Parkinson's, Profit and People: The science money wants hidden, pt. 2.

Please enjoy this additional information which along with the first part in this series, may help to clarify the scientific basis and rightful therapeutic place of many unknown and inexpensive compounds and approaches proven efficacious in the treatment of Parkinson's disease. Also, I have included some more speculative information, which in my view, deserves considerable attention and experimental development.

K(2):

a. Parkinson's is a disease of energetic deficiency stemming from mitochondrial dysfunction. http://www.vib.be/en/news/Pages/New-discoveries-place-lack-of-energy-at-the-basis-of-Parkinson%E2%80%99s-Disease.aspx From, "**New discoveries place lack of energy at the basis of Parkinson's Disease**" Molecular mechanism provides ultimate proof: Vanessa Morais studied the link between Pink1, mitochondria and Parkinson's disease in fruit-flies and mice with a defective Pink1 gene. These model organisms exhibited symptoms of Parkinson's disease as a result of this defect. She was able to demonstrate that the defect in Pink1 resulted in the so-called 'Complex I' – a protein complex with a crucial role in the energy production of mitochondria – not being phosphorylated adequately, resulting in decreased energy production. When Morais and her colleagues ensured correct phosphorylation of Complex I, the Parkinson's symptoms decreased or disappeared…"

Also see **Mitochondrial Biology and Parkinson's Disease** Celine Perier and Miquel Vila Cold Spring Harb Perspect Med. Feb 2012; 2(2): a009332.
doi: 10.1101/cshperspect.a009332
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3281591/ "Whether a primary or secondary event, mitochondrial dysfunction holds promise as a potential therapeutic target to halt the progression of dopaminergic neurodegeneration in PD."

b. Mitochondrial electron carrier, vitamin K2, rescues Parkinson's disease models based on this theory. http://www.ncbi.nlm.nih.gov/pubmed/22582012 Science. 2012 Jun 8;336(6086):1306-10. doi: 10.1126/science.1218632. From, **Vitamin K2 is a mitochondrial electron carrier that rescues pink1 deficiency.** Vos M, Esposito G, Edirisinghe JN, Vilain S, Haddad DM, Slabbaert JR, Van Meensel S, Schaap O, De Strooper B, Meganathan R, Morais VA, Verstreken P.

"We found that vitamin K(2) was necessary and sufficient to transfer electrons in Drosophila mitochondria. Heix mutants showed severe mitochondrial defects that were rescued by vitamin K(2), and, similar to ubiquinone, vitamin K(2) transferred electrons in Drosophila mitochondria, resulting in more efficient adenosine triphosphate (ATP) production. Thus, mitochondrial dysfunction was rescued by vitamin K(2) that serves as a mitochondrial electron carrier, helping to maintain normal ATP production."

Vitamin D:

Vitamin D has been demonstrated to slow the physical deterioration associated with

Parkinson's. See:

Suzuki M, et al. Randomized double blind placebo controlled trial of vitamin D supplementation in Parkinson disease. *Am J Clin, Nutr*. 2013 May, 97(5): 1004-13.

Case histories, compounds, and scientific mechanisms of cure:

Glutathione and Dr. Julian Whitaker MD: According to Dr. Whitaker, from his newsletter September, 2014:

"Glutathione is the major antioxidant produced in neurons and cells throughout the body. Oxidative stress and inflammation are implicated in the dysfunction and ultimate death of dopamine-producing cells. Restoring depleted glutathione stores slows this destructive process and improves symptoms in patients with Parkinson's. IV administrations helps ensure it gets into the brain.

I'll never forget one of the first patients we treated at the clinic with IV Glutathione. He had a significant tremor in his left arm and arrived in a wheelchair. After his second IV treatment, his tremor decreased and he was up and walking, albeit with an unsteady gait and his arms stiff at his sides. After his third infusion, he was walking more or less normally, with a confident stride, arms swinging–and no tremor."

See:

Sechi G, et al. Reduced intravenous glutathione in the treatment of early Parkinson's disease. *Prog Neuropsychopharmacol Biol Psychiatry*. 1996 Oct; 20(7):1159-70.

Diltiazem, calcium channel blockers, and Dr. S. Shanmugam MD:

From a communication with the doctor:

I will directly discuss about the hypothesis on Parkinsonism which I have conceived in 1989 and using a drug able to reduce the symptoms of Parkinsonism and published a Letters to the Editor on the same in JAPI in 1989.

The unusual improvement in the symptoms of Parkinsonism in a patient whom I have treated for CAHD with Diltiazem and the patient's observation of very good improvement within a week's time about his symptoms made me to write the letter. "Diltiazem in Parkinsonism". Unfortunately nowadays there are plenty of articles on Diltiazem producing Parkinsonism.

Hypothesis: The basal Ganglia in the brain is one of the regions with what is called *tight and end blood supply* with no possibility of collaterals to supply blood due to its position in the brain. There are no neighbourhood phenomena of helping with blood supply. So, any factor whether it is toxin or infection or atherosclerosis, once the smallest vessels supplying the basal ganglia are affected, the cellular metabolism is affected and so the neurotransmitter play. As in a car, the accelerator and the decelerator or brake mechanisms playing a major role in the outcome of any disease in neurology. So, the reflexes – excitatory or inhibitory develops depending on the level of affection of various cells and so the vast difference in the symptomatology in relation to Parkinsonism. Whether by taking careful look at the blood supply and trying to assess the blood lipids, Fibrinogen and Lipoprotein A as in a case of CAD along with smoking a great factor for small vessel constriction and pathology.

So, My **hypothesis** is that "By maintaining a good blood supply to the basal ganglia by means of avoiding factors which affect the blood supply namely toxins if any especially nicotine, prevention of atherosclerosis using the basic concepts as in heart and increasing the blood supply using end supply increasers like diltiazem as in the quoted case, Parkinsonism can be prevented even in genetically prone patients. By using a cell metabolism modifying molecule like trimetazidine as in the case of heart and tinitus the effect of pathology in basal ganglia cells can be reduced". The reason for outcome in Parkinsonism varies because of the interference in pathology is done at various stages of the disease.

Dr.S.Shanmugam, M.D., PGDHSc (Echocardiography)

Researcher in new methodologies in Medicine,

Geeyes Diabetes and Hypertension Research Centre,

Tirunelveli,Tamil Nadu, India.

Please see supporting science here: http://www.ncbi.nlm.nih.gov/pubmed/15666038

J Neural Transm. 2005 Sep;112(9):1237-48. Epub 2005 Jan 24. **Changes in vascularization in substantia nigra pars compacta of monkeys rendered parkinsonian.** Barcia C, Bautista V, Sánchez-Bahillo A, Fernández-Villalba E, Faucheux B, Poza y Poza M, Fernandez Barreiro A, Hirsch EC, Herrero MT.

In addition, I have uncovered another layer of efficacy, and a second modus operandi, to augment and support the doctor's assertions of a viable treatment. Indeed, this is quite exciting: http://d-scholarship.pitt.edu/10539/ **Understanding the Interaction between LRRK2 and PINK1: Implications for Parkinson's Disease** Cherra, Salvatore J. (2011)

"This study also found that mutant LRRK2 causes mitochondrial degradation by autophagy in the dendrites of neurons, which led to shortening of the dendrites. PINK1 suppressed the autophagy induction elicited by mutant LRRK2 and prevented the mitochondrial degradation and neurite shortening. Furthermore, mutant LRRK2 caused a

delay in calcium clearance after neuronal iv depolarization. This prolonged elevation in intracellular calcium caused mitochondrial depolarization followed by degradation. . . Indeed, calcium chelation or inhibition of voltage-gated calcium channel restored calcium homeostasis and attenuated the mitochondrial degradation and dendrite shortening induced by LRRK2 mutations."

So, it is possible that other safe and cheap substances, such as magnesium, may also demonstrate efficacy by this combined mechanism:

See: http://www.ncbi.nlm.nih.gov/pubmed/6400430 Microcirc Endothelium Lymphatics. 1984 Apr;1(2):185-220.

Microcirculatory actions and uses of naturally-occurring (magnesium) and novel synthetic calcium channel blockers. Altura BM, Altura BT.

Also see this for a second layer of connectivity between Mg and Parkinson's: http://www.ncbi.nlm.nih.gov/pubmed/15885623 Parkinsonism Relat Disord. 2005 Jun;11 Suppl 1:S17-23.

The nature of the parkinsonism-dementia complex and amyotrophic lateral sclerosis of Guam and magnesium deficiency. Oyanagi K.

I conclude: *Calcium channel blockers appear to affect both blood flow, and intracellular calcium influencing mitochondrial function, so as to ameliorate pathology*.

Approaches from depth psychology, affective neuroscience and neuropsychoanalysis

To fully understand these ideas, please read "**Limbic connectivity and sympathetic neural balance: the primary psycho-physiological locus of affect**" (Norman, 2014) available from www.mindmagazine.net at: http://media.wix.com/ugd/cf8614_243ef24742a84c69b64e998280ac34b8.pdf

The brain is a causally bi-directional electro-chemical system. Our thoughts are created within a physiological substrate—the nervous system, and in turn, we can see that our thoughts are but patterns of dynamic electro-chemistry, and the dynamic electrochemistry of the nervous system is in turn, nothing but our thoughts. Therefore our thoughts can affect the electro-chemical configuration of processes which is the physiology of the brain, and vice versa.

Affective neuroscience (Panksepp, 1998, Affective Neuroscience, Oxford Press), a new and vital discipline which rightly defines the systemic physiology of the affects and

emotions, is by far the most convincing and correct approach to understanding the human animal. Likewise, Neuropsychoanalysis also takes an unvarnished, detailed and subtle approach to the emotions which are all but the entire of the human equation, and defines our physiology in this correct context. Not surprisingly, the two disciplines fit together as hand and glove. Parkinson's is a disease of dopaminergic deficiency. Affective neuroscience recognizes the SEEKING system as a primary energetic network of dopaminergic distribution and mediation. Repressions quell dopaminergic distributions via particular circuitry. I propose based on a-priori observation and experiment, that the SEEKING system can be assessed in its expressive/repressive dynamic associated at the most basic and fundamental level with Schore's ventral sympathetic limbic circuit in distributing dopamine, curtailed by the noradrenergic parasympathetic lateral limbic circuit, which responds to social cues and circumstances (disapproval) that invoke guilt and shame (forming repressions). Also, I contend we can influence the situation for the better, to improve immune response, and delay or prevent Parkinsonian onset.

The dopaminergic sympathetic tegmental limbic circuit is primary and life sustaining. I assert: the dopaminergic sympathetic tegmental limbic circuit in its balance of dynamic activity set against the parasympathetic lateral limbic circuit, constitute the most basic level of affect regulation in man, and, are the basis of empathy, which I contend reflects more than just mirror neuronal activations, that are only a small part of an emergent world identification. This neurologic empathetic fundamental substrate, is initially innervated and formed in the first eighteen months of life, and, is triggered in its development by the exchange of gaze and glance, along with touch, between the mother and infant. The initial formative triggering impression of the mother which had begun innervation, has been deeply modified over time with the layering into memory of many other impressions. So, the dopaminergic sympathetic tegmental limbic circuit can be activated via the formative impressions if those impressions themselves are *symbolized*, as symbolism is the language of our reality, and the mind's means of unconscious representation in consciousness…our intrasystemic mental language. This will allow the circuit to be manually activated by directly accessing the unconscious impressions which triggered the neuroendocrine changes that formed the circuit. Once the balance between the two circuits has been influenced for the better, a major source of resistance to what level of dopaminergic function is present, will be removed, so as to augment function. My a-priori observations support this most clearly. Also, on a sound but more speculative note, I hypothesize the system itself, may well have been encouraged to degeneration by the constant interruption and binding of dopaminergic expression, and may be demonstrably responsive to fundamental readjustment yielding increased systemic demand.

Please read the above referenced paper and find a proposed neuroscience experiment to evaluate the validity of these propositions by way of assessment of limbic/orbitiofrontal function via sympathetic-dopaminergic/parasympathetic-noradrenergic balance within the context of the LRRK2 mutation population. You will also find a basic representation of the "Alpha Function" key…the derived symbolic image used meditatively to activate the circuitry and positively affect dopaminergic expression by accessing the unconscious formative maternal impressions. (I have myself been using this technique to good result

for a few years now).

Here are a few fresh hatched ideas which are highly speculative regarding possible alternate sites of DBS and other strategies involving neuropeptides implied by an affective neuroscientific analysis. Note: These notions below must be thoroughly checked through, but may hold a new avenue of treatment.

The mysterious fact that (bilateral) deep brain stimulation (DBS) of the subthalamic nucleus, thalamus, or globus pallidus, which by the reasoning of cognitive neuroscience (Gazzaniga, 2009, Cognitive neuroscience: the biology of the mind, p. 305), should increase symptoms by way of thalamo-cortical inhibition… but does not…may be a product of activating the SEEKING system itself, which can typically be stimulated anywhere from the medial forebrain bundle-lateral hypothalamic circuitry, up to the nucleus accumbens to the medial prefrontal cortex via the mesolimbic and mesocortical dopamine pathways.

I believe that there is a homeostatic factor…and that feedback in the system has been a contributing dynamic element, and has all but requested the condition to emerge. So, if the SEEKING system is stimulated with intense electrical high frequency activity as it is now used, then the system once aided, will re-balance to decay further. Instead, the progression of disease and degeneration may hypothetically be aided to resuscitation, or at least to end further degeneration, by another more subtle approach. I suggest several possibilities: The SEEKING (A-10) dopaminergic neurons project from the ventral tegmental area. If the system were stimulated here, or along the usual MFB-LH circuitry as in animal studies, and the stimulation were slight, not excessive, perhaps, over time without interfering with homeostasis, the demand placed upon the system, and hence demand placed upon the substantia nigra via efferent projections stemming from the nucleus accumbens-septi, would create a new systemic balance conducive to functional maintenance, or improvement.

Next, I wonder if naturally occurring systemic intervention might be simulated with DBS. SEEKING activation is associated with heightened activity in the nucleus accumbens. Sexual excitation is a sure bet to engage the system. So, low level septal stimulation should be tried. Not too much! Just enough to create a constant demand…the lowest amount to gain response in the nucleus accumbens.

Next, I wonder, has a neuropeptide been tried which activates the system…neurotensin for example? Or along the same lines…a dynorphin blocking agent?