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CAN NEWBORN BRAIN CELLS AID IN THE TREATMENT OF ALZHEIMER'S DISEASE?

by Tania Elaine Schramek

The structural stability of the brain was assumed to be established early after birth and remain unchanged throughout life. This stability was thought to result from the brain's inability to produce new cells or neurons after this critical period. In the 1960's, technological advances allowed researchers to show that the birth of new neurons (neurogenesis) occurred in circumscribed areas of the adult rat brain. Since then, neuroscientists have attempted to understand how neurogenesis occurs and to identify other brain areas, if any, capable of giving rise to new neurons. By far, the largest discovery within this field was that of adult human neurogenesis.

One question that continued to elude neuroscientists was whether injury or damage to the brain (a situation in which the brain could benefit from new neurons) could stimulate neurogenesis. Interestingly, this appears to be the case. For instance, after a stroke, newborn

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A VOYAGE IN NEUROSCIENCE LEADS TO ALZHEIMER'S DISEASE DISCOVERIES

An interview with Dr. Claudio Cuello, Professor and Charles E. Frosst Merck Chair in Pharmacology at the Department of Pharmacology and Therapeutics at McGill University

by Daniel Auld

Curiosity. Passion. Discipline. It is fair to say that the marriage of these qualities has driven Dr. A. Claudio Cuello throughout his neuroscience career, which has spanned three continents, five decades and positions at four universities thus far. Currently Professor and Charles E. Frosst Merck Chair in Pharmacology at the Department of Pharmacology and Therapeutics at McGill University, Dr. Cuello is at the forefront of aging and Alzheimer's disease (AD) related research.

Trained at the University of Buenos Aires, Argentina (M.D., 1965), it was here that Dr. Cuello began studying the brain, notably the pineal gland. After graduation and a winter as part of an Antarctic research team, he joined the Institute of Neurobiology (1967), where he continued working on the pineal.



Next, Dr. Cuello embarked upon research fellowships with William Ganong (the author of the well known Lange's "Medical Physiology" Textbook) at the University of California at San Francisco (1970) and with Les Iversen (later director and V.P. Research of Merck Neuroscience) at Cambridge University (1972). Of some of his work with Les Iversen, Dr. Cuello indicates that they were "opening the way for integrative biochemistry with pharmacology and neuroanatomy, a

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PUBLIC LECTURE SERIES AMAZING ADVANCES IN THE TREATMENT OF GLAUCOMA AND CATARACTS

by Julie Comber

Glaucoma and cataracts, the two most common eye diseases in seniors, were the subjects of the McGill Centre for Studies in Aging's February 2004 public lecture. The guest speaker was Dr. Shawn Cohen, an ophthalmologist and Assistant Professor in the Department of

Ophthalmology at McGill University. The lecture was generously sponsored by Merck Frosst and the Montreal Delta Hotel.

Beginning with the basic anatomy of the human eye, Dr. Cohen pointed out that

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neurons have been shown to travel to the site of damage, integrate into existing neural circuitry, and contribute to repair. This led researchers to wonder whether such a mechanism could exist in more chronic pathologies, like Alzheimer's disease (AD).

One brain area in which compensatory neurogenesis in AD would be advantageous is the hippocampus, an important memory structure that is often the first area affected in AD. Interestingly, a new study has found indicators of neurogenesis in the hippocampus of deceased AD patients. The authors suggested that this might be evidence that the brain is making an attempt to replace dead/damaged neurons. In keeping with this, measures that stimulate neurogenesis could be explored as possible therapeutic interventions in AD. It remains unclear however, whether the rate of cell birth would be sufficient to replace lost cells in affected brain areas. Moreover, the environment within the AD brain may be toxic to neurons and may thus prevent newborn cells from developing into fully functional neurons. Despite these unanswered questions, this new study is rather encouraging and highlights the importance of continued research on a neurological disorder that affects far too many of our loved ones.

Jin K et al. (2004) Increased hippocampal neurogenesis in Alzheimer's disease. Proc Natl Acad Sci USA. Jan 6;101(1):343-7.

An interview with Dr. Claudio Cuello, Professor and Charles E. Frosts Merck Chair in Pharmacology at the Department of Pharmacology and Therapeutics at McGill University

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multidisciplinary modality that made what modern neuroscience is today.”¹

In 1973, Dr. Cuello returned to Argentina as an assistant professor at the University of Buenos Aires. But the political situation was tumultuous – and dangerous – and research funding was cut. Dr. Cuello knew that there was “no professional future for (him) in Argentina.”¹ In 1975, Les Iversen invited him back to Cambridge at the Medical Research Council Neurochemical Pharmacology. Here, Dr. Cuello studied brain neurotransmitter systems, including neurotransmitter release from dendrites and the distribution of neuropeptides in the brain.

Dr. Cuello later (1978) took a position as Lecturer (equivalent to Associate Professor in North America) in the Department of Pharmacology at Oxford University. In addition to enjoyable teaching in the university’s famous tutorial system, Dr. Cuello’s research was exciting. With his good friend Ceasar Milstein, a fellow expatriate Argentinean and winner of the 1984 Nobel Prize, he applied monoclonal antibodies (immune molecules that detect specific targets) to neuroscience for the first time. It was using a monoclonal antibody at Oxford that Dr. Cuello first began AD-related research.

In the late 1970s and early 1980s, it became apparent that AD involved selective damage to a group of brain cells (basal forebrain cholinergic neurons) that produce and release the neurotransmitter acetylcholine, which is known to be important for learning and memory. Dr. Cuello’s group showed that these neurons are atrophied in AD and in rats after cortical damage. This and other evidence encouraged them to propose a theory that damage to cortex in AD resulted in secondary atrophy of basal forebrain cholinergic neurons.

It was around this time that Dr. Cuello was convinced to accept the Chair of Pharmacology at McGill. Under his stewardship (1985-2000) the

Department grew to one of the most productive pharmacology departments in the world. At McGill, Dr. Cuello continued investigating the cholinergic system, studying the ability of certain molecules (including nerve growth factor and ganglioside GM1) to counteract the effects of cortical damage on cholinergic atrophy. For AD, perhaps the most relevant message from these studies is that it is possible to encourage recovery of compromised neurons, raising the hope that damaged brain circuitry in AD may not be beyond repair.

Upon completing his term as Chair, Dr. Cuello has enjoyed a research renaissance. With administrative responsibilities behind him, he has had more time to focus on research and hopes to work at the bench until very late in life. His major focus is the aging cortex and AD.

The cortex, which is important for higher cognitive functions, undergoes changes as it ages. Using rats, Dr. Cuello’s group has recently demonstrated that certain cortical neurons are susceptible to age-related changes, including cell body atrophy and reduced dendritic processes, which are important for contacting other neurons. Moreover, his group has shown that there are fewer synapses in the aging cortex.

Synapses are the sites where neurons talk to one another; their cumulative conversation results in thoughts, feelings and memories. Interestingly, Dr. Cuello’s group has shown that aged rats with cognitive impairment – some rats, like some humans, appear to age better than others – show evidence of fewer cholinergic synapses. In AD, there is a massive loss of cortical and cholinergic synapses. As Dr. Cuello indicates, no matter what the primary cause of AD is, it is ultimately synapse loss that best correlates with cognitive decline.

Is there anything we can do to counteract synapse loss? As Dr. Cuello points out, synapses are regularly made

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An interview with Dr. Claudio Cuello, Professor and Charles E. Froest Merck Chair in Pharmacology at the Department of Pharmacology and Therapeutics at McGill University

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and unmade. To build new synapses, one could maintain an active mental life, for instance reading, doing crossword puzzles or other mentally challenging activities. Having more synapses may not prevent AD pathology, but the brain should be able to absorb more damage before significant cognitive impairment is observed if more synapses are available *a priori*. It is believed that this can partly explain why higher education is associated with reduced AD, even in individuals with a genetic predisposition.

Of interest with respect to synapse maintenance, Dr. Cuello's group has identified a molecule, nerve growth factor, that maintains cholinergic synapses that are vulnerable in AD. It is possible that maintaining adequate levels of growth factors could help resist AD. Although it may sound surprising, there actually are a few simple things that could encourage growth factor production. As Dr. Cuello indicates, activity is the key, with both physical and mental activity being associated with increased production of brain growth factors.

When asked if AD can be cured, Dr. Cuello responds definitively but cautiously: "Yes! It won't be cured next week, next month, or even next year, but hopefully it can be cured in the next decade." When asked how it will be cured, Dr. Cuello says that the scientific community's understanding of the molecular and cellular origins of the disease have been the force behind therapeutic progress. Indeed, at least ten potential therapeutic avenues have been generated based on basic science discoveries in the last 15 years or so. These include inhibitors of the production of beta-amyloid peptide (found in deposits AD brains), anti-inflammatories, immunization against beta-amyloid, etc. These are different from current therapies, which target symptoms rather than the root cause, and tend only to be effective for a year or two.

Can this endeavor be made more effective, and thus deliver improved therapies sooner? In Dr. Cuello's mind,

the answer is better animal models of AD. Currently, there are helpful mouse models that mimic some features of AD, for instance beta-amyloid production. As Dr. Cuello indicates, even if such a mouse does not display all features of AD, it is good enough to test a drug designed to reduce production of beta-amyloid. Even better is a mouse that has AD-like neurodegeneration and cognitive decline. In fact, Dr. Cuello's group recently found evidence that human genes known to cause AD, when put in a mouse, cause beta-amyloid deposition, cognitive decline and cholinergic synapse loss, all important features of AD.

When asked what his biggest contribution to neuroscience has been, Dr. Cuello turns the question on its head. He believes that his most important contribution is yet to come and that it will be in the area of animal models of AD. One current focus of his lab is to generate a first rate rat model. To date, most of the best models have been created by insertion of AD-causing genes into mice. But in terms of intellect, mice are not as bright as rats. The more intelligent rodent will likely be more sensitive to the genes that cause AD and should better serve as a model. Dr. Cuello expects that improved models will help to generate improved theories of pathology and to test new therapies.

Assuming new treatments for AD will be generated, one important question is when to deliver them? Dr. Cuello suggests that therapy should be delivered as soon as a cognitive decline is noticed, before full-blown AD, because this sub-clinical impairment eventually leads to AD. Thus, the advance of the disease can be stopped or impaired before irreparable damage is done.

When asked what the best strategy could be, Dr. Cuello says that it could prove to be a cocktail of drugs that target different aspects of pathology. For instance, drugs that block the production of beta-amyloid may be complemented by drugs that reduce inflammation, as well as

currently used therapies that augment activity of cholinergic neurons.

Finally, it should be said that Dr. Cuello is optimistic and excited about the possibility of a cure for AD and is happy to be part of the broader group of people pushing for this objective. Moreover, he takes pleasure in being part of the larger scientific community that exists without national borders. Indeed, it is sure that the world will hear more about AD from Dr. Cuello in the years to come.

1. A. C. G. Cuello, in *The History of Neuroscience in Autobiography* L. R. Squire, Ed. (Academic Press, San Diego, 2001), vol. 3, pp. 170-213.

POLICY AND POLITICS

HORMONE REPLACEMENT THERAPY: SAINT OR SINNER?

by Tania Elaine Schramek

Over the past year, there has been considerable debate regarding the appropriate course of action to take when at the onset of menopause, a woman stops producing the ovarian sex hormones estrogen and progesterone. Central to the debate, is whether a woman should start taking estrogen replacement therapy (ERT) or combined estrogen and progesterone replacement therapy (E+P) for the alleviation of her menopausal symptoms. Much of the controversy surrounding this issue arose when a study conducted by the Women's Health Initiative (WHI), whose aim was to examine the potential beneficial effects of hormone replacement therapy (HRT) on general health and more specifically, cardiovascular health, was terminated after 5 years because E+P use was associated with increased risk for cardiovascular incidents and invasive breast cancer.

Due to the startling nature of these findings, the study received tremendous press exposure and consequently, many women who were taking HRT rushed to their doctor's office and insisted upon being taken off their treatment regimens. The scientific community also became very interested in these findings and as a result, in February 2003, in Funchal, Madeira, a panel of the 25 top international HRT experts gathered to take a closer look at the WHI's study and to discuss its implications.

Over all, the panel agreed that the study was well designed and conducted. They did, however, call into question the clinical relevance of its findings. They argued that women in the WHI study did not fit the typical profile of those that would receive HRT in clinical settings. Specifically, 66% of the participants were over 60 years of age. Although there is no consensus as to how long HRT should be administered (ranging between 5-15 years), it IS agreed upon that HRT should begin at the onset of menopause. Given that the average age of onset is 50, many women in the WHI study were at least a decade older than those that would typically receive HRT in clinical settings. This is important because age alone is a risk factor for many health problems,

including cardiovascular disease and cancer.

Even though the primary uses for HRT in clinical settings are to alleviate menopausal symptoms like hot flushes, mood changes, and to prevent the loss of bone matter density, the goal of the WHI study was to examine the protective effects of HRT on general and cardiovascular health. Interestingly, 69% of women in the WHI were overweight, 36% had high blood pressure, 12% had high cholesterol, 40% were previous smokers, and 10.5% were current smokers. Thus, many women had cardiovascular risk factors or pre-existing cardiovascular disease. The panel therefore argued that these women were less than ideal to be included in this study and were not likely candidates for HRT in clinical settings.

Another issue raised by the panel relates to the type and dose of HRT used. Depending on a woman's medical history, doctors will either prescribe ERT alone or E+P. Women in the E+P group of the WHI study were given a uniform dose of E+P that contained synthetic estrogens called conjugated equine estrogens. First, the experts argued that it is unlikely for two women to receive the same dose of HRT. Second, when our bodies break down substances, the end-results are called metabolites. Several studies have shown that women with breast cancer have high levels of specific estrogen metabolites. Conjugated equine estrogens, which had been given in the WHI study, have been shown to increase the amount of these estrogen metabolites by 32%.

Additionally, the press overlooked two important findings. First, only the E+P portion of the study was terminated due to increased health risks, the ERT portion is still underway. Second, the increased risk for breast cancer observed was only found in women who had a previous history of HRT use. These findings are in line with new research avenues that propose that there may be a threshold amount of hormones to which a woman can be exposed in her lifetime. Therefore, in adopting this approach, researchers are highlighting the importance of individual needs with

regard to treatment. This was perhaps the most recurring and resounding criticism offered by the panel of experts regarding the study's lack of clinical relevance as well as the popular media's treatment of its findings.

The panel unanimously agreed that in clinical settings, the type of HRT and the doses prescribed are determined on a case-by-case basis. Indeed, they repeatedly stressed that individually tailored treatments are the key to positive outcomes. In fact, for the most part, HRT has been associated with significant decreases in hot flushes, increased psychological well-being, increased sexual satisfaction, increased ability to concentrate, better memory, and significant prevention of bone matter density loss. Thus, when different therapeutic approaches are applied to different women, the potential benefits can be quite substantial.

Although the negative outcomes of the WHI study reported by the popular media cannot be taken lightly, a most unfortunate and potentially dangerous result of this sensational coverage is that many women are now seeking natural remedies for menopausal symptoms, none of which have ever been clinically tested. For instance, one issue of the *National Enquirer* listed ten different medications that could be used to substitute for hormone therapy, all of which contain some form of estrogen or progesterone. Given that it is unclear whether it was progesterone alone, a combination of estrogen and progesterone, or the women's pre-existing risk factors that contributed to the negative outcomes observed in the WHI study, great caution should be exerted in taking natural remedies.

It is important to note that the panel of experts did not in any way discount the importance of the increased risks found in the WHI study, they simply wished to clarify the context in which they were observed. In fact, they clearly point out that further investigation into the effects of HRT is required. An unfortunate consequence of the media's treatment of the WHI's findings however, is that

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AMAZING ADVANCES IN THE TREATMENT OF GLAUCOMA AND CATARACTS

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the optic nerve leaving the back of the eye looks a bit like a straw connecting the eye to the brain. The optic nerve is 1.5 mm in diameter (the size of a pencil dot) and carries 1.2 million nerves to the brain. “I guess right away we won’t be discussing eye transplants here!” joked Dr. Cohen.

Glaucoma is “a characteristic acquired loss of optic nerve fibres”, he explained. “The eye is like a closed-system bathtub with a faucet, a drain and a pressure sensitive portion.” If the drain gets plugged, then pressure builds up and damages the weakest part in the eye: the optic nerve. The more damage to the optic nerve, the more the patient’s vision is reduced.

There are two main therapeutic goals for glaucoma: keep intra-orbital pressure below the target level, and stabilize diurnal variation in intra-orbital pressure. There is considerable evidence that lowering pressure in the eye will help relieve glaucoma. In his practice, Dr. Cohen tries to lower pressure with medication before resorting to surgery. Usually, pressure of more than 30 mm Hg will be treated, but it depends on how much damage the optic nerve has sustained. The more damage there is, the more important it is to lower the pressure.

There are 5 classes of glaucoma medications, and the sheer number of products available can seem overwhelming. But Dr. Cohen pointed out how fortunate we are to have so many treatment options. Still, eventually, medications might not adequately control the pressure or give the patient the vision sufficient for his or her lifestyle. At that point, surgery may be required. A new role for medications is to use them and surgery synergistically. For example, a safer, less effective surgical procedure can rely on medication to boost its ability to hit the target intra-orbital pressure and stabilize the diurnal curve.

Dr. Cohen believes that communication between the patient and surgeon is essential, and that allowing the patient to make the decision both empowers the patient and means less stress for the surgeon. He described how a modular approach takes surgery to an advanced level. “If you think about surgery in an organized way, you can do

anything.” He praised his team, the three Montreal hospitals where he works, and the high quality of Canadian eye surgery in general.

The delicacy required for eye surgery is truly amazing. Ophthalmologists use tiny, sophisticated tools, and sutures finer than a human hair. “One time, one of the sutures flew off the instrument, and you could just see it hovering there in the air; it was so light it wouldn’t fall. It was incredible to see that,” marvelled Dr. Cohen.

Elevated intra-orbital pressure is a relatively common complication for all patients undergoing cataract surgery. Glaucoma patients undergoing cataract surgery require special consideration. Dr. Cohen explained surgeons can now use a soft, foldable intraocular lens. The standard lens covered by Medicare does not fold, and so requires a larger incision, and is football shaped, so the patient will have astigmatism. Surgeons are moving away from the non-folding lens, especially when cataract and glaucoma surgery are done simultaneously. However, Dr. Cohen stressed that both kinds of lenses are excellent products that will last a lifetime.

Dr. Cohen cautioned the audience about Laser correction surgery (Lasik) to improve eyesight. Those at risk for glaucoma should not get this done, because it can complicate treatment of glaucoma.

There were many interesting questions following the lecture, which Dr. Cohen answered carefully and compassionately. One woman explained that for years she had been unable to read the newspaper without reading glasses. Then suddenly, she could read the whole thing again without glasses. She was told it was because of her cataract, which seemed contradictory to her. “Actually, it is not contradictory,” explained Dr. Cohen. “It’s called ‘second sight’, a process where the cataract grows, and changes your lens’s power, so that you can read. But that’s because it is thickening, and getting harder. So while it may temporarily allow you to see better, it may get worse, or it may have created a great situation for you, and you may not need surgery.”

Another person asked whether diet effected glaucoma or cataracts. Dr. Cohen responded that except for severe nutritional deficiency, rare here in North America, there was little evidence diet has an effect. Diabetes patients, though, must keep their blood sugar well controlled to reduce their risk of cataracts and glaucoma. And lutein does help in the later stages of dry macular degeneration, another common source of vision loss in seniors.

HORMONE REPLACEMENT THERAPY: SAINT OR SINNER?

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research in this area may now be particularly difficult to undertake.

Although there are not yet clear answers with respect to HRT, for the many concerned women out there, a combination of obtaining as much information as possible, a clear knowledge of our own definition of quality of life, and open discussions of these issues with our doctors is probably the best course of action for now.

PROMOTING THE FLOURISHING OF BOTH SCIENCE AND ANIMAL WELFARE

by Julie Comber

For those who suffer from age-related diseases, and for those who work to prevent and treat these diseases, there is much to celebrate in the cornucopia of new treatments developed every year. It can be easy to forget, in the glorious aftermath of a clinical trial proving a new drug is safe and effective, that much of the pre-clinical work would have been impossible without laboratory animals. When we stop and think about it, society gains a huge benefit from medical progress. But this benefit must come at a price, and this price is not just financial - many costs are borne by research animals. Balancing costs to research animal welfare and benefits enjoyed by society is key for developing research policies that allow both animals and science to flourish.

Russel and Burch wrote the seminal *The Principles of Humane Experimental Technique* in 1959. Their widely influential 3-Rs concept is that we should strive to Reduce the numbers of animals used in research, Replace animals with non-animal alternatives, and Refine the care and use of research animals to improve their welfare.

An excellent example of refinement in producing knockout mice is targeted Cre-loxP-mediated recombination. Before this technique, the knocked-out gene would not be expressed anywhere in a knockout mouse's body. Using the Cre-loxP system, gene expression is prevented in selected tissues only. This can mean a less severe phenotype and better welfare for the mouse, and allows scientists to ask subtler questions about the gene's function. An example of this kind of mouse model is the NIRKO mouse, which does not express the insulin receptor in brain tissue. The homozygous knockout has a relatively benign phenotype - mild obesity and reduced fertility. In contrast, when the gene is knocked out in all tissues, homozygous knockout mice die 48 to 72 hours after birth. The NIRKO mouse is now being used to explore the link between diabetes and Alzheimer's.¹

A crucial achievement in recent years has been the adoption of more humane endpoints for animal experiments.² The goal is to end the experiment before the animal experiences pain or distress beyond a pre-determined threshold. For example, staff may look for signs that an animal has started an irreversible decline, and euthanize it

immediately rather than wait for the disease or test substance to kill it. This is more humane, and allows scientists to refine their questions and garner insights unavailable without an earlier endpoint.

We are indebted to the rats, mice, dogs, cats, pigs, and other animals used in research. It is encouraging to see the progress being made to ensure good animal welfare and hence, good science.

Sources

1. Schubert M, Gautam D, Surjo D et al (2004). Role for neuronal insulin resistance in neurodegenerative diseases. *Proc Natl Acad Sci.* 101(9):3100-5. To compare TBASE ID 8181 (NIRKO mouse) to 3183 (conventional IR knockout), go to <http://tbase.jax.org/>, and click on Search TBASE 2.0 (<http://tbase.jax.org/docs/tb.html>).
2. See the Canadian Council on Animal Care's (<http://www.ccac.ca>) guidelines on: choosing an appropriate endpoint in experiments using animals for research, teaching and testing, at http://www.ccac.ca/english/gui_pol/gdlines/endpts/APPOOPEN.HTM

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