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Hope FROM THE Hill

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FROM THE

Parkinson Update

OHSU

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New Therapies for Parkinson's Disease: *Neuroprotective, Neurorestorative and Symptomatic*

By John Nutt, M.D.

The development of new treatments for Parkinson's disease is expanding from the previous focus on **symptomatic therapies** (treatment of symptoms of a disease) to **neuroprotective** and **neurorestorative therapies**. **Neuroprotective treatments** are agents that would slow progression or prevent the development of signs of parkinsonism by reducing the loss of dopamine neurons.

The first drug suggested to be neuroprotective was deprenyl (selegiline or eldepryl®). The results of these studies have been complicated by the fact that deprenyl slightly improves symptoms, which makes it difficult to separate neuroprotective effects from symptomatic effects. However there remains enough suggestive evidence of neuroprotection that deprenyl continues to attract researchers' attention and a definitive answer will eventually be found.

Evidence was presented at the 2002 American Academy of Neurology that the use of dopamine agonists (such as Requip®, Permax® or Mirapex®) might slow the progression of parkinsonism. This conclusion was based on radioactive brain scans. The interpretation of these observations remains controversial because the changes in the scans are not proved to be due to the preservation of dopamine nerve terminals, which was the basis of the conclusion. The use of dopamine agonists instead of levodopa (such as Sinemet) remains a trade-off; dopamine agonists offer less chance of developing some of the side effects of levodopa (motor fluctuations and dyskinesia) and now perhaps some degree of neuroprotection. On the other hand, levodopa offers better control of the symptoms of parkinsonism without the side effects that are more common with dopamine agonists (hallucinations and swelling of the ankles).

Other treatments are being tested for neuroprotection in Parkinson's disease. A pilot trial with coenzyme Q10, in which the Parkinson Center of Oregon (PCO) participated, has just been completed. This pilot trial was suggestive enough of neuroprotection to justify a definitive clinical trial. The results of another trial with a drug classified as a neuroimmunophilin (related to the much-publicized drug GPI 1046) were initially reported to be completely negative, but have now been reanalyzed to show some support for neuroprotection. Further studies with this drug are being planned. As an indication of the importance of

pictured above PCO director John Nutt, M.D., associate director Julie Carter, A.N.P., and research volunteer Greg Moore

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neuroprotection, the National Institutes of Health (NIH) is making neuroprotection for Parkinson's disease a priority. The NIH has recently selected centers to be part of a consortium for neuroprotection trials. The PCO has been selected as one of the centers and will therefore be involved in many more neuroprotective drug trials.

Neurorestorative therapies are therapies to replace degenerated dopamine neurons or to coax malfunctioning dopamine neurons back to full function. Neurorestorative therapies are a hot theme. Glial derived neurotrophic factor (GDNF) is small protein that has the property of stimulating nonfunctioning dopamine neurons back to full activity in animal models of parkinsonism. The PCO was a leader in a multicenter trial of GDNF administered directly into the cerebrospinal fluid of the ventricles of the brain. This trial did not find improvement in the parkinsonism, possibly because the GDNF was not able to pass from the cerebrospinal fluid into the parts of the basal ganglia containing dopamine neurons. An exciting report at the most recent American Academy of Neurology meeting was of a small pilot study (without control subjects) which found that GDNF administered directly into the basal ganglia produced dramatic improvement in parkinsonism. The GDNF was administered by constant infusion through a small tube permanently implanted into the basal ganglia and connected to a small pump implanted in the abdominal wall. The PCO has been approached about participating in a pilot study with controls (some subjects will receive placebo via the pump for part of the study) to follow up on these provocative findings.

Another approach to neurorestoration is grafting of dopamine-producing cells into the brain. A pilot trial of implanting cells, which are derived from the retina and produce levodopa, was reported to benefit Parkinson's disease. These cells would be easy to grow in the laboratory and would not have the logistical and ethical problems that limit the use of embryonic cells. Another potential source of cells for transplantation is stem cells. Embryonic stem cells are being used in animal models of parkinsonism with some success, but there remains a problem that the stem cells may continue to grow in the brain and produce tumors. More information on how to control the growth of embryonic stem cells to prevent uncontrolled growth after implantation will be necessary before clinical trials with stem cells can be conducted in humans. Finally, another controlled trial of transplanting embryonic dopamine neurons into the basal ganglia is just being completed and the results will be reported soon. We look forward to bringing you more information about this exciting area of research in the future.

In the area of symptomatic therapy for Parkinson's disease, deep brain stimulation (DBS), continues to get much attention, especially since the FDA has now approved it. However, much remains to be understood about this treatment. Veterans Affairs (VA) and the NIH have joined forces to sponsor a large trial that will compare the relative benefits and drawbacks of DBS in two different parts of the basal ganglia, the globus pallidus interna and the subthalamic nucleus. This study will be conducted in the six VA centers established as Parkinson's Disease Research, Education and Clinical Centers (PADRECCs) and their associated universities. The Portland Veterans Affairs Medical Center and OHSU will be one of the six sites for this first large controlled trial of DBS.

Do what you can with what you have where you are.

- Theodore Roosevelt

Opinions About Participation in Clinical Trials: Interview With Greg Moore

By Julie Carter, R.N., M.S., A.N.P.

Q: Please give me a little background about yourself and your involvement in research studies.

A: Sure. I am 55 years old and was diagnosed with Parkinson's disease about 13 years ago. My father also had Parkinson's disease. I have been a patient at the Parkinson Center of Oregon for about 10 or 11 years and have participated in approximately six research studies.

Q: Why do you participate in research studies?

A: It's very simple. I participate in studies because it's a tangible way for me to contribute to Parkinson's research at a personal level. Clinical trials are where science and the healing arts come together. It's where theory meets practice; real human beings with real diseases and real problems. That's where I can make the most unique and personal contribution. If the research team can learn more about this peculiar disease by poking and prodding me, and stuffing me full of pills, I'm happy to participate. As I see it, without research there is no hope of breakthroughs that can lead to a cure or prevention of the disease, or advances in the treatment of symptoms.

Q: As a participant, what kind of research most interests you?

A: I'm actually interested in participating in all kinds of research, but of course, I'm most interested in the research that offers the most hope. I keep apprised of research that is going on in Parkinson's disease and currently am most interested in studies that hold neurorestorative or neuroregenerative possibility.

Q: What about risks? No clinical trial is 100 percent risk-free. How do you decide whether the risks are too great?

A: First, I try to understand the nature of the risks. Then, I try to understand whether the more serious risks have been eliminated or somehow controlled. To understand the nature of the risks, I rely primarily on the consent form for the study. I find the consent form extremely comprehensive and objective with all the risks carefully outlined. While I think the completeness of the consent form is vitally important, it's also easy to be overwhelmed by that very completeness. I simply keep in mind that there are risks associated with everything I do in the course of my daily life. I also turn to the professionals at the Parkinson Center of Oregon for advice. You always personally explain all aspects of a study and are always available to answer any of my questions. My experience with the staff at the Parkinson Center of Oregon is that the safety and welfare of research participants is of paramount importance to them. The staff is very thoughtful about weighing scientific merit versus patient risk before the research is undertaken. Furthermore, it's always explained that a research subject may discontinue participation at any time without prejudice. I opted out of one drug trial myself because of intolerable side effects.

Q: What advice would you offer to someone considering being involved in a clinical trial?

A: First, it's clearly a personal decision. A person should only participate in a clinical trial if he or she wants to be involved. Nobody should feel pressured. Having said that, if one does want to be involved: Inform yourself about the study and its associated risks – the more you understand, the more comfortable you will be. With these caveats in mind, I would encourage anyone to participate. You can make a unique contribution, learn a lot and derive a good deal of personal satisfaction from participating. And big advantages are often the product of a lot of little steps. We're all needed in the fight with Parkinson's disease.

The Facts Behind Glutathione

by Kathryn Chung, M.D.



Many patients are intrigued by information they have read regarding a compound called glutathione (GSH). This article is intended to help reinforce the facts and expose some of the misunderstandings surrounding GSH.

Glutathione is a simple molecule, made up of three amino acids, namely glycine, cysteine and glutamate. It is interesting that this compound, which is assembled by the body, is found in low quantities in part of the brain of Parkinson's patients known as the substantia nigra. It is not well known what glutathione's purpose is in the brain, it is slightly better defined in other areas of the body where glutathione is also found. In the liver, for example, glutathione helps to detoxify compounds such as acetaminophen. Certain people with a genetic blood condition that prevents glutathione from being recycled well can develop severe acute anemias when exposed to compounds that reduce cell energy availability.

Glutathione is part of a biochemical reaction that involves removal of hydrogen peroxide and other "oxygen free radicals" that are the byproducts of normal cellular processes. It is theorized that without glutathione, these toxic oxygen species may then cause damage to the neurons and some supporting cells of the brain. It is not known why glutathione becomes depleted in the first place.

It would be very helpful to be able to take glutathione either orally or intravenously in the hope that it might replace what is missing. Unfortunately, glutathione does not penetrate the brain. The brain has a very unique defense system that protects it from exposure to the many compounds our bodies are subjected to every day, called the "blood-brain barrier". Thus, the hunt is on for compounds that may stimulate or aid the brain in forming its own glutathione, a few of which are promising.

If someday we are able to stimulate glutathione production, the hope would be that by doing so as early on in Parkinson's disease as possible, we may optimize neuroprotection, a strategy that aims to help remaining neurons survive and even hopefully repair.

Prevention of Disease Progression in Parkinson's Disease Becomes a Research Priority at the PCO

National Institute of Health (NIH) has awarded the PCO a five-year grant to be one of 40 centers nationwide to focus on research aimed at delaying or preventing the progression of Parkinson's disease. The goal of these centers will be to identify the most promising neuroprotective compounds, and design and execute protocols to test the efficacy of these drugs. One compound that may hold promise is coenzyme Q10, a naturally occurring compound currently sold as a dietary supplement. In a recent national clinical trial, partially conducted at the PCO, Q10 was shown to have some positive effects. Now, a larger study must be done so that definitive results can be reached.

Parkinson Center of Oregon Clinics at OHSU Serve Multiple Purposes

By John G. Nutt, M.D.

One goal of the Parkinson Center of Oregon (PCO) is to offer skilled, comprehensive and compassionate care of people with Parkinson's disease and their families. The PCO faculty, Matthew Brodsky, M.D., Julie Carter, A.N.P., Kathy Chung, M.D., Penny Hogarth, M.D., Steven Johnson, M.D., Jau-Shin Lou, M.D., and John Nutt, M.D. specialize in movement disorders and offer careful assessment of your disorder and the treatment options appropriate for it. In addition to the clinical team, Kate Doebke, R.N., assures that care is comprehensive and patients and families are guided to hospital and community resources that may offer assistance in coping with the patient and family problems.

The PCO clinics serve other purposes as well. The clinics are important in the clinical training of medical students, neuroscience graduate students, advanced nursing students, neurology residents and occasionally other medical professionals. Trainees may be present when you are seen in the clinic by PCO faculty or you may be seen initially by the trainee and subsequently by a PCO faculty. However, the ultimate responsibility for your visit is with one of the PCO faculty. The PCO clinics thus further another of our program's goals, to increase awareness and skills of medical professionals in managing Parkinson's disease and related disorders.

The third purpose for the PCO clinic is to promote clinical research that will lead to a greater understanding of Parkinson's disease and to better treatments. Some research projects are carried out during clinic. Examples are simple test of balance or collection of blood samples for genetic studies. You may also be told about studies for which you would be appropriate but the studies will actually be done in research clinics or elsewhere away from the clinic. You, of course, are under no obligation to participate in any of these studies. Declining to participate in studies will not affect the care you receive in our clinic. Participation in studies is, however, one way in which you can help advance research into Parkinson's disease.

We hope you appreciate being an important part of a clinical, education and research clinic. You are the essential ingredient upon which the whole operation is centered.

Portland Marathon Fundraiser

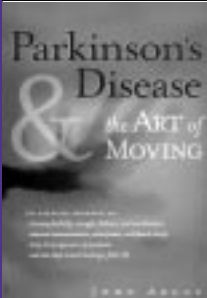


A special thanks to Jean Thorson, who ran her first marathon to benefit the Parkinson Center of Oregon (PCO). Her father, Duane "Duke" Dukart, was diagnosed with Parkinson's disease in 1983 at the age of 37. Although PD has drastically changed the course of his life, Duke's

dedication and determination to fight this neurological disorder has given her the inspiration to dedicate the marathon to him. Jean's goal is to raise \$10,000 for the PCO. Friends and family of Jean and Duke have already been very generous in honoring Duke. If you are interested in making a donation in honor of Duke, please mail your payment to:

Parkinson Center of Oregon
Oregon Health & Science University
Mail stop 45
P.O. Box 4000
Portland, OR 97208

We look forward to reporting on the total contributions from this event in our next spring newsletter.



Exercise is an important part of healthy living. We have all heard the adage "Use it or lose it!". Since your Parkinson's disease diagnosis, has your physician recommended exercise? What kind? Aerobics, weight training and stretching can be complementary. But what should I do if I have Parkinson's disease (PD)?

People with PD have a reduction in automatic motor function. We can see this by the symptoms of PD that include stiffness, tremor and rigidity. So you may experience a reduced arm swing, a shuffle when you walk, small handwriting, diminished facial expression and/or a low, monotone voice.

The unique value of this class is that the exercises are focused on your PD symptoms. We know that an exercise routine can compensate for some of the motor losses by programming your brain (your personal computer). Our movement classes are based on the Art of Moving by John Argue, published by New Harbinger Publications.

Are you afraid of falling? Learn movement strategies to conquer this fear. Learn how to get in and out of a chair gracefully.

So join us for 90 minutes of fun! We start with tennis ball exercises, move to the floor for stretching, then "sing" our way through voice exercises.

Our next class session is Oct. 22. One 90-minute class per week for 10 weeks. Contact Holly at Parkinson's Resources of Oregon at 503-413-7717.

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Health Corner

One of the ways to combat the effect Parkinson's disease can have on posture, walking and balance is to embrace some form of stretching. Take a step toward maintaining your movement abilities by checking into one of the resources listed below:

Resources for Those at Home
"Gentle Fitness" video
800-566-7780
www.gentlefitness.com

Sit and Be Fit video (Parkinson's disease)
509-448-9438
www.sitandbefit.com

Resource For Swimmers
Water Exercises for Parkinson's by Ann
Rosenstein
425-432-3231
www.IdyllArbor.com

Community Resources
Portland Metro YMCA Parkinson's Exercise
Class
Chad Swanson
503-294-3366

Parkinson's Resources of Oregon
Movement classes in six locations for people
with Parkinson's
503-413-7717
www.parkinsonsresources.org

Yoga Center
Julie Lawrence
1020 SW Taylor Street, Suite 780
Portland, OR
503-227-5524
Offers gentle level class

Attention Veterans!

The Portland Veterans Affairs Medical Center (VAMC) is one of only six VA movement disorder specialty centers in the United States of America. The Parkinson's Disease Research, Education and Clinical Center (PADRECC) is staffed with neurologists, nurses and other health care professionals who specialize in Parkinson's disease and other movement disorders. Patients receive comprehensive, individualized treatment, including referrals for physical therapy, occupational therapy, mental health, wheelchairs and other VA services. The PADRECC is also participating in a nationwide research study on deep brain stimulation treatment for Parkinson's disease.

This specialized care is available to all veterans who served on active duty, and who received an honorable discharge from any branch of the U.S. armed forces. The service may have occurred during either peacetime or wartime. For more information about enrollment, please call 503-273-5069.

Calendar of Events

Newly Diagnosed Small Group Session
Jan. 16, 2003
9 a.m. – Noon at Parkinson Center of Oregon
Kate Doebke 503-494-5620

Caregiver Series
Spring 2003 at the Parkinson Center of Oregon

Current Research Opportunities at the PCO

Are you interested in an experimental drug that might delay the progression of Parkinson's disease?

Julie Carter, A.N.P., and John Nutt, M.D., are seeking participants for a 3-year study to help find out whether an investigational drug can delay the progression of Parkinson's disease. To be eligible, you must be newly diagnosed and not taking any medications for your Parkinson's disease. All study related medications and evaluations will be provided at no charge. If you qualify and are enrolled, you would have a 1 in 4 chance to receive a placebo (not an active medicine). For more information call Pamela Andrews at 503-494-0965 or Julie Carter, A.N.P., at 503-494-7235. IRB #7004

Do you have Parkinson's disease and a living brother or a sister also affected?

Julie Carter, A.N.P., is now conducting a study to learn more about the genetics of PD from people with Parkinson's disease who have a living sibling with the disease. Participation would involve one visit at OHSU consisting of a neurological exam, a blood draw (2-3 tablespoons), and questionnaire, which will take approximately 1 to 2 hours. For more information call Pamela Andrews at 503-494-0965. IRB #5367

Do you have motor fluctuations ("on/off" or "wearing off")? Are you interested in participating in studies to better understand and or treat the motor fluctuations in Parkinson's disease?

To participate please call Barbara Alexander-Brown at 503-494-7232.

Balance and Parkinson's to be studied

OHSU's Human Balance Disorders Laboratory is seeking patients with Parkinson's disease for a study of the effect on the balance function of Parkinson's while on and off Levodopa. Qualifying participants will be 21-75 years old, have a diagnosis of Parkinson's, be free of other neurological disorders, have no significant orthopedic or muscular impairments for standing and will be able to stand independently for at least 20 minutes. The study takes approximately 4 hours to complete. Call Triana Nagel-Nelson at 503-418-2602 for details. IRB #4841

Healthy volunteers needed for balance study

OHSU's Human Spatial Orientation Laboratory and Human Balance Disorders Laboratory is seeking healthy individuals to serve as age-matched controls for patients with neurological involvement for studies in balance function. Participants must be 30-75 years of age, in excellent general health, and have no history of dizziness or balance problems. IRB #4841, #4843, #4870, #5554 and #5696. In exchange for each 2-to-3-hour session, participants will receive \$25. Call Triana Nagel-Nelson at 503-418-2602 or Sharna Clark-Donovan at 503-418-2617 for details.

Healthy volunteers and people with PD needed

We are recruiting healthy volunteers and people with Parkinson's Disease (PD) of all ages to participate in a study involving a non-invasive brain stimulation technique. This study may contribute to improving the quality of life of those who are suffering from Parkinson's Disease. We are trying to assess the therapeutic value of this stimulation technique in PD patients as compared to healthy volunteers. Participation in this study requires volunteers to attend four visits over the course of a month. Each visit lasts no longer than 3 hours. Complete participation pays \$120.00. Please contact Ryan Eaton or Brian Coakley at 503-494-4987. IRB #6892

We gratefully acknowledge the following contributors who have made gifts to the PCO from September 2001 to August 2002. We have made every effort to compile a complete list of donors. We offer our apologies for any omissions.

In addition, we would like to thank the following companies for their continued support throughout the year: GlaxoSmithKline, Pharmacia, Teva Neuroscience, and Astra-Zeneca.

If you are interested in supporting the PCO, please send your tax-deductible donation to: PCO, 3181 SW Sam Jackson Park Rd, OP-32, Portland, OR 97201. Make checks payable to: OHS Foundation/PCO.

For more information about charitable opportunities or estate planning, please contact Maureen Bradley at 503-412-6358.

\$25,000+

Anonymous

\$10,000 - \$24,999

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