ALZHEIMER'S BREAKTHROUGH

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Alzheimer's Dementia, a scourge of modern civilization, is increasing globally and threatens to deplete health care resources on a large scale. It is now in 3rd place after cardiovascular disease and cancer in causes of death. Currently there is no approved medical treatment that arrests or reverses the progression of this condition. Some drugs reduce some symptoms temporarily.

If the causes for this dementia are related to lifestyle and nutrition, could a comprehensive strategy based on foods, exercise, brain training, herbs, and nutritional supplements arrest or reverse this process?

Voila! Dr. Dale E. Bredesen, M.D., professor and founding president of the Buck Institute for Research on Aging, and professor of the Dept. of Neurology at U.C.L.A., completed a study, reported in Aging, Sept 2014 Vol. 6, #9, that resulted in a stunning turnaround for several Alzheimer's patients. A study of 10 patients for 2 ½ years resulted in 6 people, who had had to quit their work due to cognitive deficiencies, returning to work with normal function. Three others made substantial improvement, but one patient who had very advanced dementia worsened during that time. This study was small, but the results are remarkable enough to be scientifically relevant and it warrants further study.

The design of the study was based on the hypothesis that the brain degeneration and subsequent cognitive decline is in a large part driven by several complex metabolic processes, varying with each individual not just one single cause such as beta amyloid. The methods used personalized multiple strategies to achieve metabolic enhancement.

So far, the therapeutic research for drugs to treat AD (Alzheimer's Disease) has been to use a single target-based approach. This avenue has lead to no sustained success in either AD or other types of dementia or in ALS (Amytrophic Lateral Sclerosis or Lou Guerig's Disease).

The past several decades of genetic and biochemical research have revealed a network of molecular interactions involved in the development (pathogenesis) of AD. This suggests that a successful therapy would need to be network-based, and that the effects on the multiple targets may be (1) additive, (2) multiplicative, or (3) synergistic.

The model of AD advanced by Dr. Bredesen's research group is based on an imbalance, between (a) brain tissue degeneration and, (b) maintenance, remodeling, repair, and growth. This balance is called "plasticity." Multiple factors affect each of these processes favoring either (a) or (b). A major problem occurs if the balance has gone too far in the direction of degeneration. Then the results of the degeneration cause even more degeneration. This is often referred to as a "positive feedback loop" or a "feed-forward process," commonly known as a "vicious cycle." This creates an urgency

to intervene early in the process, when it can still be reversed. One patient in the study with advanced AD continued to get worse.

So then, addressing as many of the network parts as soon as possible to create a synergistic effect is called "systems therapeutics" based on "systems biology."

In the study, the intention for these metabolic targets was not just to normalize them, but to optimize them. For example, the goal for homocysteine was not to get it normal, below 12, but optimally below 7., and for Vitamin D3 not just to get it up into the normal range above 25, but optimally between 50 and 100.

The goals were varied with each person, depending on what each one's specific deficiencies were; therefore, it was a "personalized" plan. The intention also was to tackle each factor as early "upstream" as possible, as "physiologically" as possible, that is, focusing on normal physiology rather than on "pathology," catching things before they became abnormal.

Each of the therapeutic actions were expected to have a modest effect, but in concert with other interventions, to have a much stronger, synergistic effect. This contrasts directly with the single-target approach, which is expected to have a faster, strong effect by itself. That is what appeals to much of the population who want to take a single pill, the easy, simple way that may have a dramatic temporary effect but fails in the long run.

What follows is a brief summary of the 35 aspects of the program, condensed into 25 composite goals with their rationales:

1. Optimize diet with low glycemic, low grain, low inflammatory diet. The rationale was to minimize insulin resistance and inflammation.
2. Ketogenesis by fasting 12 hrs/night, including 3 hrs prior to bedtime. The rationale was to reduce insulin and amyloid-beta (AB). Ketones occur when fat is being burned and are used by the brain for fuel when carbohydrate (glucose) is not available. Ketogenic diets have been beneficial for a number of neurological conditions. (See notes to follow about Dr. Perlmutter's experience.)
3. Reduce stress. Yoga, meditation, music, etc. By reducing stress, cortisol is decreased. High cortisol has been known to be toxic to the Hippocampus, the main processing center in the brain for memory.
4. Optimize sleep. 8 hrs/night, exclude or treat sleep apnea. Melatonin 0.5mg at bedtime, tryptophan if awakening.
5. Physical exercise 30-60 min/day, 4-6days/wk.
6. Brain stimulation by Posit Science or similar mental exercise.
7. Homocysteine <7 with methyl B-12, methyl folate, pyridoxal 5 phosphate (a more available form of B-6 than the usual), and betaine.
8. Keeping vitamin B-12> 500, by supplementing with methyl B-12.
9. CRP (an inflammatory marker) <1.0 with anti-inflammatory diet, curcumin, and DHA/EPA (omega-3's from fish oil). Optimize dental hygiene and reduce gum

inflammation, with electric flosser and brush. Rationale is that AD is an inflammatory condition.

10. Keep fasting insulin <7, HbA1C<5.5 with diet, as above. Rationale is the diabetes – AD connection.
11. Hormone balance. Thyroid, pregnenolone, progesterone, cortisol optimized.
12. Gastrointestinal health – prebiotics and probiotics. Check for digestive dysfunction. Rationale is that GI microbiome imbalance (microbes out of balance or dysbiosis) and inflammation are associated with systemic inflammation, including brain inflammation. See Dr. Perlmutter's work regarding the strong gut-brain connection.
13. Reduce amyloid directly with curcumin and ashwaganda.
14. Direct cognitive enhancement with Bacopa monnieri and Magnesium threonate.
15. Optimize 25-OH Vitamin D3 to 50-100ng/ml with Vitamin D3 and Vitamin K2.
16. Increase neurotropic growth factor with acetyl-l-carnitine and Herinius erinaceus (Lion's mane herb).
17. Provide structural components for nerve synapses (connections) with citicoline and DHA. (For making acetylcholine, which is deficient in AD.)
18. Optimize antioxidants with mixed tocopherols and tocotrienols (natural forms of Vitamin E), selenium, blueberries, n-acetyl cysteine, ascorbate (Vitamin C), and alpha lipoic acid.
19. Optimize zinc/copper ratio.
20. Ensure nocturnal oxygenation. Exclude or treat sleep apnea.
21. Optimize mitochondrial function. CoQ10 (ubiquinol), α-lipoic acid, n-acetyl cysteine, acetyl-l-carnitine, selenium, zinc, resveratrol, ascorbate, thiamine.
22. Increase focus with pantothenic acid to improve synthesis of acetylcholine, a neurotransmitter, which is usually deficient in AD.
23. Increase SirT1 function, the anti-aging mechanism, by supplementing with resveratrol, mimicking the calorie restrictions effect on extending lifespan.
24. Exclude heavy metal toxicity. Mercury, lead, cadmium, etc. Chelate if indicated.
25. Medium chain triglycerides (MCT) with coconut oil, provides beta-hydroxy butyrate, a ketone used for energy production in brain cells, partly mimicking the ketogenic diet.

These measures are certainly research tools, and we have no certainty that each of these 25 factors are essential to a therapeutic program or even causative in the recovery of these 9 people in the study. Some of these measures could be symptomatic, temporarily improving function, such as for Bacopa, Magnesium, citicoline, and pantothenic acid. The others are likely to produce long-term metabolic and structural neurological improvement. None of the patients followed the program perfectly. This shows that with combination therapy, even modest adherence to the plan can be beneficial.

Plenty of corroborative research demonstrates results consistent with this study. Dr. David Perlmutter M.D., board certified neurologist and fellow of the American College of Nutrition, in his book, Grain Brain, cites a plethora of research showing benefits of

many of the 25 therapeutic goals of the Bredesen study, the background data supporting the causation of AD, and the rationale for these measures.

For example, for #1, for inflammation and insulin resistance: High blood glucose and high insulin levels damage the brain and cause inflammation. Blood sugar within the higher end of normal increases the risk of brain shrinkage, according to the Australian National University study published in Neurology. Older people who eat high carbohydrates have 4x the risk of cognitive impairment compared to average. (Journal of Alzheimer's Disease 2012, research from Mayo Clinic.) Grains are high in carbohydrates and increase blood glucose. 30% of people may have non-celiac gluten sensitivity, which causes inflammatory cytokines that induce inflammation in several organs of the body, including the nervous system. AD involves brain inflammation. Unlike our joints that hurt when inflamed, the brain does not have pain sensors, so we don't know when our brains may be "on fire" long before symptoms of AD appear. A high carbohydrate diet makes visceral fat (in the belly), which is inflammatory. The larger the belly grows, the smaller the hippocampus, and the higher the risk of mini-strokes.

Regarding #'s 2, 9, 16, and 17, Brain derived neurotropic factor (BDNF), which stimulates new neuron growth and plasticity, gets turned on by exercise, calorie restriction, ketogenic kiet, the omega-3 fatty acid DHA, and curcumin.

For #6, Intellectual stimulation fortifies new neural networks and turns on genes that protect neurons. Matteson et al, Physiological Reviews 82 #3 (July 2002): 637-72. For #'s 1, 2, 18, and 24, fasting increases BDNF, detoxification, decreases inflammation, and increases antioxidant activity. For #12, Dr. Perlmutter recommends probiotics. In his book, Brain Maker, he describes in detail how the health of the digestive system and its microbiome with billions of bacteria directly affects the brain. Certain types of bacteria in the gut either promote or decrease tendency for obesity, insulin resistance, and diabetes, all factors in AD. Bacterial imbalance promotes intestinal permeability (leaky gut) and systemic inflammation. Lipopolysaccharides (LPS) from certain gut bacteria can leak into the circulation and promote inflammation. They can decrease BDNF Brain Behav. Immun. 20, No. 1, January 2006:64-71. Alzheimer's patients have 3x the normal level of LPS in the plasma. J. Neuroimmunology 2008.09l.017 Epub Nov. 14, 2008.

For #'s 1 and 5, physical exercise increases new brain cells, BDNF, the size if the hippocampus, blood flow to the brain, cognitive function, and insulin sensitivity, and it decreases inflammation and cognitive decline.

For # 20, sleep disordered breathing increases risk of dementia. Yaffe et al JAMA 306 No. 6 (Aug 10, 2011): 613-19, and #4, sleep is the time when many toxins are removed, including amyloid in the brain.

Data supporting berries in #18 presented at Medicines From The Earth 2015, from in vitro and animal studies report that anthrocyanins in dark berries like blueberries, blackberries, raspberries, strawberries, gogi berries, pomegranates, etc. help blood sugar regulation, improve brain circulation, cross the blood/brain barrier and protect neurons

from free radical damage, increase neurogenesis, modulate amyloid precursor protein, and reduce amyloid plaques. Elizabeth Devore reported data from the Nurses Health Study 1995-2001 that women who ate 2 or more servings per week of strawberries or blueberries had significantly less cognitive decline than women who ate none, with adjustments made for economic status.

About #'s 5 and 6, from my memory of previous research, people who remained socially connected, were physically active, and had intellectually challenging activities maintained better cognitive function than those who did not. Does this not sound like a recipe for staying in the work force, not retiring, as long as the work is enjoyable and not distressing?

Dr. Perlmutter warns that use of "statin" drugs for cholesterol may increase risk for AD. A large portion of the brain consists of cholesterol, and it would stand to reason, that too much restriction of cholesterol could cause brain damage. All the steroid hormones such as sex hormones, cortisol, DHEA, and Vitamin D all require cholesterol as substrate. Statin drugs have been known to decrease testosterone, increase risk of diabetes, and if they also decrease Vitamin D, that could be 3 risk factors for AD caused by statins.

What can we do with the information from Dr. Bredesen's study? Though it is still at the stage of research and has not been approved as a treatment plan, there is much we can apply, especially since the methods are natural and carry low risks. The diagnosis needs to be correct, since there are other forms of cognitive dysfunction besides AD, such as vascular dementia, Parkinson's, depression, hypothyroidism, etc.; however, these other conditions could also probably benefit from the same program. Two recent studies reported in JAMA May19, 2015 Vol. 13 No. 19 demonstrated that positron emission tomography (PET) scans can reveal amyloid-beta in brains 20 years before the diagnosis of AD, and can help to differentiate AD from other forms of dementia. PET scans would be costly screening tests, but there is a method available now to detect amyloid in the retina of the eye with special visual technology, and this amyloid in the retina is highly correlated with that in the brain. With further testing of this equipment, it may soon be available as a useful tool for detecting early AD or pre-AD, in people at high risk, such as those with family history of AD, the APOE genotype, diabetes or metabolic syndrome, and high risk lifestyle. Since there are now natural methods that have likely been responsible for reversing early AD, it makes more sense to diagnose it early. When we had no effective treatment, what would have been the point of screening people to find out about an incurable condition?

The Bredesen protocol as published is not very detailed about dosages of supplements and herbs or implementation methods, and so for the average person, some guidance may be needed from a practitioner of nutritional or functional medicine to personalize an individual program based on this protocol and to do testing to see what is needed for each goal to be reached.

Now, probably there will be a new drug within the next 2 years that can block the development of amyloid-beta, and which would probably have potentially dangerous "side" effects (as most drugs do), which would be modestly effective, just enough to get approved for treatment, not enough to reverse the condition completely. This would allow people to be partly improved but still sick enough to provide financial benefit to the medical and drug industry as most drugs do for chronic illness. It also likely will be "blockbuster" global financial boon to the drug industry, since it would be recommended by established guidelines, that doctors should prescribe it for everyone at high risk for AD or with amyloid seen on imaging studies. It would be heavily advertised directly to consumers on TV and would be enthusiastically pushed by pharmaceutical representatives who "educate" the doctors. A drug now under investigation has already been on the evening news, with the news anchor using the phrase "sounds promising" to describe it. That is a poor word choice. It doesn't "promise" anything. "Sounds encouraging" would be much more appropriate. How many times in the last 20 years have we heard "sounds promising" regarding a new cancer treatment, which never amounted to a significant benefit? The news media think that people keep hoping for a pill, a simple solution to a complex problem, and that they easily fall prey to the seductive "promise" of a new drug that delivers false hope.

This study by Dr. Bredesen, in contrast, never hit the evening news and probably will not. Do you recall that 2 decades ago the Dean Ornish lifestyle program for heart disease proved for the first time in history that heart disease could be reversed, and it was done entirely with lifestyle methods? It did not receive the new coverage it deserved for such a landmark discovery. Meanwhile the statin drugs, which produced only half measures for reducing heart disease and have many long-term adverse effects, received immediate acclaim. They became standard recommendations in guidelines for doctors to prescribe them widely to all people with "elevated" cholesterol (with the "elevated" number being progressively lowered several times). Now globally they are a financial "blockbuster." Now, 20 some years later, the Dean Ornish program is finally being covered by Medicare in some settings because of its track record of effectiveness. It was never been proven by a randomized double blind placebo controlled trial.

The Bredesen study, likewise, will not be proven by a double blind controlled trial because of the logistic difficultly of such a protocol. Therefore, like many other safe and effective treatments, it will not likely be given FDA approval until the corruption and organized crime network of the drug industry and the FDA is cleaned up, and until the collusion to stifle competition to the drug industry by natural treatments, in violation of anti-trust laws, is stopped. Refer to my last month's article on Dr. Gøtzsche's book about the drug industry and organized crime.

So even if this protocol cannot be proven by the gold standard required by the FDA for drugs, it has scientific validity. I therefore recommend that anyone with early AD or pre-AD or at high risk for it follow the protocol as much as is practical. The entire protocol has very challenging lifestyle changes for some people, and so any part of it that can be implemented is worth doing.

A large part of the plan relates to food, and diet is #1 on the list. The major goal of the diet is to reduce insulin resistance and lower blood glucose and hemoglobin A1c. Our food supply is loaded with sugar, sugary drinks, and refined starches, which drive the obesity, diabetes, and the Alzheimer's epidemics. We need inform ourselves about nutrition in general and understand its complexities and not depend on the food industry or the medical profession to educate us. We need to "question more," (a great slogan from RT, Russian TV). The food industry pays little attention to health, and the "health" care industry pays little attention to food. It is up to us. The food guidelines from the medical or health industry may make oversimplified recommendations such as "low fat" and then 20 year later make a "flip-flop" and turn it around with "low carb," mainly out of ignorance about the complexities involved. What kind of fat, what kind of carbohydrates, what kind of protein?

So by default, due to ignorance of the medical profession and deliberate planning by the food industry, the corporations will be glad to misinform us about food, publicly proclaiming that sugary drinks are not harmful, backing it up with junk science. They put millions into misinformation and scare tactics to defeat GMO labeling laws. They say that disastrous things will happen to our food supply if consumers know what is in their food. The industry is able to sell non-GMO foods to Europe, (no problem), because Europe requires it, and they could for us too if we demanded it, but they save the GMO's for us because they know we will "just take it." What other information about our food are they hiding?

So, in evaluating Dr. Bredesen's study and in taking charge of informing ourselves and of enacting good health measures, we are in the driver's seat. We can't rely on the medical profession or the food, drug, biotech, or tobacco industries to feed us good information. Question more.