

Connecticut Parkinson's Working Group Newsletter

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Alcohol Doesn't Protect From PD. Findings Dispute 'PD Personality'

By Salynn Boyles

WebMD Medical News Reviewed By Brunilda Nazario, MD

May 15, 2003 -- New research argues against a direct relationship between PD and an aversion to addictive behaviors. The findings challenge the idea of a so-called 'PD personality' in people predisposed to develop the disease.

Investigators at the Harvard School of Public Health hypothesized that people who develop PD are less likely to drink heavily earlier in life than people who never get the disease, but they found little evidence that this was true in their study involving roughly 140,000 people. "If the PD personality hypothesis is correct, you would expect to find that heavy drinking was protective against PD," lead researcher Miguel A. Hernan, MD, tells WebMD. "But with these and other findings (the hypothesis) starts to look a bit shaky."

The suggestion that engaging in addictive behaviors is somehow protective against PD stems from more than 40 studies finding that the disease is far less common among people who smoke cigarettes or drink large amounts of coffee. Animal studies suggest that caffeine and certain components of cigarette smoke are protective against PD. But an alternative explanation is that people predisposed to develop PD have a natural aversion to addictive behaviors, due to either genetic or metabolic influences.

PD is associated with a degeneration of nerve cells in the brain that produce the chemical dopamine, and dopamine is involved in addictive behavior. With this in mind, Hernan and Harvard colleagues examined alcohol consumption and PD risk among people participating in two large ongoing prospective trials -- the Nurses' Health Study and the Health Professional's Follow-up Study. Their findings are reported the latest online edition of the *Annals of Neurology*.

Some 88,000 women and 47,000 men reported their alcohol intake, along with other dietary information, every two years as part of their participation in the study. The researchers found no difference in PD rates between people who drank little or no alcohol and those who drank moderately or every day.

People who drank moderate amounts of beer did have a 30% reduction in PD rates, but this was not seen for other types of alcohol, and Hernan says it is unclear if this association is real. He says that because the association was only seen for beer, it is likely that some component other than ethanol is protective against PD. "Alcohol does not seem to play an important role in PD risk," he says.

But PD researcher William K. Scott, PhD, of Duke University, says it would be hard to draw firm conclusions about the role of alcohol in PD from this study because people often do not tell the truth when asked about their alcohol consumption. "The findings do seem to be consistent with what other people are finding with respect to alcohol and PD," says Scott, who is with Duke's Udall PD Research Center of Excellence. "The findings may not support a PD personality, but it certainly doesn't rule it out."

RESEARCH WALK FOR IN

Was it Working Walkers or Walking Workers? It really doesn't matter what we call ourselves because at the Research Walk for the Institute for Neurodegenerative Disorders (IND) we're working while we walk. We're there to help raise money for PD research, plain and simple.

This year there are two chances to help out; walks are scheduled in two locations on Sunday, October 12, rain or shine. The site of last's year's festivities, the Penfield Pavilion on Fairfield Beach Road in Fairfield is one; registration begins at 9 a.m., the walk starts at 10 a.m. The new location is Ocean Beach Park on Ocean Avenue in New London with registration at 12 noon for the 1 p.m. walk.

The Working Walkers will be out there, with our highly visible orange hats, having fun walking or cheering on all the walkers. Come join us! Last year we helped to raise \$40,000 for Parkinson's research! If you want more information, directions, or to register on-line, visit IND's website at www.indd.org, and click on the 'What's New' icon. Be part of our team, or have your own team! If you can't make it to Fairfield or New London on October 12, please consider making a contribution directly to IND, noting that it is for the 2003 Research Walk. These can be mailed directly to the Institute for Neurodegenerative Disorders, 60 Temple Street, Suite 8B, New Haven, CT 06510. Tel: 203-401-4300.

Jackie Dorwin

Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Botulinum Toxin Type A in the treatment of Drooling in PD

F Mancini MD (lead author) Movement Disorders 2003 volume 18 page 685 **Abstract:** Drooling is a frequent symptom in Parkinson's disease (PD), occurring in almost 75% of all patients. Although it is now well known that drooling in PD is the result of swallowing difficulties rather than excessive saliva production, few treatments have been developed to reduce it. Clinical studies suggest that botulinum toxin A (BTX) injections into salivary glands are effective in decreasing drooling in PD patients.

Drooling or sialorrhea, can result in social disability, impaired speech, or serious feeding difficulties. Previous clinical studies, using different dosages and injection techniques, have shown the BTX reduces drooling when injected into the salivary glands. With our personal experience of various doses, injection sites, and methods, we carried out a double blind, placebo-controlled study (DBPCS) to verify literature data and to test an improved technique.

In this DBPCS, 20 patients with parkinsonism (idiopathic PD or multiple system atrophy), were randomly assigned to receive 450 U of BTX or 2 ml of placebo injected into the parotids and submandibular glands under ultrasonographic guidance. Treatment efficacy and safety were assessed at baseline, 1 week and 3 months after BTX injections using clinical scales (Drooling Severity and Drooling Frequency scales).

After treatment, the average secretion of saliva in the BTX group was significantly lower than in the placebo group, as appraised by clinical measurements. No side effects were observed in either group. BTX injection into parotids and submandibular glands is an effective and safe treatment for drooling in Parkinsonism.

The effect of BTX on drooling, at the dose used in this study, lasted approximately 1 month, which is less than the usual duration of this effect on muscle dystonia or sweating. In conclusion, because 450 U of BTX has been shown to be a safe dose to treat drooling in PD patients and that higher drooling severity is correlated with shorter duration of BTX effect, further studies with higher doses are warranted.

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FDA Approves Stalevo™ for Treatment of PD New Drug Reduces Signs and Symptoms of Disease

East Hanover, NJ - June 13, 2003 - Novartis Pharmaceuticals Corporation today announced that the FDA has approved Stalevo (carbidopa, levodopa and entacapone) tablets, the first new drug for PD in over three years, for patients with idiopathic PD who experience signs and symptoms of end-of-dose "wearing-off." While

carbidopa reduces the side effects of levodopa, entacapone extends its benefits, permitting PD patients to have an improved ability to perform everyday tasks and a reduction in symptoms associated with the disease.

Within one to two years, almost 50 percent of PD patients receiving levodopa therapy begin to notice that their levodopa lasts for shorter periods of time, known as "wearing off." In about 15 to 20 percent of patients, "wearing off" becomes extreme and disabling. Eventually, the effect of a levodopa dose may decrease from eight hours when patients begin levodopa therapy to only one to two hours.

"Levodopa is recognized as the cornerstone of PD therapy, but its long-term use is limited by its reduced ability to fully control PD symptoms," said Warren Olanow, MD, professor and chairman, Department of Neurology, Mount Sinai School of Medicine in New York City. "By blocking the enzymatic breakdown of levodopa, Stalevo provides more levodopa to the brain for a longer period of time. Potential patient benefits include more "on" time during which PD symptoms are well-controlled and daily activities are improved, and simpler, more convenient dosing."

The effectiveness of levodopa administered with carbidopa and entacapone in the treatment of PD was established in three 24-week multicenter, randomized double blind placebo-controlled trials in patients with PD experiencing "wearing off". In these trials, this combination increased "on" time, reduced "off" time and improved motor function and daily activities such as patients' ability to walk and dress. The most common side effects of Stalevo therapy are dopaminergic in nature (e.g. dyskinesia, nausea). These side effects may be manageable with alteration in the drug-dosing schedule. Other common side effects include diarrhea, hyperkinesias, urine discoloration, hypokinesia, abdominal pain, dizziness, constipation, fatigue, pain and hallucinations.

The following is more technical than we usually get; however it is of sufficient interest to warrant its inclusion. The main point about iron being instrumental in causing PD is that a small amount of it can, through the redox reaction mentioned, produce a disproportionate negative effect on dopamine neurons - maybe. stan

HEAVY METALS AND PARKINSON'S DISEASE

Dr Mike Harris

The idea that heavy metals, e.g. iron(Fe), copper, zinc and manganese, may have a central role in degeneration of different parts of nervous tissue has gained momentum in the past year or two. On first consideration, this may appear to be surprising given the essential role of all of these metals in the functioning of the body. They are the centerpieces of the activity of many enzymes and other functional proteins. In the context of the biochemistry of the dopamine neurons, iron is required for myriad purposes, particularly affecting the mitochondria. Copper and zinc are required in one version of superoxide dismutase (SOD) and manganese in another. SOD is a vital enzyme required for protecting neurons from attack by oxygen-free radicals. It has been proposed that deficiencies in the activity of SOD in dopamine neurons are contributory to the development of PD.

The paradox of metals being indispensable, yet potentially damaging, is given in the example of manganese. Although manganese is required for the health of the dopamine neurons through the free radical quenching activity of SOD, exposure to an excess of manganese produces a Parkinsonian condition in affected people. How is it that heavy metals may be a friend one-minute and a foe the next? The answer may be simple;

The very property that makes these metals invaluable when harnessed by an enzyme/protein is exactly the property that makes them injurious when not controlled by that enzyme/protein.

A property of some heavy metals, under utilization by enzymes/proteins, is that they can exist in different oxidation states. In the example of iron, the metal can occur in solution as either the ferrous, Fe²⁺, or ferric, Fe³⁺, form. Interconversion between these two forms is achieved by oxidation (Fe²⁺ → Fe³⁺) and reduction (Fe³⁺ → Fe²⁺). It follows that iron is often incorporated in enzymes involved in

oxidation/reduction activity, where the latent potential of the iron to undergo oxidation or reduction has essentially been harnessed by the enzyme.

Facile oxidation/reduction is the very property that often makes free metals toxic. Using the example of iron, the oxidation of Fe²⁺ to Fe³⁺ by the oxygen in air results in the formation of the toxic superoxide, hydroxyl free radicals and the substance hydrogen peroxide. Tissues are able to deal with traces of these substances but at some stage their systems become swamped. The regeneration of Fe²⁺ by reducing agents present in the tissues, such as ascorbic acid (vitamin C) or dopamine in the dopamine producing neurons exacerbates swamping. The regenerated Fe²⁺ is available for oxidation to Fe³⁺ by oxygen again. In this process, known as redox-cycling, small amounts of free iron are able to have a disproportionately large and destructive effect. Free iron, which is able to participate in such reactions, is said to be redox-active.

Iron is the heavy metal considered most likely to be involved in the development of PD. The concentrations of this metal have been known to rise in the disease. There has been a reluctance, however, to attribute blame to this metal, because of uncertainties about its availability in a redox-active state. Normally iron is kept tightly bound to carrier proteins in the body, e.g. ferritin, reducing exposure of tissue to the toxic free metal. From recent research it is now known that failure of iron binding by ferritin in a rare genetic condition can lead to a late-onset disease of the basal ganglia and the presentation of features of Parkinsonism. Further to this, there is evidence that relatives of dopamine can react with ferritin, dispossessing it of its iron, leading to toxic levels of redox-active iron.

Recent research has shown that a-synuclein, found in PD Lewy bodies, can generate hydrogen peroxide and this is able then to react with iron to produce the hydroxyl free radical. It is considered that this may be the start of a destructive chain of events resulting in free radical damage to dopamine neurons and development of PD.

If this is so, it opens up the possibility that protection of dopamine neurons may also be afforded by iron binding agents.

(And this might lead to neuroprotective drugs. Stan)

And just case there was any doubt ---

RISKS FROM EATING TOO MUCH IRON

People with high levels of iron in their diet may be more likely to develop Parkinson's disease, according to a study reported in a June 2003 issue of Neurology, the scientific journal of the American Academy of Neurology.

The study compared the diets of 250 people newly diagnosed with PD to those of 388 people without the disease. Those who had the highest level of iron in their diets – in the top 25 percent – were 1.7 times as likely to be diagnosed with Parkinson's as those in the lowest 25 percent of iron intake.

Those with higher-than-average consumption levels of both iron and manganese were 1.9 times more likely to contract Parkinson's than those with lower-than-average intake of these minerals. Iron and manganese contribute to oxidative stress, a situation in which cells release toxic substances called free radicals as part of normal energy consumption and metabolism, according to Harvey Checkoway, PhD, of the University of Washington in Seattle, author of the study.

Chronic Stress May Accelerate Aging

Long-term stress may cause health problems by prematurely aging the immune response, according to research in Proceedings of the National Academy of Sciences. Stressful experiences can stimulate the body's production of proinflammatory cytokines, substances involved in regulating the immune system. One cytokine, called interleukin-6 (IL-6), increases with age and is a risk factor in cardiovascular disease, type II diabetes, osteoporosis, and other age-related conditions.

To investigate the health risks of long-term stress, Ronald Glaser of Ohio State University and colleagues measured IL-6 levels in older men and women who were taking care of a spouse with dementia. Over the course of the 6-year study, levels of IL-6 increased four times faster in caregivers compared to people not providing care. In addition, former caregivers continued to have elevated IL-6 rates for up to 3 years after the death of the impaired spouse, indicating that the adverse health effects continued past the cessation of the stressful situation. These results suggest that caregiving and other chronic stressors may accelerate normal age-related increases in the risk of disease.

"Chronic stress and age-related increases in the proinflammatory cytokine IL-6" by Janice K. Kiecolt-Glaser, Kristopher J. Preacher, Robert C. MacCallum, Cathie Atkinson, William B. Malarkey, and Ronald Glaser

SHALLOW WATER EXERCISE PROGRAM FOR PWP

A new eight-week shallow water exercise program for PWP will begin on Tuesday, Sept. 9, at 1: 30 PM at the New Haven Hotel on George St. The cost for the eight sessions is \$40. If deemed necessary by the Instructor, a caregiver may participate at no cost. Valet parking is available at the hotel for a reduced rate of \$2 per class.

The sessions will focus on improving balance, gait, posture, muscular balance and flexibility. The pool temperature is 90 degrees allowing comfortable movement, strengthening and stretching. A doctor's permission for exercise, water shoes, a bathing suit and towel are all you will need. Class size is limited, so prior registration is required.

Joanne Turecek, B.A., will be the Instructor for the group. She is an AEA certified Aquatic Fitness Instructor and has received certifications from ATRI in Rheumatology, Ai Chi and Intro to Aquatic Therapy and Rehab.

For more information and to register, contact Joanne Turecek late afternoons or evenings at (203) 481-2238.

A Parkinson's View of a Biography (fictitious)

Stan Wertheimer

Where a life is described when later on the person is diagnosed with PD.

I was born in June of 1936 in New York City where my parents had a walk-up on the third floor of a six-story building. The weather was typical - hot and sticky and there were flies and mosquitoes for everyone. My parents sprayed liberally with the standard bug spray, Flit, which was DDT based (insult #1).

I was breast fed for six months and grew well. My crib was near a window that had a thick coat of paint on the sill. When my teeth were coming in I eased the pain by chewing on that painted windowsill (insult #2). At about this time my father got a better job and we moved to the "suburbs" in Brooklyn. We still rented, but now it was a house. My folks were excited about the new place and started fixing it up by painting with oil-based paint; the brushes were cleaned with turpentine (insult #3) which I often managed to splash my hands in. We were far out enough so that our water still came from a well (insult #4).

When I got a little older we would take weekend trips to a nearby farm. The farmer thought I was cute and let me help to spread the pesticides and fertilizer that he used on his fields (insult #5). We would buy produce from him in the summer. This produce was bug free because he had sprayed it with bug killer during its growing time (insult #6).

My father had a passion for welding sculpture and whenever he had the time he would work in the garage. As I grew I would often help him; he taught me to weld, which I thought was great (insult #7). We also did some brass sculpture that only had to be soldered, which was much easier than welding (insult #8).

I enjoyed school, especially the experiments we were doing in chemistry. Since I was only in grade school we were not allowed to handle the chemicals, but my parents noticed my interest and got me a beginner's chemistry set (insult #9). I was also interested in oil painting, and got a set of oil paints for my birthday (insult #10).

When I turned 14 we could finally afford a car! We got one of those torpedo Olds which like all other cars, burned fuel containing significant amounts of lead to improve combustion (insult #11). I was interested in basketball, and played regularly in the school playground. It wasn't as rough as football, but I had my share of spills and bumped head traumas (insult #12).

After school I had a part-time job in a small manufacturing shop near home where solder was repackaged in the many forms that other businesses needed it as opposed to the usual rolled-up form. I handled it daily (insult #13).

I went to college in a small town in upstate New York; the water was from a well (see #4). I took classes in English, history, mathematics, and chemistry (see #9). During the summers I worked at a plastics research lab in New Jersey where the chief plastic we studied was poly-vinyl chloride (PVC); I regularly cleaned up with acetone (insults #14, 15). In my senior year I got hooked on pottery making; one of our most popular glazes was made with manganese, another contained lead to make the glaze melt at a lower temperature and be shiny (insults #16,17). I was not a drug user, but a few times I tried some chemical compounds made by my classmates when we were at a party, some of which may have included MTPT (insult #18).

I could go on and eventually get to the present; the number of conscious insults would probably be at least 100, with unknown insults being many more. I suppose I wrote this to point out that it is impossible to be raised in a technologically advanced society without consequences, one of them being the acquisition of bad diseases. Perhaps a more important point is that from societies' point of view it is crucial that these risks be discovered and mitigated; from the individual's perspective it is best not to dwell on what caused the disease (unless the cause continues) and get on with one's life.

GDNF in the treatment of Parkinson's Disease

by Dr Michael John Harris

This article is meant to provide an introduction to a promising line of research.

At SPRING's first Members' Forum, in July 1997, Professor Harry Bradford of Imperial College, London gave an insight into the use of substances called Nerve Growth Factors in the treatment of PD. His lecture focused on Brain Derived Neurotrophic Factor, a close relative of GDNF in terms of both structure and properties.

Nerve growth factors are naturally occurring substances found in the central nervous system and in some peripheral tissues, substances that promote the growth, regeneration and protection of nervous tissue (so called neurotrophic activity). They are believed to act as signaling molecules without which neurons would cease to function and die. GDNF is one of a family of such nerve growth factors, first identified in the laboratory in a media of glial cell line cultures. (Glia are cells from nervous tissue, which form part of the support structure of the brain). Nerve growth factors are important in embryonic development of the brain and in the continuing function of the different parts of the brain, after development.

GDNF is a protein, which is a substance made up of amino acids strung together in chains. The GDNF molecule consists of two protein chains, each containing 134 amino acids and cross-linked together. It is, therefore, a very large and complex substance. In its natural form GDNF is produced in trace amounts for export to surrounding tissue, where it is highly potent in promoting the survival of dopaminergic neurons (i.e. those neurons which produce the neurotransmitter dopamine and which degenerate in PD). Proteins produced for export in this way are often modified by the attachment of side chains of carbohydrates and there is evidence for GDNF having such attachments. GDNF can be isolated and harvested from nervous tissue, although in practice this is difficult to do on a large scale and almost impossible to do in the human case. It is easier for pharmaceutical companies to obtain the piece of DNA (gene) that is responsible for the biosynthesis of the GDNF, put this into another organism and grow the protein up to requirement (making the product a so-called recombinant protein). Such genetic engineering, for that is what it is, is quite a respectable and successful

practice in the pharmaceutical field, with therapies for medical conditions such as diabetes, hemophilia, anemia, etc., all now based on functional proteins created in this way.

The pharmaceutical company AMGEN has been working for several years on the treatment of PD by neurotrophic drugs. Among the drug portfolio of this company is recombinant GDNF. While this may not be an exact replica of the natural product made normally in the human brain, it is likely to be the same in terms of amino acid sequence to the natural product, but may have subtle differences in respect of carbohydrate side chains (see above). AMGEN has also been concerned with the experimental treatment of PD with other neurotrophic drugs, which are not native to the human body, called immunophilin ligands. Drugs based on proteins, e.g. GDNF, cannot be administered orally as the enzymes of the digestive system will normally break down the protein, which will not anyway be absorbed through the wall of the digestive tract. Treatment by injection into a vein or soft tissue is sometimes possible for this type of drug, but may be problematic as the protein may induce an immunological reaction, if recognized as foreign and the protein will be subject to degradation while in the circulation. For GDNF, which needs to be directed to the brain to have any effect in the treatment of PD, there would also be a need for the drug to pass from the circulation across the blood brain barrier. Attempts have been made to apply GDNF by intraventricular injection, but these attempts have apparently been unsuccessful due to insufficient drug getting through to the relevant brain tissues.

The work conducted at the Frenchay Hospital has involved the application of recombinant GDNF, supplied by AMGEN, to the putamen structure in the brain. The putamen is part of the basal ganglia, into which area of the brain the dopamine neurons of the substantia nigra project. This is the area of the brain in which grafts of embryonic tissue have been placed in the implantation treatment of PD. The administration of the drug over a prolonged period has been carried out via pumps situated in the trialist's abdomen, connected by tubes to the specific area of the brain. The treatment has been preceded by work on animal models in many centers across the world, many of which have reported a beneficial outcome.

The trials at the Frenchay Hospital have been conducted on five people with PD, all of whom have shown improvement of symptoms from the prolonged application of GDNF to the brain. The Frenchay research team claims this is the first time that there has been such improvement in a chronic neurological disease following infusion of a growth factor. However, they point out the early status of the research and caution against over-optimistic projections on widespread and early availability of a clinical treatment. The trialists are also being assessed for anatomical improvement as determined by PET (Positron Emission Tomography) scanning at the Hammersmith Hospital in London.

The results of the Frenchay trial are very promising. It remains to be seen whether this application of GDNF in the treatment of PD will prove successful in the long term and/or will be a beneficial way of treating the illness in the 10,000 or so cases occurring annually in the UK. In the meantime, other groups in this and other parts of the world are still working on other methods of using GDNF in the treatment of PD. These include using viral vectors for administering GDNF or using drugs for boosting the natural level of GDNF in the brain - GDNF levels are reported to be lower in the brains of individuals with PD than those without.

Next two meetings: September 20 and November 15 - special treats.

The next meeting is September 20 at 10 a.m. for which you will receive a post card; the same for the November 15 meeting. In September we shall host a naturopath who will speak of the way he approaches medical care; it should be of universal interest.

In November we start a new program, which many have asked for. Gunilla Norris will conduct introductory sessions in eastern exercise/meditative techniques before each meeting at 9:15 a.m. SHARP. She will lead the group in T'ai Chi, Chi Kung, and other forms of eastern movement techniques. One need have no experience, just a desire to learn. Wear loose, comfortable clothing and be prepared for about 30 minutes of gentle movement. Gunilla feels it is important for those who come to arrive at or before 9:15 so as not to disturb the flow. Open to all. Be prepared to thoroughly enjoy yourself.

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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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