Ray Peat's Newsletter

"We know not through our intellect but through our experience." --Maurice Merleau-Ponty

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Parkinson's disease:
Some contexts for tremulous stiffness

Most people have now heard the idea that "cancer is a metabolic disease, not a genetic disease," and that's a real challenge to the ideology of reductionism in biology and medicine. However, many of these people are thinking of the problem as a metabolically defective cell, and that the problem is to be solved by taking advantage of the cell's defect to kill it, for example by starving it in various ways, or poisoning it with something that kills only cells with that type of metabolism. This is just a new kind of reductionism, that finds disease in certain cells with defects. Whenever there is a medically diagnosed disease, the reductionists look for the cells that are responsible, and if their particular chemical defect can be identified, treatment will center on that.

The idea of metabolism—change of substance, adaptive interaction—implicitly includes the interactions of cells with the organism in its environment. Reductionists prefer to explain things in terms of molecules, genes, or cells, to avoid the implications of "metabolism," but that avoidance requires the denial of the unique properties of life. To the extent that the medical industries have been built on reductionism, they have ignored many opportunities to improve human health.

Parkinson's disease, a "movement disorder," is very different from cancer, a "growth disorder," but I think each of these conditions can help to illuminate the other. Many people think of Parkinson's as a genetic disease, and several mutant genes have been identified as causes, and current treatments center on specific cellular-molecular defects, but in the 200 years since James Parkinson wrote "An Essay on the Shaking Palsy," many observations have been made that suggest that it should be considered to be a metabolic disease, a systemic metabolic disease.

In his essay, Parkinson described six cases with the symptoms that define the "shaking palsy," a disease that can be distinguished from other conditions that combine tremor and paralysis, and he gives several examples of other conditions, showing their similarities and differences. While this specific disease comes on gradually, over a period of years, and usually starts in middle age or later, without any identifiable cause, he observed that some similar symptoms could be produced by specific types of injury. Observing that tremors and paralysis could occur without affecting perception or thinking, he reasoned that damage to the nerves in the upper part of the spinal cord or lower part of the brain was the proximal or immediate cause of the symptoms, and he didn't directly express an opinion about a more remote or indirect cause.

However, he was aware of John Abernethy's view that "local diseases" have a "constitutional origin," and one of the cases that another doctor had described as "shaking palsy," was a boy whose legs, head,

and hands "were in continual agitation" for many weeks. The doctor cleared his bowels with purgatives and gave him a grain of opium daily, and "in three or four days the shaking had nearly left him." Parkinson commented: "By pursuing this plan, the medicine proving a vermifuge, he could soon walk, and was restored to perfect health."

In his general comments on the true shaking palsy, Parkinson had said that in the later stages "The bowels, which had been all along torpid, now, in most cases, demand stimulating medicines of very considerable power ...." Describing his sixth representative case, he wrote "Of late years the action of the bowels had been very much retarded; and at two or three different periods had, with great difficulty, been made to yield to the action of very strong cathartics."

He ends his essay expressing the hope that the progress of the disease can at least be stopped, and, to illustrate the way that the disordered function of a distant part can derange anatomical structure, he describes a 54 year old man who had gradually developed weakness and trembling of the hands, who, with laxatives, was restored to health in about ten days.

About 40 years after Parkinson's essay was published, the famous French neurologist J-M. Charcot was greatly influenced by it, and had the opportunity to study a large number of cases. He and others had some success treating the tremor with belladonna or hyoscyamine. He noticed that when patients would travel a considerable distance, by train, carriage, or horseback, to consult him in Paris, their symptoms would often disappear temporarily. Charcot believed it was vibration that caused the improvement, but more recent studies show that it was stimulation of a different sort that was responsible. Parkinson had described the way that a sudden change of posture could, for a couple of minutes, completely stop the shaking, but he didn't explore the implications of that.

In the 20th century, a few people following Kurt Goldstein's ideas about holistic, organismic brain rehabilitation applied his idea to various neurological diseases, including Parkinson's. New patterns of stimulation, new meanings, can often be established by working around brain areas that are damaged.

In traveling, and in sudden changes of posture, the perception of motion causes a massive, coordinated stimulation of the whole brain. Most people are aware of the effects of vestibular stimulation only as the after-effect of spinning, on a swing or merry-go-round, for example, but every time we change our posture, signals from our inner ear change our mental image of the location of the surrounding world. Some therapies have used an apparatus to move a person into varied attitudes and postures, others have done it in a swimming pool. Currently, when people speak of "vestibular stimulation" for Parkinson's disease, they are likely to mean electrical stimulation, which can be applied externally, or through electrodes in the brain, but simple movement in space is probably the most effective.

Without knowing the basic causes of Parkinson's disease (and it isn't very helpful to keep hearing that "it's caused by the death of dopaminergic cells in the substantial nigra"), we don't know how much can be achieved by way of modifying sensory experience, but if we consider the powerful biological effects of "learned helpless," and the simplicity with which it can be alleviated, we can imagine that the therapeutic possibilities in that direction might be great.

From the early 20th century until around 1970, much of mainstream medicine's interest in the disease concentrated on cutting

out, or otherwise destroying, the tissue that seemed to be responsible for the tremor. Norbert Wiener, the mathematician who coined the word "cybernetics," worked on the first automatic control systems for using radar to aim anti-aircraft guns, and he noticed a similarity between the wobble in his aiming devices and the tremor of Parkinson's disease. Following his suggestions, surgeons found that destroying an area on one side of the brain could balance an existing defect on the other side, allowing the tremor to stop.

That small success stimulated a kind of "systems thinking" about biology, but it was an extremely abstract approach, not at all approaching a systemic, metabolic and environmental way of thinking about the movement disorder.

When it was discovered that the production of dopamine was reduced by the death of cells in the brain stem, L-dopa was introduced as the main drug treatment, since it can temporarily increase the amount of dopamine in the brain. The "dopamine theory" of the disease has become a sort of framework for thinking about the brain, such that other drugs that are helpful for Parkinson's disease have come to be defined as dopaminergic drugs, though their benefit might involve other systems, such as inhibiting serotonergic (Maj, et al., 1977) or cholinergic or glutamatergic nerves (amantadine or memantine).

These surgical and chemotherapeutic treatments are analogous to the reductionists' approach to cancer and the other chronic degenerative diseases. In the last 40 years, there has been a considerable increase in the prevalence of, and mortality rate from, Parkinson's disease, so it might be time to try some different ideas.

Since the time of Abernethy and Parkinson, we have learned some of the ways that the bowels can influence the brain, and we have discovered a variety of things that damage the substantia nigra, producing the shaking palsy, and a few practices—drinking coffee or alcohol, smoking, using aspirin—that significantly reduce the risk. These observations suggest that there are effective ways to treat Parkinson's disease with diet, laxatives, and anti-inflammatory substances.

Intense or prolonged stress injures the intestine, damaging its barrier function, and allowing bacterial toxins, especially endotoxin, to be absorbed into the blood stream. Glucose is the critical factor in protection of the intestinal epithelium during stress (Huang, et al., 2017). The endotoxin, lipopolysaccharide, has a general excitatory effect effect that activates cell inflammatory processes and damages energy production, with the mediation of cell products such as nitric oxide, carbon monoxide, serotonin, histamine, prostaglandins, estrogens, and various cytokines (interleukins and tumor necrosis factor,TNF). Some of these substances enter the blood stream from the intestine, others are produced elsewhere in the body, but some are produced in the brain itself, when endotoxin is absorbed into the brain (Liu, et al., El-Shimy, et al., Banks, et al., 2015).

Every organ has its particular pattern of metabolism, so that it is susceptible to particular variations in the person's history of interactions with the environment. The substantia nigra has some particular vulnerabilities; one is that it has fewer mitochondria than other sections of the brain. This suggests that smaller amounts of mitochondrial toxins might be able to kill these cells selectively.

Toxins, such as the insecticide rotenone, that are suspected to be among the causes of Parkinson's disease, produce effects in

animals that resemble the human disease, and these animals are used to test chemicals that might be protective or therapeutic for people. For example, caffeine, aspirin, and melatonin protect the substantial nigra against rotenone (Soliman, et al., 2016; Madathil, et al., 2013; Carriere, et al., 2016). When endotoxin is used experimentally to produce experimental Parkinson's, the protective substances are similarly effective.

Nitric oxide, like endotoxin and rotenone, is a powerful inhibitor of mitochondrial respiration. Endotoxin and other harmful stimuli can increase the formation of nitric oxide, but it's also produced in the normal excitatory processes of nerves, and with an excess of excitation relative to energy production and inhibitory influences, it can become the central agent of excitotoxicity.

Hypoglycemia activates the excitatory glutamatergic system, leading to increased nitric oxide, which, in the presence of an energy deficit, produces excitotoxicity. Besides excitoxicity and mitochondrial damage, nitric oxide contributes to inflammation, DNA damage, and oxidative and nitrosative damage to other cell components. These processes interact with other mediators of inflammation and excitation produced in the same or nearby tissues, including prostaglandins and products of lipid peroxidation.

Nitric oxide, even in the presence of oxygen, causes a metabolic shift to glycolysis, wastefully producing lactate from glucose (Brix, et al., 2012; Erecińska, et al., 1995). Shifting the balance from oxidation to reduction tends to increase the level of excitatory processes. This aerobic glycolysis is the characteristic metabolism of cancer, but it occurs in other stressed conditions, including heart failure (Ryan and Archer, 2014), in which something interferes with the oxidation of glucose.

In response to stress and inflammation, the enzyme heme oxygenase breaks down the heme molecule (from enzymes and blood), producing carbon monoxide, biliverdin, and iron. In people with Parkinson's disease, increased amounts of iron, nitric oxide, and prostaglandins have been observed.

During a normal 24 hour cycle, the body is able to change adaptively, renewing and changing cells and tissues. As our tissues accumulate polyunsaturated fats with aging, the production of prostaglandins becomes greater, and the balance is less likely to be fully repaired. The enzyme that synthesizes prostaglandins can react with dopamine, converting it to a toxic product (Mattamal, et al., 1995).

In general, during deep sleep, inhibitory processes are able to restore stability to the cells that were damaged by toxic excitatory processes, but a degenerative disease such as Parkinson's disease involves a progressive inability to relax; energy continues to be spent faster than it can be restored. In the early stages, changes in sleep behavior are noticed; decreased mobility during sleep, with increased muscle tension, is typically followed by increasing muscle activity, and sometimes violent movement during dreams.

The first signs of the disease are usually noticed in middle age, as the reproductive hormones are declining. Men with Parkinson's disease have been found to be deficient in testosterone, one of the hormones involved in tissue maintenance and repair, and supplements of the hormone relieve some of the symptoms. Men's testosterone declines with stress and aging, and its conversion to estrogen is increased by stress and inflammation. Endotoxin specifically increases the conversion of testosterone to estrogen (Christeff, et al., 1992).

When stress causes metabolism to shift in the direction of reduction, with lactic acid formation, iron atoms react cyclically with oxygen and the reductants, producing hydroxyl radicals and other very reactive toxins. The high local concentration of dopamine in the substantial negra, reacting with iron, produces a variety of toxins (Wang, et al., 2008). With aging, iron and the polyunsaturated fats accumulate in the brain. Estrogen slows the removal of dopamine, increasing its opportunity to react toxically with iron and highly unsaturated fats, especially arachidonic acid and DHA; it also tends to increase the formation of prostaglandins and nitric oxide. Progesterone's opposite effects probably account for the lower prevalence of Parkinson's disease in women than in men.

Despite its toxicity, L-DOPA continues to be the main medical treatment for Parkinson's disease, though the more appropriate drugs bromocriptine, amantadine, and memantine are also widely used. Anticholinergics, similar to the hyoscyamine and belladonna that Charcot used, are sometimes used to control excessive salivation. Amantadine and memantine happen to protect against nitric oxide, serotonin, inflammation, and endotoxin, and to protect mitochondria. They are starting to be used to treat cancer, stroke, epilepsy, and even arthritis, as the understanding of them spreads. Drugs of this sort should be thought of as structurally active substances that can approximately correct the harmful structural effects of endotoxin and other pathogens.

Treatment with dihydrotestosterone (which can't be converted to estrogen) might be more effective than with ordinary testosterone, considering the increased activity of aromatase with age, stress, and inflammation, and the probable role of estrogen in the excitatory degenerative process. Most of the things that are likely to be protective in Parkinson's disease are broadly protective against estrogen and the inflammatory-degenerative processes: Progesterone, minocycline and other anti-inflammatory antibiotics, agmatine, aspirin, coffee, niacinamide, citrus flavonoids, vitamin D, ACE inhibitors, fibrous-antiseptic foods.

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