



A New Generation of Anti-Parkinson Treatments: Are We There Yet?

By Marina Emborg, M.D., Ph.D.

In the Spring 2004 issue of *News & Review*, we reviewed a variety of potential new treatments for Parkinson's disease (PD). Where do we stand with these therapies? How safe are they? Is the emergence of new therapies keeping pace with our increased understanding of PD? In this article, we provide an update on the state of PD treatments.

Gene Therapy

Gene therapy is the method by which a gene (a piece of nucleic acid containing information to produce a molecule of interest) is introduced inside a cell using a "vector" (usually a modified virus that cannot cause disease) that can gain access to the cell. At this time, gene therapies for PD rely on surgery to inject the vector into the brain.



Several genes have already been identified as having the potential to treat PD, and a few of these are being examined in early stage clinical trials.

One being explored is the gene for neurturin, a trophic factor that helps neurons remain alive and healthy. A Phase I clinical trial of neurturin, also known as

CERE 120, was successfully completed and a Phase II trial is close to completion.

Another is the gene that produces an enzyme known as aromatic amino-acid decarboxylase (AADC), that in turn transforms levodopa (the main ingredient in Sinemet®) into the neuronal messenger dopamine. Its safety is currently being investigated in a Phase I trial.

A third option is the gene for glutamic acid decarboxylase (GAD), an enzyme involved in the synthesis of the neuronal messenger gamma aminobutyric acid (GABA). People with PD have overactivity in the area of the brain called the subthalamic nucleus. Researchers propose that since GABA

has inhibitory properties, injection in the subthalamic nucleus of vectors encoding for the GAD gene (which increases GABA) will restore balance in the PD circuit. A Phase I trial to test its safety has already been successfully completed and a Phase II trial is under way.

As promising as these potential therapies may be, scientists caution that they are not without risks, including the risk of complications and infection that comes

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NEWS IN BRIEF

PD Linked to Flawed Recycling in Cells

For years, scientists have tried to explain the loss of dopamine-producing neurons that is found in people who have Parkinson's disease (PD).

In the January 2 online issue of *The Journal of Clinical Investigation*, Ana Maria Cuervo, M.D., Ph.D. and her colleagues at Albert Einstein College of Medicine of Yeshiva University, along with scientists from Columbia University, the University of Pennsylvania, and Harvard Medical School suggest an explanation.

The team reports that in people with Parkinson's, neurons die because an important cellular process called *cell-mediated autophagy* — essentially a cell's recycling system — does not function properly. Autophagy keeps aging cells healthy by filtering damaged molecules through the cell, thus avoiding any potentially harmful build-up. Dr. Cuervo traced the PD-related malfunction, in part, to the role of a protein known as alpha-synuclein, which had already been known to build up abnormally in the brains of people with PD.

Researchers found that in PD, when alpha-synuclein interacts with

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with any brain surgery. There is also concern about the potential toxicity of the viral vectors that are used to transport the genes and about the lack of control doctors have over the vectors, once they are injected into the brain. Even if the molecule is doing its job, there could be cases in which a physician would want to stop or slow its production, but would be unable to do so.



Dr. Marina Emborg

Glial-derived Neurotrophic Factor (GDNF)

GDNF — a growth factor that is chemically similar to neurturin, mentioned above — has received significant media attention, both for its neuroprotective promise and for its potential risks. Since it is a naturally occurring substance in the body and has the ability to slow or reverse the loss of dopamine neurons (still seen as the process by which PD occurs), GDNF has been a target of hope and attention in the PD community.

Initial laboratory research showed that GDNF could protect neurons in PD. However, clinical trials showed mixed results. In 2004, the Amgen Corporation, which holds the GDNF patent, halted all trials of GDNF — citing as their reasons concerns about safety and efficacy.

Research since that time has shown that the problem with the GDNF clinical trials may have been not in the molecule itself, but in its delivery. To be effective, GDNF requires long-term, direct delivery to the brain. It cannot be delivered as a pill or an injection. Because of this, many clinical trials employed a technique involving surgical implantation of a pump and catheter system, permitting continuous intravenous delivery of the GDNF to the designated target area of the brain.

Scientists now understand that it is very difficult to ensure that GDNF, delivered in this way, does not spread to areas of the brain outside the target area. Additionally, various trials used different versions of the pump/catheter system, which may be why their results differed.

Accordingly, more recent research is studying different dosing regimens and delivery systems.

There is also increasing agreement among investigators that GDNF treatment may be most helpful for people in the early stages of PD — those people who have larger numbers of neurons available to be protected.

As with all treatments, GDNF does involve risks, including those associated with surgery. By contrast with gene therapy, the GDNF approach gives the treating physician the ability to control delivery externally. This means that if a person were to experience complications with the treatment, his or her physician could easily shut off delivery.

Investigators are eager to continue using GDNF and there is new hope that trials may begin again.

Other Approaches to Neuroprotection

Through gene therapy and growth factors, scientists hope to protect remaining healthy neurons in the brain (neuroprotection) and perhaps restore function to some that have been damaged (neurorestoration). These strategies would be much more proactive than the treatments that are currently available.

Scientists are currently testing the neuroprotective qualities of two nutrition supplements that also play a role in cell energy metabolism. The NET-PD (Neuroprotection Exploratory Trials in Parkinson's Disease) study is a randomized, double-blind trial studying the potential of creatine and was launched in 2007. There is also an upcoming Phase II trial for Coenzyme Q10 (CoQ10), a naturally occurring substance in the body that plays a key role in the function of the mitochondria, the part of a cell that generates its energy.

Cell-based Therapies

Stem Cell Therapies

Stem cells are primitive cells that have the potential to transform into other types of body cells. Scientists see promise in stem cells for people with Parkinson's because they could be transformed into neurons, replacing the ones that have been lost or damaged by PD. Types of stem cells include those derived from human embryos (the most versatile), from bone marrow, and those known as adult

neural and neural progenitor cells.

Researchers believe that stem cell treatments for Parkinson's might be best delivered by transplantation, which requires brain surgery. However, this approach presents challenges. Once stem cells are injected into the body, they can form tumors, called teratomas. Another problem is that because the transplanted cells are recognized by the body as foreign, they can come under attack by the body's own immune system.

To address the latter problem, researchers are working to develop new combinations of immunosuppressants, medications that could decrease immune system attacks. They are also exploring the exciting potential of a recent discovery of stem cells that are derived from a person's own skin cells, which can be reprogrammed to behave like embryonic stem cells. These cells would be free of the immune response problem, because they would be "personalized" — matching the DNA of the person being treated.

Stem Cell Alternatives

Other cells in the body, such as pigmented cells of the retina and glomus cells in the carotid artery, are also seen as potential sources of dopamine. Scientists are looking to these as potential treatments that would work mainly by pumping dopamine into areas where it is needed.

In one study, scientists are investigating retinal cells obtained from cadavers. A Phase I safety study has already been completed, and a double-blind placebo-controlled trial is now underway. In another study, scientists investigating the auto-transplant of glomus cells (obtained from the patient him- or herself) have observed improvements in PD symptoms.

Looking for Safe, Global Therapies to Prevent PD Progression

Many of the therapies mentioned in this review aim to treat the symptoms of Parkinson's by replacing or protecting the dopamine neurons in the substantia nigra. However, scientists are increasingly realizing that a full explanation of PD's complex symptoms requires investigation of other areas of the brain. This leads many of them to conclude that halting PD's progression may require therapies that would address these other areas.

One response to this understanding is

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SPOTLIGHT

on Research

Supported by PDF

William T. Dauer, M.D.

It is common for someone recently diagnosed with Parkinson's to question whether the disease can be passed on to children, grandchildren or other members of the family.



Dr. William T. Dauer

Dr. William Dauer, of Columbia University, notes that most Parkinson's disease (PD) cases are sporadic — meaning that genetics and family

history have not played a clear role in the onset and development of the disease. Of the one million individuals in the US who live with PD, scientists believe that only about five percent have an inherited form of the disease.

Over the past decade, there has been growing recognition of the role that genetic *susceptibility* plays in the development of PD — meaning that genes may not themselves cause Parkinson's, but may play a role in making some people more vulnerable to developing the disease

than others. Dr. Dauer believes that while the percentage of people who inherit PD is very small, the study of genetic forms of PD can teach us about the more common, non-inherited, forms — and thereby help us develop better therapies to treat it.

In the late 1990s, while working on a PDF-funded Fellowship in Movement Disorders at Columbia University, Dr. Dauer began studying alpha-synuclein, the first protein to be identified (in a mutated form) as a genetic cause of Parkinson's. Although the cases of genetically-induced PD via alpha-synuclein are rare, the protein is commonly found in substances known as Lewy bodies, which are found in the brains of people with classic PD. This relationship confirms that the study of rare genetic forms of Parkinson's can lead to insights relevant to sporadic PD.

In 2002, Dr. Dauer developed an important mouse model, in which natural alpha-synuclein had been removed, to examine the link between the genetic and environmental causes of Parkinson's. His model demonstrated that when an alpha-synuclein-free mouse is exposed to MPTP (a neurotoxin that is widely known to cause PD-like symptoms), the animal does not develop PD symptoms.

The fact that these mice were resistant to MPTP is significant because it showed that a PD-causing gene (mutant alpha-synuclein) affects the role that an environmental toxin plays in causing dopamine

loss and PD symptoms. In other words, genes and environmental toxins may act by regulating similar pathways.

Dr. Dauer is now studying LRRK2 (leucine-rich repeat kinase 2), the most common mutated gene to be found among people who have inherited PD. Most people who have PD because of a LRRK2 mutation exhibit symptoms very similar to those found in people with sporadic Parkinson's. Dr. Dauer reports that the pathologies of LRRK2 PD and sporadic PD are also very similar. This suggests that LRRK2 may also participate in the neuronal pathways that go awry in people with typical PD. Scientists hope that LRRK2 may be a promising drug target as well.

While the links between LRRK2 and alpha-synuclein in classic PD are not yet clear, the work on these and other genes offer hope for understanding the mechanisms underlying classic PD, and for devising new treatment strategies.

William T. Dauer, M.D. is an Assistant Professor of Neurology and Pharmacology at Columbia University Medical Center. His work is supported as part of PDF's Center Grant to Columbia University amounting to \$2.6 million in 2008. Dr. Dauer served on the Scientific Program Committee for PDF's 50th Anniversary Educational Symposium, where he presented a session entitled, Biology and Pathology of LRRK2. His presentation is available for viewing online at www.pdf.org/50th/webcast.cfm.

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dopamine (a neurotransmitter), the alpha-synuclein gets 'stuck' in the cell-cleaning process. This malfunction leads to a harmful build-up of molecules and, in turn, to the death of cells, which then causes symptoms of PD.

Dr. Cuervo's earlier studies focused on mutations of alpha-synuclein and how they disrupted the same cellular process. However, this research applied only to a small group of people who had a relatively rare genetic form of PD. Her new findings are much more compelling because they may apply to all people with PD. Additionally, the cellular glitch that Dr. Cuervo has found

can be targeted by therapeutics in a number of ways, so her study opens the door for researchers to investigate new treatment options for Parkinson's disease.

NSAIDs May Reduce Parkinson's Risk

Researchers at the UCLA School of Public Health reported in the November 5 edition of *Neurology* that the use of non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin and ibuprofen, may reduce a person's risk of Parkinson's disease (PD).

Angelika Wahner, Ph.D., and her team studied the impact of NSAID use among 579 people, about one-half of whom had PD and one-half that did not.

Dr. Wahner's team questioned participants about their use of both aspirin and

non-aspirin NSAIDs (naproxen, ibuprofen), asking whether participants had taken either type of NSAIDs once a week or more for at least a month at any point in their lives.

Researchers defined regular users of NSAIDs as those who took two or more pills a week for at least a month, and classified people who fell below those standards as non-regular users.

The UCLA team found a mild protective effect against PD among the regular users of *non-aspirin* NSAIDs. A protective effect was also found among women who were regular users of *aspirin* NSAIDs, especially for those who reported two or more years of use. Dr. Wahner hypothe-

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PDF and Partners Bring Leading Scientists to You

Responding to continuing demand from people with Parkinson's and their families for up-to-date research information, the Parkinson's Disease Foundation (PDF), announces a series of four educational symposia and webcasts entitled, *Parkinson's Science: Innovations and New Perspectives*. The series will allow people with Parkinson's, their families, support groups and healthcare professionals nationwide, to receive scientific updates directly from leading Parkinson's authorities — both in-person and via the web.

The traveling series will bring experts to four cities across the US to discuss the latest discoveries in Parkinson's disease (PD) science. PDF is launching this program in conjunction with four leading

regional Parkinson's organizations: the Parkinson Association of the Carolinas, the Michigan Parkinson Foundation, the Northwest Parkinson's Foundation, and the Houston Area Parkinson Society.

Each half-day symposium will feature national and local scientists and clinicians presenting their latest insights on research that has potential impact both upon current treatments and upon the quality of life for those who live with PD. Webcast technology will enable those who cannot attend in person to view all four programs on the web, both live and after the event. For people who can join the live webcasts, the technology will provide the opportunity to submit questions about PD directly to researchers during their presentations. Those who cannot join the webcast live can view archived sessions 24 hours a day, 7 days a week, for one year following each event.

Robin Elliott, Executive Director of PDF, says, "This unique series is of great

importance in the PD community — and by community, I mean all those who live with PD, and those professionals who seek to treat and cure the disease that burdens them. Every person who lives with PD deserves access to the most current information. We are excited to bring the best and brightest to you and look forward to the stimulation that will be generated by these interactions."

The Carolinas: What's in the PD Pipeline?

The first installment of the series will take place on Friday, May 9, 2008 in Charlotte, NC, in collaboration with the Parkinson Association of the Carolinas. The theme of this session is, *What's in the PD Pipeline?*, and presenters will include Dr. Katrina Gwinn of the National Institutes of Health, Dr. Mark A. Stacy of Duke University and Dr. Clive Svendsen of the University of Wisconsin-Madison.

Please see below for other upcoming dates and locations and to learn how to attend or watch on the web.

Parkinson's Science: Innovations and New Perspectives

Friday, May 9, 2008 – Charlotte, NC – Jointly with the Parkinson Association of the Carolinas

Friday, July 18, 2008 – Lansing, MI – Jointly with the Michigan Parkinson Foundation

Saturday, October 11, 2008 – Spokane, WA – Jointly with the Northwest Parkinson's Foundation

April 2009 – Houston, TX – Jointly with the Houston Area Parkinson Society

For more information, contact PDF or our partners listed above. Visit www.pdf.org or www.parkinsonassociation.org to register for the first symposium in Charlotte, NC. To learn more about joining the webcast, email webcast@pdf.org. The educational symposia and webcast series is made possible by a generous unrestricted grant from UCB, Inc.

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to assess the potential of molecules that target cell metabolism. For example, when scientists noted an association between high blood levels of urate (a salt in the body) and lower PD risk, they began studies to assess urate's neuroprotective potential. Other scientists have suggested that the polyphenols that are found in vegetables and brightly colored fruit — that show antioxidative activity — may have implications for the treatment for PD. New research also points to exercise as a low-risk, high-gain treatment to help slow PD progression. For those people with PD who also have diabetes, it is interesting to note that pioglitazone, an

antidiabetic treatment with anti-inflammatory properties, has shown neuroprotective properties in animal studies.

Scientists are also looking for ways to more easily administer existing and potential PD treatments. Currently, treatments such as gene therapy and GDNF require surgery because the molecules involved are too large to cross into the brain by themselves. Some researchers are looking to develop alternative transport systems that would allow these big therapeutic molecules to cross the blood brain barrier without recourse to surgery.

Conclusion

Which of these therapies will be "the" next PD treatment? We don't yet know, but what we do know is that there

is unlikely to be a single "silver bullet" in the fight against Parkinson's.

The good news is that the ingenuity of investigators has led to the discovery and testing of candidate therapies on several fronts — which is what we need to more effectively treat PD. And that's something to be excited about.

Marina E. Emborg, M.D., Ph.D., is Director of the Preclinical Parkinson's Research Program at the Wisconsin National Primate Research Center and an Assistant Professor of Medical Physics at the University of Wisconsin-Madison. Her research is focused on understanding neurodegeneration in order to develop and test novel neuroprotective and restorative strategies for the treatment of PD.

Stem Cell Breakthroughs: What Do They Mean for Parkinson's?

Stem cells are often touted for the potential they hold to treat diseases, including Parkinson's disease (PD). So, when a new development in stem cell science is referred to as a 'breakthrough,' you may wonder what the true implications are for PD treatments.

Since the last issue of *News & Review*, two studies have been published, each highlighting an alternative source of stem cells. In November 2007, scientists announced they had created stem cells by reprogramming human adult skin cells. More recently, on January 17, researchers at the Stemagen Corporation announced they had been successful in using adult skin cells to clone embryos.

What do these results truly mean for research funding, for governmental policy and, most importantly, for the development of treatments that may affect people living with PD?

Why are Stem Cells Important?

Researchers see promise in stem cells because of their ability to become any type of cell in the body. They foresee manipulating stem cells to create specialized cells that may be used to replace the cells or tissue damaged or destroyed by disease — such as the unhealthy or missing cells that are found in diseases such as Parkinson's, diabetes, and Alzheimer's.

In the case of Parkinson's, this would entail manipulating stem cells into dopamine-producing neurons and using these to replace the cells that are lost in PD.

Prior to these recent developments, scientists looked to human embryonic stem cells (hESCs) as the most ideal type of stem cells for disease research and treatment development because they are the most versatile of stem cells. This is both because their structure allows them to transform into any type of tissue in the body and because they can be easily multiplied. The ability to multiply allows researchers to develop stem cell lines, groups of cells that make research much

easier to perform.

Conversely, neither adult stem cells nor stem cells derived from cord blood have these abilities. Stem cells from these sources are more difficult to study and to translate into treatments.

Stem Cells Derived from Skin Cells

In November 2007, reports published in the prestigious journals *Science* and *Cell*, led respectively by Dr. Junying Yu, working in the lab of stem-cell pioneer Dr. James Thomson of the University of Wisconsin-Madison, and Dr. Shinya Yamanaka of Kyoto University, announced the successful creation of stem cells through the manipulation of human adult skin cells. With these accomplishments, both teams have created the first

“It is hoped that the sheer increase in the amount of research that can be performed will speed scientific progress”

stem cells that have the same potential as human embryonic stem cells, but which do not require the use of human embryos.

Why is This a Breakthrough and What Does It Mean for Disease Treatments?

Scientifically, skin-derived cells are important because they hold potential similar to that of hESCs. That is, they are easily replicated and they have the ability to develop into any type of cell in the body. Therefore, skin-derived stem cells hold the potential to develop into cell replacement and tissue therapies — the same treatments that researchers have hoped to develop from hESCs.

Since skin-derived cells can be taken from adults who have a particular disease, they also open up the possibility of growing replacement tissue in a lab that

is unique to the person who is being treated. Having a customized therapy of this kind could eliminate the concern about immune system rejection that comes with hESCs.

The discovery of skin-derived stem cells will have political and financial ramifications as well. Because the source of these cells is something other than a human embryo, the research will not be subject to the same constraints that were set by President Bush in 2001 for hESCs. These regulations limit federal funding for human embryonic stem cell research to lines developed before August 9, 2001. The rules essentially require institutions to house stem cell research in separate facilities, using separate equipment, from research funded by the government — creating a burden for institutions in terms of cost, logistics and liability. This problem was compounded by the fact that the available stem cell lines turned out to be many fewer than was originally thought and not always of the high quality necessary for research. Such issues have discouraged institutions and researchers from entering the field.

However, because stem cells derived from skin cells do not involve embryos, they bypass all of these regulations, meaning they will be eligible to receive federal funding. In fact, the President has already moved to encourage funding of research involving skin-derived cells, as evidenced by his statement in the State of the Union Address on January 28.

With the possibility of increased funding present and the belief of scientists that skin-derived stem cells can be easily and quickly replicated at institutions across the country, it is hoped that the sheer increase in the amount of research that can be performed will speed scientific progress.

What Scientific Barriers Still Exist in Developing Treatments?

While skin-derived stem cells appear to offer the same flexibility and potential as hESCs, they also possess some of the same inherent limitations as their predecessors, along with some new ones.

For instance, when hESCs are developed into treatments, they are able to transform again within the body. In cases where this proliferation is uncon-

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The PD Partnership: Tips for People with PD and Their Care Partners

By Rhona Johnson

Life with Parkinson's disease (PD) has profound effects not only on the person who is diagnosed, but also on his or her family members and friends. More often than not, there is one person — a spouse, partner, child, parent or other loved one — who takes on the role of primary care partner to the person who has PD. It

is this person who shares responsibility for daily PD-related tasks and challenges — making appointments, managing medications, etc. — with his or her partner.

I prefer to call this relationship a “care partnership” because I believe it is one that is truly reciprocal. As a person with PD adjusts to physical changes and, at times, to changes in personal independence, the care partner must learn to adapt to a different relationship dynamic and perhaps to greater “ownership” of duties that their partner had previously handled (e.g., finances or household management).

As a former caregiver — my late husband, Bob, lived with PD — I have gained some insight on what it is to be a caregiver and on what it is like to have PD. I would like to share some of our experiences with those of you who may be in a care partnership. Before I do this, I ask you to keep two things in mind.

First, remember that your experience with PD is unique. The nature of Parkinson's is that it is a chronic neurodegenerative disease. It is never acute. It progresses at very different rates in different people and there is no way to accurately predict its course. What one person with PD may experience five years after diagnosis, another may face in 10 to 15 years,

or may never experience at all. So, there is no reason to look at the other people in the neurologist's waiting room and think, “that will be us in a few years.”

The second point, which is for caregivers, is that while you did not choose this role — and in most cases were not trained for it — this does not mean that you cannot be good at it. Assess your individual strengths, which will shape your role as a caregiver. With support from others, you will also be able to supplement your abilities in those areas in which you are less confident.

With those thoughts in mind, I would like to share some ideas that helped Bob and me navigate the experiences we faced together. I believe these

“ I hope that you will take care of yourselves...so that PD, while a part of your life, is not what defines it. ”

can apply to those who live with a spouse or a partner as well as those whose care partner relationship is with a son or daughter, or with a friend or family member. Please remember that these suggestions are drawn from personal experience, so there is no science behind them, but rather lessons from my own life.

1. Respect your partner's own journey with PD. It will be different from yours. You may feel the need to talk to others in order to better cope and feel less alone. Your partner may want to keep the diagnosis to him or herself; indeed, the person with PD may need to do so if the disclosure of PD might affect his or her work. One of you may be reluctant to seek out information and help, or more ready to do so than the other.

Respect these differences and ask your care partner to respect how you are feeling and reacting.

2. Talk openly to each other about the disease. This is vital if you are to respect each other's feelings. Discuss the impact PD has on each of you and how you want to handle it. Learn to listen.

3. Don't let the disease take over or define your lives. Be sure to maintain your individuality, and put your relationship as a couple first. The aim should always be to avoid becoming “identified by the disease” in the eyes of your family, friends and others.

4. Find a good doctor. As soon as possible, find someone who is (i) a movement disorders specialist and (ii) someone with whom you both feel confident and comfortable. I think the caregiver should accompany his or her partner to as many doctor appointments as possible. Two pairs of ears will always be better than one, and two people asking questions will cover more ground at each visit.

5. Feel free to seek out a second opinion. If you are the caregiver, encourage your partner to seek an additional opinion if you think it will help, and do not hold him or her back if this is what he or she wishes to do. A second opinion may help to confirm the diagnosis, to open a window on clinical trials of new medications, or to determine an appropriate course of treatment. A confident and understanding doctor will not mind if you seek a further opinion; you should not feel, as many of us are conditioned to, that you need to apologize for doing this. As my husband's PD progressed, I grew more confident, more assertive and active on his behalf. Both of you can learn to become a good advocate for yourself or your care partner.

6. Educate yourself about PD in stages. When you are coping with the early stages of living with a diagnosis of Parkinson's disease, you need to find your comfort level with learning about the disease. You don't have to dive in and learn everything all at once and spend hours on the Internet — unless you wish to. Remember, the disease progresses slowly and you and your care partner have time to adjust. Denial may be part of the process for one or both of you and that is

Janet Charles



Rhona Johnson

perfectly normal and okay. However, when you are more comfortable with PD, it can be helpful to search the Internet and to call some of the national Parkinson's organizations. PDF has a wonderful information service right on its website and a toll-free helpline, which can help answer your questions.

7. Educate others about PD — not only friends and family, but also health care professionals. The wider public's perception of Parkinson's too often is limited to "shaking." But you can change this. Others' lack of knowledge does not indicate a lack of engagement or interest on their part. When you help others to better understand PD, they will be more comfortable around you and other people with the disease. Explain why your voice or your partner's voice is quieter than it used to be, or why your/their face may lack mobility or expression. Describe why sometimes a person with Parkinson's can walk easily, but at other times may shuffle.

8. Find a support group. In a support group, you can ask any question, express any concern, compare your experiences, and discuss medications. Besides providing the opportunity for you to talk with others who are facing the same thing, a support group will also provide you with valuable information about PD — which will make your doctor visits much more productive.

9. Actively seek out support from friends, family, and other caregivers. Many of them will come to understand the challenges of a chronic disease and of caregiving and will be supportive and present for both of you. If people do not offer to help, it is often because they don't know what you need or how to offer. So you both may need to learn to ask for help.

10. Support other people with PD. When you are both comfortable with PD, you can be a wonderful resource to others. My husband, Bob, had a scientific and technical background and wanted to understand everything he could about PD. He researched questions raised by people with PD whom he met via the Internet and through our support group. He maintained an extensive email list, sending out results of important research,

trials, and so on. We attended every regional meeting and conference on PD we could. This empowered us tremendously and it can do the same for you.

11. Tackle life planning decisions.

This is something we all put off, but it is important for both of you to address estate planning, advance directives, and so on. I strongly support having a living will, appointing a health care proxy, and a backup. I was my husband's advocate and health care proxy, and, when I needed to assume those roles, I was very fortunate to have a wonderful friend as backup who helped me through the tough medical decisions that arose. Discuss these issues with your families or those involved and circulate copies of your living will, if you have one, to all of them, to ensure that your wishes are respected.

12. Take care of yourself. Neither of you can do it all. If you are the caregiver, you may be very inclined to put the needs of your spouse or partner first. Try consciously to teach yourself to relax, set priorities, and make time for yourself. I found it was one of the most difficult things to do. It was hard to find time to participate in an organized activity or to pay the bills. I came to realize that part of the problem was me. I needed to make these things top priority. I could have asked more often for someone to drop in and keep Bob company while I took a walk. Accept support from your family, friends, and neighbors.

I hope that both of you will take care of yourselves, because in doing so, you will be helping each other. I also hope that these suggestions will help you to navigate your partnership, so that you can live your lives more fully and so that PD, while a part of your life, is not what defines it.

This piece was adapted from a session, entitled, Caregiver Support Issues, that Rhona Johnson originally presented at PDF's 50th Anniversary Educational Symposium — available online at www.pdf.org/50th/webcast.cfm. Ms. Johnson is a member of PDF's People with Parkinson's Advisory Council (PPAC) and a long-time spokesperson for caregiving. In October 2007, she became the first recipient of PDF's Award for Leadership in Caregiving.

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sized that the gender difference may be attributed to dosage. She speculated that women are more likely to have taken aspirin in higher doses, perhaps for arthritis or headaches, while men may have taken it in lower doses for other conditions, such as heart problems.

Dr. Wahner's results are interesting because they suggest that the role of inflammation — already linked to cell death in PD — needs to be further studied and could be an avenue for future treatments. However, the design of this study — a retrospective dietary survey which attempts to match people with PD and normal control subjects — cannot provide definitive information about the relationships between NSAIDs and PD. The relative risk of PD among people who are not taking NSAIDs was actually very slight, and the differences between groups could have occurred for unrelated reasons. Therefore, researchers are not yet recommending NSAIDs for prevention against PD. The area needs more investigation, both to clarify more specifically which NSAIDs may be protective and why a protective effect may exist.

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Engaging Community Physicians in Parkinson's Clinical Research

By David Eger, Ph.D.

Whether you are a person with Parkinson's disease (PD), a family member or a health professional, you are certainly familiar with the medications that are available to improve PD symptoms. Such treatments are available because they have been successfully navigated through the clinical research process — the phases of study that assess their safety and efficacy and allow physicians to prescribe them to you and me.

Crucial in this process is the role of the general physician or neurologist — the person to whom people with PD are likely to turn for suggestions about their medical care, including their participation in clinical trials. Yet within the PD community, according to a 2005 Harris Interactive® survey conducted on behalf of *PDtrials*, the vast majority of physicians neither serve as trial investigators themselves, nor tell their own PD patients about the availability of trials.

Why aren't physicians talking to their patients about clinical trials? Why aren't they using their skills to lead trials testing promising new therapies? What can be done to close this gap, so that people with PD have the option to participate in studies that could lead to new treatments?

Engaging Community Physicians in Parkinson's Clinical Research

To help answer these questions, the Parkinson's Disease Foundation (PDF) led a roundtable on February 14 entitled, *Engaging Community Physicians in Parkinson's Clinical Research* — the second in a three-part series sponsored by PDF through Advancing Parkinson's Therapies (APT), a program that aims to identify and address non-science barriers to the acceleration of PD treatments and therapies.

Held at the New York Academy of Sciences and facilitated by Ira Shoulson, M.D., Professor at the University of Rochester and Founder and Former Co-Chair of the Parkinson Study Group (PSG), the roundtable brought together 26 community leaders, including physicians, people with PD, government officials, researchers, and pharmaceutical industry representatives to discuss the issues.

Challenges and Opportunities

Ken Getz, Co-Founder of the Center for Information and Study on Clinical Research Participation (CISCRP), began the day with a discussion on current trends in clinical research, highlighting the complicated environment that exists for physicians involved in the process. Problems commonly encountered include time delays, high participant drop-out rates, and complex protocol design requirements. His observations were confirmed by a community neurologist, who noted the excessive demands placed on his and his colleagues' time. He said that asking them to serve also as clinical investigators would overburden the office infrastructure and cost the practice money.

As to why physicians are not referring their PD patients to clinical trials, participants expressed several concerns, including the fear of losing patients to other centers or not being kept properly informed about their patient during the course of the trial. One suburban physician said she had the opposite concern — she would recommend patients to participate in trials, but has found that many of them dislike traveling to the urban centers where trials are frequently conducted.

Models and Pilot Projects: The Neurology Community and Beyond

The group then heard reports on successful models of physician engagement in clinical research — both within and beyond the field of neurology.

One was a new initiative of the National Institute of Neurological Disorders and Stroke (NINDS), described by Anne Lindblad, Ph.D., which aims to raise community neurologists' interest in trials by providing outreach and training in clinical research skills. Danna Jennings, M.D., of the Institute for Neurodegenerative Disorders in New Haven, CT, spoke of her experience working with an independent

research institute which provides no regular clinical practice and thus does not compete with other community practitioners for patients. Her center provides constant feedback to referring physicians on care that their patients receive. As a result, it fosters mutual trust between the scientists and the community neurologists.

Dr. Jennings was followed by representatives of the cancer and dentistry communities, each of whom stressed the importance of physician input in trial design. Jonathan Ship, D.M.D., of New York University, reported on the success of the PEARL program (Practitioners Engaged in Applied Research and Learning), which creates studies that are of immediate relevance to practitioners and their patients and that can be conducted in practitioners' own offices. He said that this model reduces the delay between clinical research outcomes and use of new treatments.

Identifying Core Issues and Action Items

The group concluded by analyzing the models presented and suggesting action steps to improve the PD model of physician involvement in trials. While it was generally agreed that the issues were complicated, a recurring theme was that clinical trial participation should become an appealing and easy part of physicians' lives, rather than one that creates extra work, administration and costs.

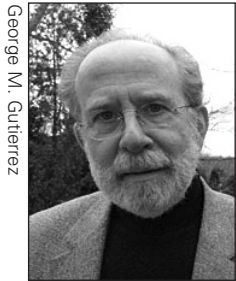
Overall, the day was successful in opening up dialogue among people with varied perspectives and in suggesting that the process of sharing, and putting lessons into action, will help to improve the research process that is so crucial to developing therapies that will one day make your life, and mine, better.

David Eger is a member of PDF's People with Parkinson's Advisory Council. He is a practicing clinical psychologist with 25 years of experience.

PDF wishes to thank Vernalis Pharmaceuticals as the primary underwriter of the roundtable and Teva Pharmaceutical Industries for its support.

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George M. Gutierrez

David Eger

Stem Cell Breakthroughs

Continued from page 5

trolled, the result can be the development of tumors (known as teratomas) in people being treated with stem cell therapies. Scientists have not yet figured out how to prevent this from happening, whatever the source of the stem cells.

In addition, skin-derived stem cells cannot be used as actual treatments as they currently exist because the process that transforms them into stem cells involves injecting them with viruses that could be harmful to patients.

Scientists Use Adult Skin Cells to Create Cloned Embryos

On January 17, researchers from Stemagen Corporation led by Andrew French, Ph.D., published a study in *Stem Cells* announcing that they had created five human embryo-like structures and brought them to the blastocyst stage by using somatic cell nuclear transfer (SCNT) — also known as therapeutic cloning.

These results represent the first time that a research team has brought a cloned embryo to the blastocyst stage. This is the point at which stem cells can be produced, although this study did not proceed far enough to do so.

Why is This a Breakthrough and What Does It Mean For Disease Treatments?

Because the study did not yet produce stem cells, its findings do not

mean that the development of treatments is right around the corner. However, the approach is certainly promising.

The team, using the SCNT technique, took adult skin cells from two of the researchers and eggs (oocytes) donated from women who were undergoing fertility treatments at a nearby clinic. Following SCNT protocol, researchers removed the nuclei from adult skins cells and placed them within the donated eggs, whose own nuclei (and therefore, DNA) had been removed.

Through the use of this technology, the scientists were able to manipulate the eggs into becoming embryos containing the genetic material of the adult skins cells. Out of 25 eggs, researchers produced three blastocysts that were proven to be clones, meaning the blastocysts genetically matched the parent cells taken from the researchers.

If stem cells *had been* developed using this process, then, like skin-derived stem cells, they would have had the potential to lead to cell replacement and tissue therapies. Moreover, because the cells produced in this way would be genetically-matched to the donor, they could potentially be used as personalized treatments for diseases like Parkinson's.

Researchers hope to one day use SCNT technology — taking body cells from an individual with a disease along with donated eggs — to create an embryo-

like structure that carries a person's own DNA. Unlike cells derived from other sources, the stem cells created from SCNT would be recognized as 'self' not as something for the immune system to attack.

What Scientific Barriers Still Exist in Developing Treatments?

Before proceeding to the development of treatments, researchers must first go one step further by yielding actual stem cells from the blastocyst stage and subsequently growing them into lines to be studied. Developing the stem cells into treatments for Parkinson's will require further investigation. In addition, the health of the embryos created in the study will need to be assessed and verified by outside groups.

Conclusions

Overall, while important scientific challenges continue to exist with respect to stem cells derived from skin cells and from therapeutic cloning, these newly-discovered technologies provide the opportunity for researchers and institutions to explore more deeply the potential of stem cells to cure human diseases.

Although this research is exciting, scientists emphasize that studies involving human embryonic stem cells should continue in tandem with new techniques. Together, further research on stem cells from all sources will speed our understanding of disease and of possible treatments.

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pdfchampions in action

PDF Offers Slots for Two of the World's Major Marathons!

Each year, hundreds of thousands of people in the US complete a marathon. The 26.2-mile race is becoming so popular that it is increasingly competitive to gain entry into the most sought-after events. This year, for those of you who are inspired to run a marathon and who also have an interest in furthering Parkinson's research, the Parkinson's Disease Foundation (PDF) Champions program has an exciting new offer.

PDF has noticed, over the years, that our own Champions — creative fundraisers who have chosen PDF as their charity of choice — are no exception to the marathon trend. Many have chosen to run races — from 5ks to 10ks to marathons — to raise funds for PDF's research, education and advocacy programs and to create awareness about Parkinson's disease (PD) in their communities.

PDF is proud to announce that the 2008 PDF Champions Marathon team has spaces available for eight runners: six for the Chicago marathon on October 12, and an additional two for the Berlin Marathon on September 28.

Runners who choose to take on this challenge, in addition to receiving a coveted marathon spot, will commit to raising a minimum of \$2,500 for PDF. Each will receive a PDF singlet to wear on race-day and a fundraising packet with helpful tips — plus a personal fundraising page and access to an online training marathon program, available through www.active.com.

If you are interested in running for PDF at the Chicago or Berlin Marathons or at a race of your choice, please contact Patrick Johnson at info@pdf.org or (800) 457-6676 or visit http://www.pdf.org/Fundraising/be_a_champion.cfm.



If you are thinking of beginning an exercise program, consult with your physician first to make sure that it is safe.

Why Run a Marathon? An Interview with Dan Kiefer

Dan Kiefer, a member of PDF's People with Parkinson's Advisory Council (PPAC) and a long-time member of Team Parkinson, a group that raises money for PD research, is familiar with the challenges and rewards a marathon brings. Below, he shares reflections on distance running with PDF's *News & Review*.

Q. Dan, thank you for chatting with News & Review! We would love to hear about your marathon experiences. Can you tell us a bit about the races you have completed?

A. I ran the Los Angeles Marathon in 2006. It was my first and, so far, only full marathon. I also ran half-marathons in 2004 and 2007, along with several 5k races. These races have been empowering experiences for me personally. I have used each race to raise money, through Team Parkinson, for PD-related research.

Q. What inspired you to start? Were you always a runner?

A. I've always loved exercise — I played golf and skied and I was a recreational runner — but before I was diagnosed with PD, I had never run more than eight miles. I first became involved in distance running through John Ball and Team Parkinson. John has run many marathons and lived with PD for over 25 years. I owe a lot to the encouragement I received from him and his wife, Edna.

Q. Marathons and half-marathons are challenging for people with and without PD. Can you explain the benefits of running in general and of longer races?

A. First, running has so many physical benefits. Since my PD can make it difficult for me to stay still, I find that when I am running, my symptoms actually improve. In my opinion, running is also the best antidepressant. Marathons and half-marathons give a great sense of accomplishment. It is a good feeling to not allow PD to limit what I can do. It was also wonderful to have so much sup-

port on the course — to run by cheering friends, family and team members.

Q. Can you tell us about the challenges you experienced during the marathon, and any that are specific to being a marathoner with PD?

A. Marathoners always talk about 'hitting the wall' and I certainly did, around mile 18. The last eight miles were particularly painful. In terms of PD, I have to be very careful in the timing of my medications, and invariably, at some point, I experience PD symptoms and have to medicate. I carry some of my meds with me on the course. In my everyday life, I basically can't move in the morning until my pills begin to work, and I experience "wearing off" intermittently.

Q. How do you feel about being a person with PD in a marathon, where most runners may not face the same obstacles that you do?

A. Proud! I think that when people with PD run a marathon, it raises awareness of PD and among many people, reminds them that not everyone with PD is limited to a wheelchair or to certain activities. I am open about what I have and proud of the things that I can do to defy it, or despite it.

Q. How has your life changed since you began running?

A. Running these races has taught me to be a lot less self-conscious about my PD and how it affects my gait. Before I started running, I didn't want anybody to notice my symptoms. I wouldn't tell anyone that I had PD and I tried to hide it. The marathon and half-marathon races and training runs helped change that. I also feel very good about the money I've raised to help fund Parkinson's research.



To learn more about exercise and PD, view a session that was presented by Dr. Michael Zigmond and Dr. Giselle Petzinger at PDF's 50th Anniversary Educational Symposium at www.pdf.org/50th/webcast.cfm.

AROUND & ABOUT THE COMMUNITY

PINS: Answering Your Questions about PD

Have you or has a loved one recently been diagnosed with Parkinson's disease (PD)? Are you adjusting to life several years into PD? Do you need help finding a physician? ... managing your medications? ... or finding a support group?

All of these questions, and more, can be answered through PDF's Parkinson's Information Service (PINS).

PDF is pleased to announce two exciting updates to this program.

Helpline Extends Its Hours

Due to popular demand, the PINS toll-free helpline, (800) 457-6676, has extended its hours and is now available from 9 AM – 6 PM ET.

This resource will place you in direct contact with PDF's information specialists who have a wealth of knowledge about Parkinson's-related treatments and symptoms. Additionally, our team keeps comprehensive listings of physicians and support groups around the country and can help refer you to local resources.

Ask the Expert Now Available in Spanish

PDF is also proud to announce that, *Ask the Expert*, the online feature of PINS, is now available in Spanish.

This feature allows people who have questions about Parkinson's to reach PDF's team of information specialists through the web. All questions are answered within 8 – 10 days.

Please call (800) 457-6676 or visit www.pdf.org/ask to learn more about PINS. PINS is managed exclusively by PDF and is supported by a generous grant from Boehringer Ingelheim.

Parkinson's Awareness Month

For more than a decade, April has been designated as Parkinson's Awareness Month. Parkinson's groups nationwide are taking this opportunity, the month in which James Parkinson was born in 1755, to raise greater awareness about Parkinson's and to recommit themselves to finding a cure.

PDF is recognizing the month by hosting a Second Annual Parkinson's Awareness Day at Stratford Square Mall in Bloomingdale, IL, on Saturday, April 12. We invite you to join us for a day that includes a mall walk, a demonstration of a seated exercise program designed specifically for people with Parkinson's disease, a stress management session and an in-person question and answer segment with the specialists behind the Parkinson's Information Service (PINS) toll-free helpline.

For those of you who are closer to New York, the Parkinson's Unity Walk in Central Park on Saturday, April 26, presents another way to join the PD community and support Parkinson's research. This year, PDF will be fielding a team consisting of members of our Board of Directors, our national staff, and our own People with Parkinson's Advisory Council (PPAC). If you are not connected with another team and would like to join us, let us know.

To learn more about these events or to find a support group in your area that may know of local activities, please call us at (800) 457-6676 or email us at info@pdf.org.

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Presente sus preguntas, y un especialista le responderá en un plazo de 8 – 10 días.



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PDF Launches Clinical Research Learning Institute in July 2008

This new PDF initiative provides people with Parkinson's with the tools they need to serve as informed leaders in the clinical research process.

For more information, contact PDF at (800) 457-6676 or info@pdf.org.

Calendar of Events



**Parkinson's
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Parkinson's Awareness Day

Date: Saturday,
April 12, 2008

Time: 9 AM to 3 PM

Place: Stratford Square Mall
Bloomington, IL

PDF's Second Annual PD Awareness Day includes a mall walk, a stress management session and a question and answer segment with PDF's information specialists.

For more information, please call
(800) 457-6676.

Parkinson's Disease Research in the 21st Century

Date: Saturday, May 3, 2008

Time: 10 AM to 1 PM

Place: Welte Auditorium
Central Connecticut State University
New Britain, CT

The Connecticut Parkinson's Working Group hosts a symposium featuring leading PD scientists including Ira Shoulson, M.D., Xiangzhong "Jerry" Yang, M.D., Ph.D., and Andrew Feigin, M.D.

There is no charge for this event.
Please register by calling (860) 343-8278,
(860) 347-0134, or (203) 453-2655.



PAC Annual Luncheon

Date: Tuesday,
April 22, 2008

Time: 12 PM to 1 PM

Place: Charlotte Country Club
Charlotte, NC

The Parkinson Association of the Carolinas presents its annual luncheon, which honors PDF and PAC Board member, Mrs. Sarah Belk Gambrell, with the Bill and Betty Ray Award for Parkinson's Disease.

Please contact Debbie Huffman at
dhuffman@parkinsonassociation.org
or (866) 903-7275.



14th Annual Parkinson's Unity Walk

Date: Saturday, April 26, 2008

Time: Program begins at 12 PM
Walk begins at 1 PM

Place: Central Park
New York, NY

Join the PD community for a two-mile walk to raise awareness and find a cure for Parkinson's. Because all expenses are covered by corporate sponsors, one hundred percent of donations will go directly to PD research.

For more information, call (866) PUW-WALK
(789-9255) or visit www.unitywalk.org.

Parkinson's Science: Innovations and New Perspectives



Date: Friday, May 9, 2008

Time: 9 AM to 3 PM

Place: Harris Conference Center
Charlotte, NC

PDF and the Parkinson Association of the Carolinas present a half-day symposium, asking *What is in the PD Pipeline?* with leading researchers present to answer your questions. The symposium will be available via webcast on PDF's and PAC's websites.

For more information, contact Eli Pollard at
info@pdf.org, call (800) 457-6676 or visit
www.pdf.org or www.parkinsonassociation.org.

Bal du Printemps

Date: Wednesday,
May 14, 2008

Time: 6:30 PM

Place: The Pierre Hotel
New York, NY

Led by PDF Chairman Page Morton Black, PDF's annual gala, *Bal du Printemps*, is an elegant evening to celebrate philanthropy and raise funds for Parkinson's disease research.

For more information, contact Carla Capone
at (212) 213-1166 or pdf@carlapapone.com.



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The Parkinson's Disease Foundation® (PDF®) is a leading national presence in Parkinson's disease research, education and public advocacy.

We are working for the nearly one million people in the US who live with Parkinson's by funding promising scientific research and supporting people with Parkinson's, their families and caregivers through educational programs and support services. Since its founding in 1957, PDF has funded over \$70 million worth of scientific research in Parkinson's disease, supporting the work of leading scientists throughout the world.