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POLICY AND POLITICS

Debating the Ethics of Placebo Drug Trials

by Jeff Boyczuk

As the age group that spends the most dollars per capita on prescription medication, seniors play a necessary and vital role in the development of new drug treatments. This comes through their participation as subjects in clinical drug trials. In the development of any type of pharmacological therapy, regulatory agencies require rigorous experimental testing to ensure the safety of potential users of the drug, as well as to gauge the drug's efficacy. However, safety standards must also extend to the smaller group of patients who volunteer for these experiments. This tenet raises some serious questions about the use of placebos - inert pills or other inactive treatments - which are commonly employed in clinical trials.

Why are placebo groups used in pharmacological research? The short answer is that they provide a control condition against which to measure the effectiveness of an experimental treatment. If a patient group that is receiving a test drug does not show a significantly better response than a placebo group, then the drug can be deemed ineffective. However, one interesting twist to this method is the fact that some patients who participate in research trials tend to show benefits, regardless of whether they are receiving an active, or inactive, treatment. On average, about 1/3 of the members of the group receiving no active treatment shows this "placebo effect". As such, an experimental drug must outperform this effect, demonstrating that it possesses some benefit beyond what is psychologically garnered in patients through consuming, or believing to consume, a medication. Thus,

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GENE EXPRESSION, GENE THERAPY AND AGING

An interview with Dr. Josephine Nalbantoglu, Associate Professor, Department of Neurology and Neurosurgery, and Department of Experimental Medicine, McGill University

by Alison McTavish

Dr. Josephine Nalbantoglu has covered a lot of ground in her career. An Associate Professor in two McGill University departments, Neurology and Neurosurgery, and Experimental Medicine, she has explored Alzheimer's Disease, learning and memory, and brain cancer. The link between these diverse fields is genetics. "Although my background is in biochemistry and molecular biology," she explains, "my interest has always been in gene expression and gene transfer."

Nalbantoglu's interest in aging began with her research in Alzheimer's disease. Her laboratory developed a strain of mice that expressed one part of the human amyloid precursor protein. A small peptide cleaved from this protein is found to accumulate in the well-known amyloid plaques of Alzheimer's disease. Tests showed that although the mice did have spatial memory deficits, they didn't form senile plaques in their brains. These plaques



were long thought to be important in causing deficits in Alzheimer's patients.

"It was kind of controversial at the time," Nalbantoglu says. "When I first started, the whole question was, does amyloid matter? Or is it just the garbage that's left behind? That's why we made the mice, just to see whether it mattered. Since then, others have also shown that you don't need the senile plaques to have the memory deficits." It was this finding that led to Nalbantoglu's interest in gene expression during learning. "How do you learn?" she asks. "What happens in the hippocampus when you learn?"

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PUBLIC LECTURE SERIES

The Prevention and Treatment of Cataracts, Glaucoma, and Double Vision

by Hannah Hoag

"Now that I'm retired and have time to golf, I have trouble seeing the ball!" The audience at Dr. Francine Mathieu-Millaire's lecture entitled: "Everything on the Prevention and Treatment of Cataracts, Glaucoma, and Double Vision", sponsored by the McGill

Centre for Studies in Aging, roared with laughter at the irony of aging.

Dr. Mathieu-Millaire completed her medical training at the University of Montreal before heading south of the border to Johns Hopkins where she specialized in neuro-ophthalmology. She currently

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Debating the Ethics of Placebo Drug Trials

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employing a placebo group in a clinical pharmacology trial creates a tightly controlled test situation in which a novel drug can be judged by its active medicinal capacities.

In cases where drug treatments are being developed for medical conditions with no proven therapy, the use of placebos poses no ethical dilemma. However, the situation is not as clear-cut when running clinical trials with patients suffering from disorders such as Alzheimer's disease, depression, or arteriosclerosis, which all have established treatments. Is it ethical to deprive such patients of a proven therapy during the course of an experimental trial?

Unfortunately, there is no simple answer to this question. An international guideline that has been widely adopted by ethics review boards is the World War II-era Declaration of Helsinki. The Declaration, which was amended as lately as October 2000, stresses that all patients in a medical study should be provided with the best available therapeutic method. Needless to say, this statement has been controversial among researchers, because it implies that placebo use is always unethical in situations where a proven treatment exists, regardless of the level of risk to subjects. Yet, as a measure to protect individuals who consent to participate in drug trials, such a rigid position on placebo use may have the opposite effect of what is intended, potentially increasing the chance of negative effects on patients. This becomes apparent when examining the other experimental options.

An alternative to running experimental trials with a placebo group is to test a novel drug against an existing drug therapy. This is, in fact, a commonly used methodology. However, there are pitfalls associated with such a design. For example, in any clinical trial in which no difference is found between two groups, the possibility remains that a true difference does exist, but an error has occurred because of a lack of statistical power. Such an error may be the result of too few subjects in the study. If a test drug is pitted against an existing treatment, no difference between the two groups might be erroneously interpreted as a demonstration that both drugs are equally effective. Clearly, this would be a troubling outcome, particularly if it led to the adoption of a non-effective experimental drug as a therapy technique.

Several other methodological variations that employ varying doses of the experimental drug as control conditions have also been used as alternatives to placebo trials. A drawback is that most of these designs require larger numbers of experimental subjects to test for differences between groups. Unfortunately, experimental drugs often prove to be both

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An interview with Dr. Josephine Nalbantoglu, Associate Professor, Department of Neurology and Neurosurgery, and Department of Experimental Medicine, McGill University

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The hippocampus is an area of the brain that stores temporal, spatial and sensory memories. This is thought to be accomplished by the activation and expression of genes that are mostly unknown. "We say that a region of the brain is activated because some genes are being expressed. Some are turned on very fast when you're doing specific tasks and when you're learning something. Transcription factors get turned on, and they in turn cause other genes to get turned on. That's what's responsible for the learning, and for the retention of the learning."

In the model that Nalbantoglu is using, rats have to learn to swim to a platform in a water maze. The platform is then hidden and the rats have to find it again by remembering spatial cues that they had in the maze. Gene expression in the brains of these rats is then compared to that of rats that are just swimming in a bucket with no maze, and with rats whose hippocampus has been disconnected from other brain pathways. The rats with the disconnected hippocampus are unable to learn.

After the experiment, samples of hippocampal tissue from the brains of all the rats are examined and compared to see which genes have been turned on. Identification of the genes has been helped along by a sophisticated new technology called microarray analysis that allows researchers to pick out a few genes among thousands. Of the 24,000 genes in the rat, it is possible to narrow the field down to 40 or 50 possible candidates. Once the candidates are narrowed down, the work really begins. Nalbantoglu has a lot of questions about these genes that she wants answered.

"Now the question is, what happens to these genes during aging? When an aged animal learns, are there some pathways that are used preferentially, or lost preferentially? What happens in the aged animals that are impaired versus those that are unimpaired? In the Alzheimer's disease

mice, which one of these pathways is first affected when they start getting learning problems? Is it across the board, or just one pathway that's affected? I'm really excited about that one. I think it's a fun project to think about."

Gene therapy

Nalbantoglu isn't just interested in finding out how genes are regulated and expressed, she's also working on how missing or faulty genes can be replaced with normal genes. That's where her interest in gene therapy comes in. Gene therapy works by putting the normal gene usually into a virus such as an adenovirus or a retrovirus. Once the virus is injected into the patient, it "infects" cells with the normal gene.

"Gene therapy is one of those concepts that has a lot of promise," Nalbantoglu explains, "particularly in hereditary diseases where a gene is missing, or mutated. But it's still a daunting challenge. What percentage of the cells should take up the normal gene? You have to establish that for your organism to become normal again. And you want something that's going to last for the lifespan of the individual. You want the gene to be expressed at proper levels and to function like the real copy would have been expected to function. But it's very hard to regulate transferred genes and to keep them expressed for a long time."

Despite the obstacles, successful gene therapy may soon be a reality in Nalbantoglu's laboratory. She has been working on glioblastomas, which are brain tumors with a very grim prognosis. Patients often survive only eight or nine months after diagnosis. Although the tumor is deadly and will spread within the brain, it doesn't usually metastasize anywhere else. If it could be treated within the brain, patients would have a good chance for survival. This may be accomplished with what Nalbantoglu refers to as suicide genes.

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Debating the Ethics of Placebo Drug Trials

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inactive and toxic. Thus, under these methodologies, a larger number of subjects are being put in a precarious situation, relative to a placebo control design. This is of particular concern when dealing with geriatric patients, who tend to be more vulnerable to drug side effects than younger individuals. It seems clear that existing alternatives to placebo control designs do not necessarily guarantee that patients will be exposed to less risk.

In Canada, the complexities of these issues have been acknowledged in the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, first released in July 1997. The Tri-Council is a body formed by the three granting councils (NSERC, SSHRC and CIHR) in order to tackle issues common to all research disciplines. While the statement of the Tri-Council adopts the spirit of the Helsinki declaration that prescribes the best available treatment for research subjects, provisions are also made for situations in which the risk/benefit ratio in a placebo trial is low. For instance, placebo control is deemed acceptable in cases where treatments exist, if the particular volunteer patients used have proven to be unresponsive to the established treatment. It also suggests that placebo use is acceptable for consenting patients with minor conditions, provided that they are fully informed of the risks of discontinuing a proven treatment during the course of the experiment.

Ultimately, it is left up to government and institutional ethics review boards to wade through these issues and decide on a study-by-study basis whether a placebo trial is ethically sound. While the debate over placebo trials between drug companies, scientists, and regulatory agencies will likely continue, further investigations of the utility and ethical considerations of placebo control are needed to help researchers define the best available testing methods, while at the same time protecting the safety of individual patients.

For further discussion of the ethics of placebo trials see:

Young SN, Gauthier, S. Is placebo control in geriatric psychopharmacology clinical trials ethical? *International Journal of Geriatric Psychopharmacology* 2000; 2: 113-118.

Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (available online)

<http://www.nserc.ca/programs/ethics/english/policy.htm>

HOT TOPICS IN AGING RESEARCH The Human Genome Project

by Alison McTavish

The Human Genome Project is an international effort to sequence the entire human genome. The project was first proposed by researchers in the early 1980s, and was launched in the United States by the National Institutes of Health. Genome centers were also created in Canada, Britain, France, Germany, Japan and China. By the late 1990s the official Human Genome Project was well underway.

In February of this year, the international consortium's first draft of the genome was published in *Nature* along with a series of papers on the human genome. So far researchers have been able to assign about 5,000 human genes to the correct site in the genome. According to the authors of the *Nature* paper, their goal is to compile a complete list of all human genes and their encoded proteins, to serve as an atlas for biomedical research.

An atlas of the human genome will revolutionize both medical practice and biological research. The hope is that all human genes will eventually be found and sequenced, including those that code for inherited diseases and diseases associated with aging. Once found, research can focus on the development of diagnostics, preventive measures, and possible new gene-based therapies. (See interview with Dr. Josephine Nalbantoglu in this issue.)

Already, researchers have identified genes associated with a number of diseases including cystic fibrosis, Duchenne muscular dystrophy, myotonic dystrophy, neurofibromatosis, and retinoblastoma. In addition, genetic susceptibilities are thought to be important for many major diseases including heart disease, stroke, diabetes, and several kinds of cancer. As research progresses, investigators will also uncover the mechanisms for diseases caused by multiple genes, or by genes interacting with environmental factors.

Researchers have put 2005 as the date they envision the entire genome being fully

mapped. By then we should have a clearer understanding of not only the biology of genome organization and gene regulation, but also of the mechanisms behind the development of humans from single cells to adults, and the changes that occur during aging.

References:

1. Birney, E. et al. Mining the draft human genome. *Nature* 2001; 409: 827-8.
2. The Genome International Sequencing Consortium. Initial sequencing and analysis of the human genome. *Nature* 2001; 409: 860-921.

These articles and other materials on the human genome are available for free at the Nature Genome Gateway Website.

<http://www.nature.com/genomics/human/index.html>

The Prevention and Treatment of Cataracts, Glaucoma, and Double Vision

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conducts public consultations at the Sacré-Coeur and Sainte-Justine hospitals in Montreal.

Dr. Mathieu-Millaire began her talk by taking the audience through a detailed visual history of the eye and how it works. She described the eye as a sophisticated camera that ages with time and becomes more susceptible to wear and tear. Cataracts, glaucoma, macular degeneration, and circulatory problems are the most common ocular problems to affect the aging eye. However, she stressed, it is important to recognize the symptoms of these disorders because an early diagnosis and treatment can successfully restore the patient's vision or prevent further degeneration.

Cataracts are a common affliction of the aging eye. A cataract is a progressively increasing opacity of the eye's lens that leads to a reduction in the field of vision. During the initial stages of cataract development, highlights will begin to wash over objects that appear in a subject's visual field. As the cataract grows, sight becomes increasingly obstructed and may severely affect an individual's quality of life.

Without turning back the clocks of time, it is difficult to prevent the formation of cataracts. Aging, more than any other event, is the most common cause of cataract formation. Likewise, Dr. Mathieu-Millaire warned that certain medical conditions associated with aging, such as diabetes and hypocalcemia, and certain medications, such as amiodarone and cortisone, used to treat arthritis, may lead to cataract formation.

Although corrective lens wearers with cataracts may achieve some relief by obtaining a new prescription, Dr. Mathieu-Millaire recommended that individuals consult a physician before investing more money into prescription lenses that may offer little improvement. A visit to the doctor can provide a patient with an objective assessment of the cataract that can determine the necessity of a prescription change. Ultimately, however, the decision to pursue treatment lies in the hands of the patient. While some patients experience only a mild reduction in quality of life, others may be severely affected with only a slight obstruction. It all depends on the individual's lifestyle, explains Dr. Mathieu-Millaire; some people depend on their vision more than others.

Cataracts may be removed with

surgery. Approximately 20% of the population will require cataract surgery. Cataract surgery involves the removal or destruction of the cataract from the bag that encloses the lens. In many cases, the lens will also need to be replaced. If the sack remains intact, the new lens is inserted into the sack. If the sack is damaged, the lens may be placed in front of the iris and the pupil.

Since long-term exposure to UV light leads to cataracts, Dr. Mathieu-Millaire recommends investing in a pair of UV blocking sunglasses to reduce the risk of developing cataracts later in life.

After wrapping up her discussion on cataracts, Dr. Mathieu-Millaire dove into her next topic: macular degeneration. The macula, which lies at the centre of the retina at the back of the eye, provides detail to the visual image. Macular degeneration leads to a loss of visual acuity. While the field of vision remains normal, clarity is lost.

Like cataracts, age is the most common risk factor that leads to macular degeneration. Heredity, UV exposure, trauma, and perhaps circulatory problems may also lead to macular degeneration.

Laser surgery, anti-oxidant regimens, and the use of visual aids can be adopted to reduce the visual impairment caused by macular degeneration.

Dr. Mathieu-Millaire's third topic of the day was glaucoma. Increased intraocular pressure can lead to acute or chronic glaucoma. While regular intraocular pressure checks are usually sufficient to expose glaucoma, it is important to remember that secondary glaucoma, which represents 5% of all cases of glaucoma, can occur even when intraocular pressure is normal.

Acute glaucoma represents only 20% of recorded glaucoma cases. Symptom onset is sudden: patients experience pain, red eyes, nausea and vomiting, and heart burn, and complain of cloudy vision. Acute glaucoma is treated by creating a small incision in the iris to relieve intraocular pressure.

Chronic glaucoma, on the other hand, affects a greater number of individuals (75% of glaucoma cases), but develops slowly over time. Dr. Mathieu-Millaire stressed that only regular check-ups will ensure the detection of chronic glaucoma. Despite the lack of pain or of sudden vision changes, chronic glaucoma should not be taken

lightly. If chronic glaucoma is not detected early and treated, vision may never be completely restored. Where possible, chronic glaucoma is treated with eye drops; laser surgery may be used if the eye drops are ineffective.

Before turning to the audience's questions, Dr. Mathieu-Millaire broached her final topic of discussion. Elevated cholesterol levels, diabetes, and tobacco use may affect the circulation to the arteries of the retina and obscure vision. Cholesterol plaques or emboli that migrate from the carotid arteries of the neck to the retinal vessels may cause vision loss for 3 to 4 minutes. Although vision loss may be a disturbing experience, it may be an early sign of pending cardiovascular problems, and people who experience short-term loss of vision should take it as a sign to seek more extensive medical advice.

While number of age-related ocular afflictions are common, Dr. Mathieu-Millaire's strongest message was to try to intercept the onset of these conditions before they become untreatable. Regular check-ups, protecting your eyes from the sun, and continually monitoring changes in your vision could lead to a long and healthy visual life, with plenty of time to play golf.

An interview with Dr. Josephine Nalbantoglu, Associate Professor, Department of Neurology and Neurosurgery, and Department of Experimental Medicine, McGill University

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“With the adenovirus we can transfer efficiently genes we call suicide genes. You can give the patient a drug that’s well tolerated, but in the presence of the suicide gene, it’s converted to something that’s toxic. So locally you get very high levels being produced, and the rest of the body is not being exposed to the drug.” According to Nalbantoglu, results in rats were very encouraging, and her group is now ready to begin Phase I trials in human patients.

Although gene therapy may soon be a reality for some brain cancer patients, gene therapy for aging diseases like Alzheimer’s is a more difficult proposition. “I never really thought it would work for Alzheimer’s,” says Nalbantoglu, “because the question would be what are you

replacing? Most Alzheimer’s cases are sporadic, but is there one master pathway that’s gone wrong? We don’t know yet.”

One area she suggests may turn out to be useful for Alzheimer’s disease is cell therapy. Cell therapy involves implanting cells that have already been modified in some way. If the patient’s own cells are not secreting enough nerve growth factor, for example, replacement cells can do the job instead. The key is finding the right kind of cells for the job, ones that will grow easily and not be rejected by the immune system.

Nalbantoglu thinks the right cells may be stromal cells, and that may well be the next new area for her to explore. “I’m fascinated by stromal cells,” she says. Stromal cells from the bone marrow can be

manipulated to develop into many different cell types. “They can become mini-factories that will secrete whatever you want. You could even get them to make the appropriate connections in the brain,” she enthuses. “In terms of therapy, my bet is on stromal cells. But I’m going to have to get some money to make it move further!”

CHROMOSOME 10 IMPLICATED IN LATE-ONSET ALZHEIMER’S DISEASE

by Hannah Hoag

Although the early-onset autosomal dominant form of Alzheimer’s disease (AD) is rare, mutations in a number of genes (those that encode the β -amyloid precursor protein, presenilin 1, and presenilin 2) have been implicated in its development. The genes that influence the development of late-onset AD (LOAD), however, are more elusive. To date, only the E4 allele of the apolipoprotein E (APOE) gene has been identified as a genetic risk factor for LOAD. But scientists know that others must exist: 50% of individuals diagnosed with LOAD do not express the APOE4 allele.

In a trio of papers published in *Science* in December 2000, researchers performed linkage analysis of LOAD probands and their families to identify other putative LOAD genes. The 3 groups independently identified a region on the long arm of chromosome 10 (10q) that might qualify as a LOAD susceptibility locus.

Using a large group of sibling pairs with a definite or probable diagnosis of AD at age 65 or later, Myers et al. executed a genome-wide screen for susceptibility loci. Narrowing in on chromosome 10, the investigators identified a region of suggested linkage that falls on the long arm of chromosome 10. The results of others (see below) also suggested that this region might contain a susceptibility locus for LOAD.

Bertram et al. approached the puzzle from a different angle, by focusing on genes that

might affect the deposition or aggregation of β -amyloid (A β) in the brain. The A β peptide is the primary component of the senile plaques that are strewn throughout the brains of patients with AD. Thus, genes that affect A β deposition or aggregation may play a crucial role in the development of AD. Recent studies by Vekrellis et al. suggest that insulin-degrading enzyme (IDE), which is found in neurons and microglia, degrades A β . Consequently, Bertram et al. performed linkage analyses with 6 genetic markers that lie close to the possible location of the IDE gene. The study evaluated 1426 individuals from 435 families with AD. Two of these markers showed evidence of linkage: one in the entire sample, and one in the LOAD subsample.

Meanwhile, Ertekin-Taner et al., while also focusing their attention on A β , approached the problem from a slightly different perspective. One form of the A β peptide, A β 42, is significantly elevated in the blood plasma levels of individuals with early-onset familial AD. After verifying that A β 42 is elevated in individuals with LOAD and their unaffected first-degree relatives, the researchers performed linkage analysis in the chromosome 1, 5, 9, 10, and 19 regions identified by Myers et al. Only those families with a proband with a plasma A β level in the top 10% of AD patients were included in the analysis. The study revealed a region on chromosome 10 that may influence A β 42, the same region, in fact,

as identified by Myers et al.

Combined, these 3 studies suggest that a LOAD susceptibility locus lies on the long arm of chromosome 10, and that the gene may modify A β 42 metabolism, influencing LOAD development. Not only did these researchers uncover a quantitative trait (A β 42 plasma levels) that can be used to identify individuals with novel LOAD loci, but they managed to identify a specific region of chromosome 10 that shows linkage with the disease. Future studies need only to narrow in on this region before identifying candidate genes for LOAD.

Suggested readings:

Myers A, Holmans P, Marshall H, et al. Susceptibility Locus for Alzheimer’s Disease on Chromosome 10. *Science*; 290:2304-2305.
 Ertekin-Taner N, Graff-Radford N, Younkin LH, et al. Linkage of Plasma A β 42 to a Quantitative Locus on Chromosome 10 in Late-Onset Alzheimer’s Disease Pedigrees. *Science*; 290:2303-2304.
 Bertram L, Blacker D, Mullin K, et al. Evidence for Genetic Linkage of Alzheimer’s Disease to Chromosome 10q. *Science*; 290:2302-2303.

REGISTRY OF AGING-RELATED WEBSITES

by Alison McTavish

According to Canadian government statistics, today's seniors spend a significant portion of their leisure time travelling both in Canada and abroad. The Websites listed below contain travel tips and information to help seniors have safe and enjoyable trips.

<http://www.seniors-site.com/travel/index.html> (English)

This site provides a wealth of information for travelling seniors including how to prepare for trips, what to do about health concerns, and how to ensure personal safety while abroad.

<http://www.elderhostel.org> (English)

Elderhostel is a non-profit organization that provides seniors with access to learning programs at universities, national parks, museums and conference centres in the United States, Canada and in countries throughout the world. Seniors can attend programs in their own hometown, or can travel across the globe. There is a wide range of programs that include classes, field trips and social activities, each lasting five to six days.

<http://www.lcnd.com/travel/seniors.htm> (English)

The Canadian Travel Resource Centre has a seniors and snowbirds page with information for Canadians travelling abroad and links to other useful Websites for travelling seniors.

<http://www.50plus.com/travel> (English)

This is the Website of CARP, the Canadian Association of Retired Persons. They provide information on how to get good travel discounts, and provide links for travelers who are disabled.

<http://voyage.dfait-maeci.gc.ca/menu-e.asp> (English)

<http://voyage.dfait-maeci.gc.ca/menu-f.asp> (French)

For seniors who want to retire abroad, either seasonally or permanently, the Canadian government has a guide available to help with the planning of financial, medical and legal issues.

<http://www.snowbirdhelper.com> (English)

This comprehensive site covers retirement, real estate, tax and health issues for Canadian seniors who spend time travelling in the United States and around the world.

These Websites are presented as reference tools for readers. Geronto-McGill does not guarantee the accuracy of information found at these sites, nor endorse any of the products found therein.



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