stress-induced analgesia." He found that when animals are put into new environments, they don't feel pain as much. As the animals get to know their surroundings, they begin to respond more to pain.

His interest in aging began when he first came to the Douglas Hospital. "When I got to the Douglas, people like Judes Poirier, Michael Meaney and Rémi Quirion were doing work on these old rats." The researchers were looking to see how the animal's ability to learn and remember things changed with age. Some animals were successful agers that performed well on standardized memory tests, while others were impaired.

Rochford theorized that the behavioral

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PUBLIC LECTURE SERIES
OSTEOPOROSIS: BOOSTING FRAIL BONES

by Julie Comber

A silent, stealthy and potentially devastating illness, osteoporosis, was the subject of the McGill Centre for Studies in Aging's January 2003 public lecture. The guest speaker was Dr. Line Vautour from the Division of Endocrinology at the McGill University Health Centre.

The definition of osteoporosis, "a progressive systematic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to increased bone fragility and risk of fracture", can hardly summon to mind how devastating the disease can be for

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CUT BACK ON THE CALORIES AND LIVE LONGER?

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lower half of the population. The researchers discovered that men in the BLSA who had higher levels of DHEAS, and lowered blood insulin and body temperatures, appeared to live longer, paralleling the monkeys who were on reduced-calorie diets and shared the same biomarker characteristics.

The dominant theory of the link between calorie-reduction and increased life span is a change in metabolism (as indicated by reduced body temperature and insulin levels). Metabolic changes are accompanied by a decrease in the production of cell-damaging "free radicals", which have been fingered as a primary source of human aging. However, it is interesting to note that the male participants in the BLSA did not report any systematic practice of calorie restriction, but still possessed the biological markers that paralleled monkeys in the reduced calorie group. The authors of the study suggest that further research may reveal ways in which humans may activate the same biological processes that have been tied to increased longevity in animals, without resorting to the difficult practice of calorie restriction.

1. Roth, G., Lane, M., Ingram, D., Mattison, J., Elahi, D., Tobin, J., Muller D., and Metter, E. Biomarkers of Caloric Restriction May Predict Longevity in Humans. Science Aug 2 2002: 811.

An interview with Dr. Joseph Rochford, Co-Director of Research on Disorders of Mood, Anxiety and Impulse Regulation, Douglas Hospital

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impairments seen in the rats were more extensive than just memory deficits, and started testing them. "We wanted to know what they liked to go after and what they preferred to avoid," he explains. He found that animals that had difficulty remembering things also didn't like anything new.

"It's almost as if they're walking around with a veil around them. I think it's kind of intriguing that these animals are shutting themselves off from any novel experience. In a sense they're shutting themselves off from the world and living in the past."

It's not clear why some animals are successful agers and others are not. Researchers are looking at different systems, and the hippocampus, a region of the brain involved in taking an experience and turning it into a memory, seems to be a leading candidate. "That's the million dollar question," says Rochford.

Successful aging was a theme Rochford took to school children. He was involved in Joining Generations, an intergenerational program of the Education Task Force of the McGill Centre for Studies in Aging. The goal of the projects was to visit high schools and see what kind of impressions high school students had about the elderly. "That was fun," says Rochford. "We would talk, and then the kids would talk. I asked them what they thought the brain of an old person looked like compared to theirs." Not surprisingly, Rochford got some interesting answers to that question.

Rochford wanted to impress on the kids that sometimes we do lose some brain function as we get older, but that there's a great diversity of how the aging process affects the brain. Many people age successfully and others don't. Was he successful in convincing the students? "According to the report, we were," he laughs. "Yes, I think maybe they're more sensitive to the fact that not all old people are the same. Many are pretty sharp, and that's what we're trying to get at."

Joining Generations wasn't Rochford's only involvement in teaching youngsters. He was also involved in Brain Awareness Week, an international program set up by the Dana Alliance for Brain Initiatives and the Society for Neurosciences to advance public awareness about the progress, promise, and benefits of brain research. Rochford helped set up the program in Montreal in 1998.

"Actually, a graduate student came to me with the idea for setting up the program in Montreal," says Rochford. "He did all the leg work for Brain Awareness Week. I just pointed him to some people who could help him get some funds, and then acted as an advisor for the first two years to help him set things, and then the students took over."

The program has taken off, and now students from most Montreal universities are involved. Each year the students volunteer to give presentations about the brain to elementary and secondary school students in 250 classrooms throughout Montreal. "The students give presentations about illusions to fourth graders and then explain how the brain sees the illusion," says Rochford. "In high schools they orient it towards drugs of abuse and the brain, so it's really geared to interest each audience."

Rochford's interest in the brain also involves studying how antidepressant drugs work. Depression can be a cyclical disease that Rochford believes may involve stress sensitivity. He likens depression to a snowball effect; you get exposed to various stressors, and if you can't deal with them, the detrimental effects add up and snowball, leading to a depressive episode.

He decided to look at the way animals deal with stress by examining rats with increased behavioural reactivity to subtle environmental stressors, like bright lights. Bright lights are not a major stressor for rats, but they prefer to avoid them. Some animals, however, are impaired and have an exaggerated reaction to the lights. Rochford decided to give the impaired animals antidepressants.

When the rats were placed in a novel, brightly lit environment, the rats on antidepressants still had an exaggerated reaction to the light, but they were able to habituate faster. "The antidepressant doesn't remove the reactivity to the stressor," he explains, "it allows the animal to cope with it better."

"This may also be true for humans," says Rochford. "It may well be that people who are hypereactive to these stressors may be predisposed to developing depression." Now he's trying to figure out what antidepressants do in the brain to allow the

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THE FOUNTAIN OF YOUTH GENE

by Alison McTavish

The FoxM1B gene has been shown to regulate the expression of a network of genes that are essential for cells to multiply and for tissues to heal and replenish themselves. As organisms age, the FoxM1B gene doesn't work as well. As a result, cells don't multiply as efficiently as before. Injuries take longer to heal, the skin wrinkles, and muscles atrophy.

A group of scientists working on the FoxM1B gene fitted aged mice with a promoter to increase the expression of the gene. After undergoing a partial hepatectomy, in which a portion of the liver was removed, the mice rapidly regenerated new tissue, unlike typical aged mice.

The DNA in the regenerating liver cells replicated normally, and cells divided just as they do in the livers of young mice. This finding led the researchers to call FoxM1B the fountain of youth gene.

In a new study, the same team set out to understand how FoxM1B works in cells. They created mice with no FoxM1B genes in their liver cells and then measured the rates of regeneration in these mice and in mice whose FoxM1B gene was intact. Without FoxM1B, regeneration was slow.

In cells that lacked the FoxM1B gene, the DNA often failed to copy and the cells couldn't divide. In addition, a protein called p21Cip1 accumulated inside the cell. This protein is known to accumulate during aging. It prevents the DNA from duplicating and turns on genes associated with aging. It looks like FoxM1B is responsible for producing the enzyme that removes p21Cip1 from the cells.

The research also revealed that FoxM1B controls a key enzyme essential for the final step in cell division. If division can't take place, tissues fail to heal and replenish themselves, contributing to the age-related decline seen in many tissues.

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An interview with Dr. Joseph Rochford, Co-Director of Research on Disorders of Mood, Anxiety and Impulse Regulation, Douglas Hospital

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animal to cope. "We're looking at serotonin systems and a little bit at noradrenalin and a lot at the hypothalamic-pituitary-adrenal axis."

What does the future hold for Rochford? "There's just so much to do," he says. "I like to coat-tail. I have all kinds of colleagues doing interesting work on different kinds of animal models. They do it within their area of expertise, which is mostly neurobiology. Sometimes they want to know something about behavioural changes, and that's when they come to see me."

Brain Awareness Week in Montreal
http://www.douglashospital.qc.ca/brain/

OSTEOPOROSIS: BOOSTING FRAIL BONES

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those who have it, nor what an economic burden it places on the Canadian medical system. Osteoporosis is a "silent" disease because a person who has it may show no symptoms – until she or he sustains a fracture. The most likely fractures are of the hip, wrist, and vertebrae. For a woman over the age of 50, the lifetime risk of breaking the hip, wrist or spine is roughly 16% for each, and her overall lifetime risk of sustaining a fracture of any kind is 40%.

It's these fractures that compromise the quality of life of a person with osteoporosis and that cost so much to treat. Hip fractures are associated with long-term morbidity, and all require hospitalization. One year after suffering a hip fracture, 40% of patients are still unable to walk without assistance, and 60% still require help with daily activities and self-care. Sequelae of vertebral compressions (fractures of the spine) include chronic back pain, kyphosis (i.e. curvature of spine), low self-esteem, and a paralyzing fear of getting another one. There may be a long stay in hospital, and the patient's ability to perform daily household and self-care activities may be reduced. In 1993, health care costs due to osteoporosis (long-term and acute care) were estimated at $1.3 billion. The majority of the costs were due to hip fractures. It is great that we're living longer, but this means we can expect even more hip fractures in the future. In 1993, 12% of the Canadian population was over the age of 65, and 1% over the age of 85. There were 23,376 hip fractures. It is projected that by 2041, 25% of our population will be over the age of 65, and 4% over age of 85. This translates to 88,124 hip fractures – almost 4 times as many as today!

The statistics highlight the importance of treating and preventing osteoporosis. For both women and men, bone density increases throughout childhood and up until a person is 30 or so. Between the ages of 30 to 35, people plateau at their peak bone density. Thereafter, bone density decreases, usually by around 1% per year. But after menopause, women lose bone density more rapidly, 2-3% per year, for about 10 years. That is a loss of 20-30% of one's peak bone mass! Then the rapid rate slows to around 1% again. However, by then, a woman may already have slipped below the threshold for fractures. Men are less at risk of osteoporosis because they start off with a higher average peak bone density and they don't experience a sudden drop in testosterone the way women do with estrogen during menopause.

Besides being a postmenopausal woman, other risk factors for osteoporosis include being Caucasian or Asian (people of African descent are less prone to osteoporosis), early menopause for women, and having a family history of the disease. Other risk factors involve lifestyle, which means a person can potentially take steps to reduce their risk. Smoking, excessive alcohol, a sedentary lifestyle, and inadequate calcium intake are all risk factors for developing osteoporosis.

What can we do to protect ourselves from osteoporosis? For women, it has been shown that estrogen does help prevent the loss of bone density. However, Dr. Vautour cautioned that due to the recent results of one of the Women's Health Initiative's studies, this protection can come at a terrible cost that may not be worth the gamble. (For more, see Bursting the HRT Bubble in this issue of Geronto-McGill.) Fortunately, there are other protective things one can do, such as weight-bearing exercise and eliminating risk factors like smoking and alcohol abuse. A key strategy is to get enough calcium and vitamin D to maintain bone density. This is especially important for seniors since older people may not absorb calcium well, nor does their skin produce as much vitamin D. The optimal daily calcium intake is 1000 to 1500 mg for women over age 50 (and less for men and younger, non-pregnant women). Dairy products, such as milk and yogurt, are rich sources of calcium. However, for either ethical reasons or because of lactose intolerance, many people avoid dairy products. Fortunately, dietary supplements can ensure that everyone gets the calcium they need. The optimal vitamin D intake per day is 400 to 800 IU. Sources of vitamin D are sunlight (UV) exposure (so that the skin synthesizes the vitamin), fish liver oils, and fortified milk. In Canada, we are not blessed with enough sunlight to generate sufficient vitamin D in the skin (and due to the risk of skin cancer, overexposure to the sun is dangerous), so again, dietary supplements can ensure sufficient vitamin D intake.

Dietary supplementation alone will maintain bone density, but will not increase it. Therefore, once osteoporosis has been diagnosed, medication may be prescribed in conjunction with dietary supplementation to try to increase bone density. At the moment, Dr. Vautour thinks two drugs from the bisphosphonates class are the best options: Fosamax® (alendronate, which can now be taken once weekly instead of daily), and Actonel® (residronate). In the wings are a new bisphosphonate that can be taken as a convenient once a year injection, and parathyroid hormone treatment, which is going through FDA approval in the USA.

Another important factor for managing osteoporosis is preventing falls. Every year, 30% of elderly people fall, and these falls can cause fractures in osteoporosis-weakened bones. Exercise can help by improving strength, coordination, balance and flexibility. Also, there are now padded hip protectors available that reduce fractures by 50%, but few people like to wear them! Work on more user-friendly models is underway.

A dynamic and highly interactive question period followed Dr. Vautour's information-packed osteoporosis lecture. The seminar provided insight, hope, and bone-boosting strategies to prevent this silent and stealthy threat.

POLICY AND POLITICS

IMPLEMENTING ROMANOW: THE JURY IS STILL OUT FOR ELDERLY CANADIANS

by Jeff Boyczuk

Optimism about Canadian medicare flourished last November with the release of the report "Building on Values: The Future of Health Care in Canada", the product of a Royal Commission headed by Roy Romanow. Advocacy groups for the elderly were especially encouraged, citing the report's emphasis on home care, and patient relief from catastrophic drug costs. In fact, the National Advisory Council on Aging assigned the report an "A+", and Chairperson Patricia Raymaker remarked: "If acted upon, the Romanow recommendations will reform Canada's health care system for Canada's aging society."

Sighs of relief were heard across the country when the federal and provincial governments reached an accord on health spending in February, with Ottawa providing a cash infusion to the provinces, contingent on the adoption of several of Romanow's recommendations. Front and centre in the media were agreements about new programs in home care and drug coverage. And while the public hastily welcomed the promise of any expansion in these two crucial areas, underlying it all were serious questions about what real changes these new programs will effect, particularly for the large population of Canadian seniors.

The provinces have agreed to study and define a set of core services that comprise "universal home care", and to implement a revised program at the provincial level by 2006. On the surface this is a welcome initiative; however, early reports suggest that the provinces will use these new dollars primarily for short-term home care targeted at post-operative patients. At-home nursing care following surgery is one means by which provinces can reduce pressure on hospitals, but it seems that individuals with long-term home care needs such as those suffering from Alzheimer's Disease, or the frail elderly, may fare no better under this new initiative. The caregiving burden for such individuals is most often placed on relatives, who may or may not receive occasional assistance from community organizations. Nothing in the recent accord suggests that this situation will dramatically improve.

The ill-defined "catastrophic drug plan" is also an area of concern. The intent of such a program is to set a ceiling on prescription drug costs for individual patients, an important lifejacket for those with chronic illness who may be saddled with extremely high costs for medication. The key unknown here is the spending threshold before catastrophic drug coverage kicks in. While the Romanow report suggested a level of $1500, a report from a senate committee chaired by Michael Kirby suggests $5000 (which includes costs paid by private drug plans).

Even if Romanow's lower threshold is adopted, some seniors may still be burdened by $1500 in annual drug costs. Medical professionals have observed some low-income elderly patients cutting back on prescribed dosages in an effort to reduce their expenses. Obviously, such "under-medicated" patients are at an increased risk of requiring emergency hospital services, or premature institutionalization, which ultimately places a greater resource and financial strain on the health care system.

Despite questions regarding the provincial implementations of the new health programs, the recent federal budget offered one bright spot based on the Romanow recommendations: the expansion of employment insurance benefits to those who leave work in order to take care of a gravely ill child, spouse or parent. Until now, family members needed to rely on personal wealth, or benefits from their employer, to leave work and care for a terminally-ill family member. This new initiative, which begins in January 2004, will have the effect of relieving financial stress for individuals, while they deal with the even greater stress of caring for a dying loved one.

Time will tell how the "new" medicare system pans out for Canadian seniors. Romanow himself has endorsed the recent accord between Ottawa and the provinces, as well as health spending set out in the federal budget. However, as he has stressed at almost every public appearance since his report was issued, it is up to individual Canadians to keep governments honest on their promises. The future of the health care system is in their hands.

BURSTING THE HRT BUBBLE

by Julie Comber

The buoyant dogma that long-term hormone replacement therapy (HRT) was beneficial for postmenopausal women recently ran aground on the unforgiving shores of hard data. Once touted as a panacea for almost anything that could ail older women, from heart disease to cancer to depression, a recent large-scale randomized control trial of combined estrogen and progestin HRT was halted early because of concerns over the safety of participants[1].

In the four decades since Dr. Wilson extolled the virtues of estrogen to prevent postmenopausal women from sinking into a "vapid cow-like state" in his influential book *Feminine Forever* (1966), HRT has become the most frequently prescribed medication in the United States[2]. Approximately 38% of postmenopausal women in the US use HRT in the hopes of preventing a range of chronic diseases, especially cardiovascular disease. Yet the FDA had only approved HRT for short-term relief of menopausal symptoms (such as hot flashes and mood swings) and for the prevention of osteoporosis[3].

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TRANSLATION
Lacoste Royal
LAYOUT AND PRINTING
Imprimerie Miro inc.

WE THANK NOVARTIS FOR THEIR GENEROUS SUPPORT TO THE GERONTO-McGILL.

There was a lot of observational evidence that HRT was, overall, a great thing. A momentary rain on the parade occurred in the mid-1980s when it was discovered that unopposed estrogen significantly increased the risk of endometrial cancer. But the addition of progestin seemed protective for women with an intact uterus[3]. Meanwhile, hesitations about HRT mounted.

Finally, the Women's Health Initiative (WHI) was launched in 1991 to try to get some definitive answers on the risks and benefits of HRT and other therapeutic strategies for preventing the diseases of aging, especially heart disease (the number one killer of women in the US), breast and colorectal cancer, and osteoporosis. WHI enrolled 161,809 postmenopausal women aged 50 to 79 into a set of clinical trials. One of the trials recruited 16,608 postmenopausal women with intact uteri for a randomized controlled trial of combined estrogen and progestin HRT. There was also a parallel trial of estrogen alone in women with hysterectomies[1]. The planned end-point for both trials was after a mean follow up of 8.5 years.

However, the estrogen and progestin trial was stopped in 2002 after a mean follow-up of 5.2 years because of the increased risk of breast cancer (up 26%), heart disease (up 22%), stroke (up 41%) and blood clots (up 111%). Estrogen plus progestin was protective against osteoporosis (26% less fractures) and colorectal cancer (reduced the incidence by 37%), but the overall health risks outweighed the benefits. These results were consistent across racial/ethnic and age strata and were not influenced by prior disease or antecedent risk status. Therefore, the results should be generally applicable to all postmenopausal women. (It is still too early to tell if the estrogen-only trial will find if estrogen is protective of brain function; those results will come out in 2005.) The study concluded that estrogen and progestin HRT was not a viable intervention for primary prevention of chronic disease, and that this intervention should not be initiated or continued to prevent heart disease.

Naturally, these results provoked frustration, confusion and fear in many of the millions of women on HRT. Perhaps one thing to consider is why menopause was turned into a disease that had to be treated in the first place. Of course, just because something is a natural process doesn't necessarily mean it is good, but in the case of menopause, there may be a good reason why women evolved it.* Does this mean women should eschew HRT altogether? As with any decision concerning healthcare, each woman is a unique individual and thus should consult with her own health care practitioner to decide what is best for her. This definitive study does suggest, however, that HRT may be used as an effective short-term course to ease the menopausal transition into postmenopausal life, but not as a long-term solution to everything that ails you.

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