



Connecticut Parkinson's Working Group Newsletter

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February 2008

Support for this newsletter comes from
Ruth Manson and other donors to CPWG

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FROM YOUR EDITOR:

Read only the next question, then look away and form an answer before looking back.

QUESTION: *What is Parkinson's disease?* (You weren't even supposed to read this—no more peeking!)

Okay, one more: *What would you consider a PD cure?*

I am willing to bet a nickel that your answers contained some or all of the words: dopamine, substantia nigra (SN), tremor, rigidity, gait, balance, stiffness, Sinemet, brain. The reason is that we equate PD with movement disorders; we even call the people we go to see for help "movement disorder specialists". So, what am I getting at? It is the simply stated fact that:

PARKINSON'S DISEASE IS A WHOLE BODY (WB) CONDITION.

I'm being dramatic to the point of being silly. Silly is exactly how I felt when I realized that I knew that this was so, but was acting as if any "cure" that might come along in my time would involve that list of words I wrote above. What those words refer to is a collection of *symptoms* of PD, symptoms brought about by some as yet unknown process that attacks nerve cells in the substantia nigra (and elsewhere) and does them in. Any cure might, but probably will not, be specific to the SN. PD attacks other systems before it gets to the SN, probably, one of which is your sense of smell. It also gets to your GI tract, your blinking mechanism, and your autonomic nervous system, to name a few. Perhaps we concentrate on movement disorders because they are so bothersome, perhaps because that is where the drug company money goes, who knows?

Why is it important to be aware that PD is WB? Well, it affects what clinical trials you choose to participate in, what medications you will try, who you support with your donations, both time and money — every aspect of your relationship with PD. Another offshoot is that you do not rule out PD as the cause of some unknown aberration in your body, such as dry eyes (lack of blinking as a result of PD), cramping of your foot, or loss of nighttime contrast in your vision. PD causes all of the above, not all the time, not in any one person.

So get the word out — PD is a WBD. As to what it is in the specific sense, I ask you: What is PD? I think a personal answer is the best, so here is my attempt at a response:

PD is a disorder in which many functions that I used to do either easily or automatically, like walking (easily) or blinking (automatically), are now harder, cannot be done, or I have to do them consciously because my body won't do them automatically. Many, but not all of these functions have to do with movement. No one knows what causes PD, but we do know that it kills dopamine-producing neurons, and is progressive. A cure would involve stopping the destruction of the affected parts of the nervous system and restoring the lost function of certain body parts.

This being said, we must also acknowledge that some of the symptoms mentioned may be the result of other factors (such as age, pre-existing conditions, or even other diseases that afflict a PWP after the onset of PD). Since each of us experiences PD differently, we recommend, as always, consulting one's physician to determine the origin of any symptoms.

— Stan Wertheimer

The next article looks like a repeat of another we presented last issue but it is not. It represents a follow-on study (same number of people) that corroborates the previous trial. This is good news, and the reason it is included here. – Stan

PET SCANS SHOW GENE THERAPY NORMALIZES BRAIN FUNCTION IN PARKINSON'S PATIENTS

Nov. 20, 2007 — Brain scans used to track changes in a dozen patients who received an experimental gene therapy show that the treatment normalizes brain function - and the effects are still present a year later.

Andrew Feigin, MD (*an invited speaker at our May 3 symposium - Ed*), and David Eidelberg, MD, of The Feinstein Institute for Medical Research, collaborated with Michael Kaplitt, MD, of Weill Cornell Medical Center in Manhattan and others to deliver genes for glutamic acid decarboxylase (or GAD) into the subthalamic nucleus (STN) of the brain in PD patients. The study was designed as a phase I safety study, and the genes were delivered to only one side of the brain to reduce risk and to better assess the treatment.

A recently published study included the clinical results of the novel gene therapy trial, but this new report from the same study focuses on the power of modern brain scans to show that the gene therapy altered brain activity in a favorable way.

The patients received only the viral vector-carrying genes to the side of the brain that controls movement on the side of their body most affected by PD. It was a so-called open-label study—everybody received the gene therapy so the scientists knew that there could be a placebo effect. That is why brain scans were so critical to the experiment. Dr. Eidelberg and his colleagues pioneered the technology and used it to identify brain networks in PD and a number of other neurological disorders.

In PD, they identified two discrete brain networks—one that regulates movement and another that affects

cognition. The results from the brain scan study on the gene therapy patients show that only the motor networks were altered by the therapy. "This is good news," said Dr. Eidelberg, "You want to be sure that the treatment doesn't make things worse." The gene makes an inhibitory chemical called GABA (neurotransmitter Gamma-aminobutyric acid) that turns down the activity in a key node of the PD motor network. The investigators were not expecting to see changes in cognition, and the scans confirmed that this did not occur.

Positron emission tomography (PET) scans were performed before the surgery, repeated six months later, and again at a year. The motor network on the untreated side of the body got worse, and the treated side got better. The level of improvements in the motor network correlated with increased clinical ratings of patient disability, added Dr. Feigin.

"Having this information from a PET scan allows us to know that what we are seeing is real," Dr. Eidelberg added. The scans also detected differences in responses between dose groups, with the highest gene therapy dose demonstrating a longer-lasting effect. "This study demonstrates that PET scanning can be a valuable marker in testing novel therapies for PD," he said.

Neurologix Inc., a New Jersey-based company, developed the gene therapy technique. Scientists are now working on a design for a phase 2-blinded study that would include a larger number of patients to test the effectiveness of the treatment.

This next article points out that PD may be affected by factors not obviously to do with dopamine production.

OVER-THE-COUNTER PAIN MEDICATIONS MAY REDUCE RISK OF PARKINSON'S DISEASE

October 31, 2007 – Over-the-counter pain medications known as non-steroidal anti-inflammatory drugs (NSAIDs) may reduce a person's risk of PD, according to a study published in the November 6, 2007, issue of *Neurology*®, the medical journal of the American Academy of Neurology.

"Given our results and the growing burden of PD as people age, there's a pressing need for further studies explaining why these drugs may play a protective role," said study author Angelika D. Wahner, PhD, with the UCLA School of Public Health in Los Angeles.

The study involved 579 men and women, half of whom had PD [*It must have been painful for the one they cut in half! - Ed*]. The participants were asked if they had taken aspirin and if they had taken non-aspirin NSAIDs, such as ibuprofen, once a week or more at any point in their life for at least a month. Participants were considered regular users of aspirin or non-aspirin NSAIDs if they took two or more pills a week for at least one month. Non-regular users were those who took fewer pills.

The study found regular users of non-aspirin NSAIDs reduced their risk of PD by as much as 60 percent compared to non-regular users and non-users. Women who were regular users of aspirin reduced their risk of PD by 40 percent, especially among those who regularly used aspirin for more than two years.

“Our findings suggest NSAIDs are protective against PD, with a particularly strong protective effect among regular users of non-aspirin NSAIDs, especially those who reported two or more years of use,” said Wahner. “Interestingly, aspirin only benefited women. It may be that men are taking lower doses of aspirin for heart problems, while women may be using higher doses for arthritis or headaches.”

“It’s possible the anti-inflammatory agent in NSAIDs may contribute to the observed protective effect of the drugs, but the exact mechanism isn’t clear and further research is needed,” said the study’s principal investigator Beate Ritz, MD, PhD, with UCLA School of Public Health.

The study was supported by grants from the National Institutes of Health, the National Institute of Environmental Health Sciences and the American Parkinson Disease Association.

INTEL CO-FOUNDER’S BIG MOVE TO FIGHT PARKINSON’S

By Sally Beatty

January 11, 2008

Who gave it: Andy Grove, co-founder and former chief executive of giant Intel Corp.

How much: as much as \$40 million

Who got it: The Michael J. Fox Foundation for Parkinson’s Research, New York

Purpose: an unrestricted gift to fund basic research and to jump-start a “Grove Circle,” a community of givers set up to encourage donations through wills and other planned gifts.

How it happened: In 2000, Mr. Grove was diagnosed with Parkinson’s disease, a neurological disorder that can produce symptoms ranging from tremors to dementia. Five years earlier, he battled prostate cancer. After he spoke publicly about it, patients seeking advice inundated him with questions, and he wasn’t eager to repeat that experience. “I was tired of being an icon for a disease,” he says. Word of his condition circulated anyway, and within a year, officials

approached him from the Michael J. Fox Foundation. He first met the actor, a longtime Parkinson’s patient, in 2001 after asking him to speak at a stem-cell conference in San Francisco.

Currently, Mr. Grove’s Parkinson’s symptoms are under control with medication. At 71 years of age, he has begun to think about how to provide continuity for various Parkinson’s research projects he supports, and Mr. Fox’s foundation seemed a ready-made vehicle to oversee such work after he is gone.

He says funding and learning about Parkinson’s research has unexpectedly given him a second life, metaphorically speaking. “I should be embarrassed, but I’m not; I am having a good time doing this,” he says. “I’m playing scientist again.”

Too often, he says, wealthy people confronting serious illnesses respond by starting up new “disease foundations” from scratch, when collaborations may be more effective.

“These things are bigger than all of us.”

PWP AS RISK-TAKERS!

They say that people with Parkinson’s are not risk-takers, but one Friday morning not so long ago, Jeff Lincoln and I defied that description. We went to a store in Guilford that sells and rents Segways, just to see if they are something that might be of use to PWPs. While we were there, Rich Petrillo, the owner of the store, let us try one. (Rich is definitely a risk-taker!) Jeff and I are pleased to say that we were able to maneuver the Segway around the store without knocking anything over and without falling off. It is fascinating to use, but we can’t recommend it as a helpful addition to our assistive devices list. If you would like us to explain this in more detail, please feel free to call either of us.

— Jackie Dorwin

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INTERVIEW WITH DR DAVID RUSSELL (IND & YALE) by Jeff Lincoln

JL: In what order did you get your advanced degrees — the Ph.D. and the M.D.?

DR: Concurrently. I was in a program called “M.D.–Ph.D. program”. I went up on the stage and got one hood and diploma and then got right back up and got the other hood and diploma. This was at the Cornell Medical School and Sloan Kettering in 1991. I started research in high school, working in a lab during summers for a researcher who thought that platelets were involved in cancer. In college, I continued to work for that lab and became interested in how growth factors worked, which led to an interest in clinical medicine. I graduated in biology, then took a year off to be a high school teacher in Cincinnati, Ohio, concerned with various science classes and environmental issues. After a year, I went into the M.D./PhD. program

JL: So you weren't born a Neurologist?

DR: No. While in Med School, I became interested in Neurology and did work in Neurology clinics. I visited Mt. Sinai where they had a good group of clinicians. I did my Neurology residency at Yale and also got back into the lab. During that time, I started working with Ken Marek and the Movement Disorders Clinic studying the Dopamine system. My question was: What goes wrong at a molecular level that gives rise to PD? I soon started my own lab. For a few years, Ken and I were the only people *[studying basic movement disorders at Yale - JL]*; then we brought in Danna Jennings. Eventually, when Ken and John Seibyl left to found the Institute for Degenerative Disorders (IND), I stayed on at Yale for several more years. Recently I have become interested in clinical research. Last summer I joined IND but I also maintain a lab at Yale, where I'm on the faculty of the Med School and still teach.

JL: Why did you choose Neurology?

DR: Because the big questions are fundamentally more interesting. It's the brain, it's who you are, it's what makes us tick. I like thinking about what motivates us, what makes us do what we do and what is the underlying process. How is the way we create movements similar to how we create emotions? What are the thought processes? How do we put things together mentally? What is consciousness? These and many other issues drew me to neurology. Movement disorders allow you to look at those kinds of issues

but they are also clinical. My own interest has been the focused on the dopamine system and what happens to it over time. Probably, normal adaptive processes go awry, and become dysfunctional and pathological. I was also interested in dyskinesias, off times and fluctuations. Those still are my main interest. [At IND] we've gotten interested in cognitive issues and what we call non-motor symptoms, such as anxiety, autonomic problems and dementia.

JL: We're fortunate that PD has a pretty good animal model.

DR: It's a pretty good model. It's different *[from PD -Ed]*. The animal model is: you give a drug [MTPT] which wipes out the dopamine neurons. In PD, the cell death accumulates slowly, and the patient usually has treatment going on. None of this tells us why cells die. Thus, we have a good model of making animals Parkinsonian, but we don't have a great model of PD overall.

JL: Any advice for people who are newly diagnosed?

DR: Advice is subjective, but there are some generalities that hold. Don't be shocked. Don't overreact. People don't die of PD. PD is often mentioned as an annoying disease, but not as a disabling disease. They can often do most of the things that could be done before PD. They can still enjoy their lives. They can enjoy their families. It's not like Alzheimer's disease or Cancer. It's not like rheumatoid arthritis or even congestive heart disease. After introspection, some PWP's feel that they have a better quality-of-life.

Don't do anything rash. You have time. I give this advice to patients, caregivers, families and doctors (especially doctors). You don't have to take medicines right away. PD is slow and it probably doesn't make any difference if you do an intervention now or six months from now. Think about it, read about it, but don't do anything that has long-term consequences. This is not a disease that strikes out of the blue. So have patience and try to keep things in perspective. These two things are often lost caring for a person with PD. By the way, I see the CPWG as a good support group because newly diagnosed people see people staying active, and working productively for a cause.

JL: Can we quote you on that?

DR: Sure.

JL: Speaking of diagnosis, how do you diagnose a person with PD?

DR: Same question I ask medical students and residents. I ask, "If somebody comes to you and you don't know if she/he has PD, what would you do? How do you make the diagnosis?" They suggest a trial of Levodopa. No, don't do that. Bad idea. Then they suggest, "Send them to IND for a Beta CiT scan. It's often not easy to arrange this, especially if you are in Kansas. They go around and around. I step in and suggest, "Why not tell them what you are asking yourself, that it might be and it might not be PD". Arrange to see them in 3 to 6 months. It never occurs to the students to do this, but the patient appreciates your honesty. They also appreciate that you're not panicking. In the early stages of PD, many people don't need much support or support groups. *[Our experience has been the opposite - often this is when a person most needs THE RIGHT KIND OF SUPPORT. — Jeff]*

JL: What are the types of research you are interested in?

DR: Well, I was surprised at how quickly I was pressed into service on many fronts. It's a remarkable place [IND]. My overarching interest is based on the view: PD gets to be a real problem when motor fluctuations kick in. Until people start fluctuating, most PWP's can be treated well. If we didn't have to worry about developing dyskinesias or on/off times, we would give a lot of levodopa right up front. *[Since that isn't practical -JL]*, my interests have always been: What can we do to delay motor fluctuations and to minimize the effect on a patient once they have them? One way to delay motor fluctuations is neuro-protection, preventing the disease from progressing at all, and that fits well into my research on neu-

rotrophic factors and using them to reverse processes in the brain. The complete process would be to predict early who is going to develop PD and get them into treatment early. Later, develop techniques to prevent motor fluctuations. The big idea is, if we could prevent motor fluctuations and non-motor symptoms in PD, we would be much more successful at preserving function, quality of life, ability to maintain a career and patient productivity. These factors are often neglected, but that is changing.

JL: It's a big deal!

DR: There's going to be a wave of new research coming from places such as the human genome project. These will open new doors both in understanding the pathways that lead to cell death and also what proteins and processes to target. We just know so much more about what is occurring in a dopamine neuron than we did three years ago.

JL: I like the way you described this effort in the IND Newsletter, "Studying the incredibly complex processes may lead someday to a breakthrough" Any final words?

DR: Stay involved in research at IND. We're moving fast. It is a hopeful time for PD as we look back on 10 years of research and see how far we've come. The research feels right now. Ten years ago the direction of research didn't make much sense. As a scientist who understood the biology, it seemed haphazard and simplistic. Now there's been a confluence of basic science and clinical trials in a way that is cogent and focused. Looking forward I see a much more productive process. The horizon is definitely getting closer.

{Note that our own Dr Danna Jennings is a co-author of this Study-2 publication.}

COFFEE DRINKING AND THE RISK OF DEVELOPING PARKINSON DISEASE

Published by WE MOVE Judith Blazer, Executive Director

Recent studies looked at the relationship between coffee drinking and the risk of develop PD or having the ability to detect smells. There were two studies done:

STUDY 1

BACKGROUND Who took part in the study and what did they do? Since 1982, almost 30,000 people in Finland have been completing health surveys on a regular basis. They fill out a questionnaire that is mailed to them in their homes, including answering questions about the amount of coffee or tea that they drink each day.

WHO WERE THE RESEARCHERS AND WHAT DID THEY DO? Finland has a national health system, and everyone has his or her own ID number. This number was used to identify the 30,000 people who completed the surveys. People who have been diagnosed with PD get their medications free of charge, and this information is

then included in a national registry. Dr. Hu and the other researchers in this study linked the answers to the questions about coffee and tea drinking to the people with and without PD in the national registry to see if there was a connection.

WHAT WERE THE RESULTS OF THE STUDY? Both men and women who drank at least one cup of coffee every day had a lower risk of developing PD, as compared with people who did not drink coffee. Those who drank five or more cups a day had the lowest risk. Women who drank three or more cups of tea a day also had a lower risk, but those who drank only one or two cups did not have a lower risk than those who did not drink tea. There was no connection between drinking tea and PD in men.

WHAT WERE THE AUTHORS' CONCLUSIONS? "The biological mechanism behind the association of coffee consumption and PD risk is thus far not clear; however, the caffeine content of coffee is the most possible suggestion from previous investigations. The protective effect of caffeine should be investigated within total caffeine intake in future studies."

STUDY 2

In another study, which took place in the US, researchers found that relatives of people with PD who drank little or no coffee were more likely to have a decreased sense of smell and ability to identify odors (hyposmia [hī pōz' mē ä]).

BACKGROUND Hyposmia can have any number of causes, but it is often one of the first signs of PD, appearing even before the more typical movement features appear. Finding people who are at the earliest stages of developing PD may be important, particularly if methods to slow the rate of the disease become available in the future. First-degree relatives of people with PD have a higher risk of developing PD than do those people in the general population. Testing the sense of smell is very easy to do.

WHO WERE THE PEOPLE WHO TOOK PART IN THE STUDY AND WHAT DID THEY DO? At two movement disorder centers, people with PD gave the researchers a list of their first-degree relatives for contact purposes. The 173 relatives who agreed to take part in the study were older than 50 years of age, did not have PD or another nervous system disorder that gets worse over time, and did not have other conditions that could affect their sense of smell. The relatives received a packet in the mail that included a questionnaire, a consent form to sign to take part in the study, and the University of Pennsylvania Smell Identification Test (UPSIT). They filled out the forms and completed the UPSIT, sending their results back to the researchers. Who were the researchers and what did they do?

The researchers at the University of Pennsylvania and the Institute for Neurodegenerative Disorders in New Haven, Connecticut, analyzed the results of the UPSIT and the questionnaire. They examined whether there was a relationship between number of cups of coffee that a person drank each day and the person's ability to detect the 40 different odors in the UPSIT.

WHAT WERE THE RESULTS OF THE STUDY? The more coffee that a person drank, the more likely they were to be able to identify more smells on the UPSIT, particularly among men and people who were older. Twenty-eight percent of people who did not have a lifetime history of drinking coffee had hyposmia, as compared with only 8% of those who reported that they drank one or more cups of coffee daily.

WHAT WERE THE AUTHORS' CONCLUSIONS? "In conclusion, abnormal olfaction is associated with significantly lower lifetime caffeine consumption in first-degree relatives of PD patients. Further research is warranted to determine whether a history of lower caffeine consumption confers additional risk for the development of PD in hyposmic relatives of PD patients."

STUDY 1: Hu G, Bidel S, Jousilahti P, Antikainen R, Tuomilehto J. Coffee and tea consumption and the risk of Parkinson's disease. *Mov Disord* 2007;22:2242-2248.

STUDY 2: Siderowf A, Jennings D, Connolly J, et al. Risk factors for Parkinson's disease and impaired olfaction in relatives of patients with Parkinson's disease. *Mov Disord* 2007;22:2249-2255.

{Aside from the interesting results, which should not be diminished by what follows, note the bolded sentence. The first words "PD is ..." should be replaced with "Some of the symptoms of PD are ...". As written, it perpetrates the erroneous definition of PD as just a loss of dopamine producing neurons. — Stan}

OMEGA-3 BARRIER FOR PARKINSON'S

Rebecca Knight Financial Times. London (UK)

Nov 30, 2007.

Omega-3 fatty acids protect the brain against PD, says a study by researchers at Universite Laval in Quebec. Published in the journal of the Federation of American Societies for Experimental Biology, the study is the first to demonstrate that a diet rich in omega-3 fatty acids could help prevent the PD and, potentially, slow its progression.

PD is caused by the progressive death of the neurons responsible for producing dopamine, a neurotransmitter closely connected with movement control.

PD is typically diagnosed when 50-80 per cent of these neurons are already dead and there is no medication to halt the process. The study's researchers found that when mice were fed an omega-3 rich diet they seemed immune to the effect of MPTP, a toxic compound that causes the same damage to the brain as PD. By contrast, another group of mice that were on an ordinary diet developed the characteristic symptoms of the disease when injected with MPTP.

In the following article one group was treated with levodopa plus Sinemet. This is confusing, since Sinemet is levodopa plus carbidopa. However, the source seems eminently respectable. We hope it is also reliable. The part we have extracted says, in effect: Elevated homocysteine levels are an indicator of potential cardiovascular problems. PWP often have elevated homocysteine levels due to taking Sinemet. Folic acid (with B6 and B12) can reduce these levels, indicating alleviation of some of the cardiovascular factors leading to those higher levels. Stan

THE IMPORTANT ROLE OF FOLIC ACID IN HUMAN HEALTH

M. Saljoughian, Pharm.D., Ph.D., Department of Pharmacy Services, Alta Bates Medical Center, Berkeley, CA

New research and clinical studies have shown that the role of folic acid in human health is far more important than its use as a vitamin and dietary supplement; in fact, folic acid is an important compound that is highly effective in preventing birth-defects, cardiovascular and cerebrovascular diseases, and certain types of cancer. In recognition of its importance, the federal government has mandated the fortification of cereal grains with 0.14 mg (140 micrograms) of folic acid per 100 grams of grain. The goal of this decision is to reduce the risk of heart diseases and the risk of women giving birth to babies with neural tube defects (spina bifida) and orofacial clefts. Women of child-bearing age are encouraged to consume 400 mcg of folic acid a day. The protective effects of folic acid are even more pronounced when it is combined with a high dietary intake of vitamin B6 and vitamin B12. It is now proven that vitamins B6 and B12 markedly increase the homocysteine-lowering effect of folic acid in cardiovascular diseases.¹

Parkinson's Disease: People suffering from Parkinson's disease (PD) have an increased risk of heart attack and stroke. Some German and Swiss medical scientists believe they have found a solution to these patients' problem. They studied a group of 48 to 73 year-old patients with PD. One group was treated with levodopa plus Sinemet, one group was not treated with any drug, and the last group were healthy subjects. All participants had their homocysteine blood levels measured after a 12-hour fast. The drug-treated group had an average of 17 micromol/L homocysteine and the other two groups had a blood level of close to 9 micromol/L. The researchers found that prolonged treatment with levodopa and Sinemet increased the blood levels of homocysteine. The conclusion of their study is that patients with PD who are treated with levodopa should have their homocysteine levels monitored on a regular basis and should supplement their diet with folic acid as required. Folic acid is nontoxic and no cases of overdosing have ever been reported.²

¹ Wald DS et al., Arch Intern Med, 2001;161:695-700.

² Muller T, et al., The Lancet, 1999; 354, 126-127.

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DISCLAIMER:

*Articles in this newsletter are for information only.
Any questions of treatment should be discussed with your physician.*

Write your Representatives in Congress!

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