The Care and Feeding of Your Brain

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Table of Contents

Introduction

In the past few decades, Americans saw a spike in neurological diseases and dementia that can't be completely explained by an aging population. During the same decades, Western countries – especially the United States – were drastically changing their diets and experienced a rise in heart disease, diabetes, and gastrointestinal issues like gluten sensitivity. If these diseases are studied in isolation, it can be easy to miss the common links.

Luckily, more doctors are taking a functional medicine approach and heeding the scientific studies that point to elements in the modern diet that may underlie these diseases. One overarching theme in 20th and 21st century diet is the concurrent increase in sugar consumption, and the well-intentioned advice of doctors touting low-fat diets.

Dr. David Perlmutter, a board-certified neurologist and a fellow of the American College of Nutrition, reviewed the recent medical literature to explain how research is revealing links between diet-induced inflammation and neurological dysfunction, metabolic disorders and cardiovascular disease. These diet-based inflammation mechanisms are body-wide, meaning that a brain-healthy diet is also a heart-healthy and nerve-healthy diet. On the other hand, an unhealthy diet is likely to cause inflammation of the heart and nervous system. Yet diet interventions and observational studies indicate there is the hope that changing the American diet can help combat, and perhaps prevent, these modern maladies.

Dementia is increasing, and mitochondria are a clue

Brain disease is on the rise

There is an ongoing rise in the rate of dementia and neurological disorders that is threatening to cripple Western cultures, yet the issue is not getting a lot of attention in many circles. One 2013 paper by Dr. Colin Pritchard in the journal *Public Health*, studied disease-related deaths in 10 of the largest Western countries between 1979 and 2010. He found that the United States saw the largest jump in deaths from brain diseases of any Western country in the world. The death rate from brain-related disorders in U.S. men increased 66 percent during that time – for U.S. women it increased 92 percent. These brain-related diseases were striking people as young as 55. Yet, Americans aren't so genetically different from people in other countries. Obviously, some cultural factors are at

play.

Figure 1: The modern American diet is full of carbohydrates.

Dementia is a preventable disease that's also breaking the bank. A 2010 study from the RAND Corporation found that caring for a dementia patient for just one year in the U.S. costs $50,000. That adds up to about $200 billion a year nationwide. In fact, the cost of caring for dementia is twice the cost of caring for heart disease, and three times the cost of cancer treatments. Of course, cost alone shouldn't be the only motivation to act. The emotional costs for patients and families are a louder call to action.

If culture and location are impacting the rates of dementia, then it follows that preventative medicine should be in any discussion of Alzheimer's disease. The rate of brain diseases in a whole nation is not just a roll of the dice.

Mitochondria power the brain

The fundamentals of brain health and the fundamentals dementia prevention have to do with brain energetics as a function of the mitochondria. Neurology now recognizes mitochondria dysfunction as a root of dementia. Alzheimer's disease is an acquired mitochondriopathy. In a process called microglial activation, the brain's macrophages get activated. This turns on the production of what is called inflammatory cytokines. In turn, this leads to up-regulation of free radical production, which damages the very mitochondria that make the free radicals and, ultimately, neuronal death results.

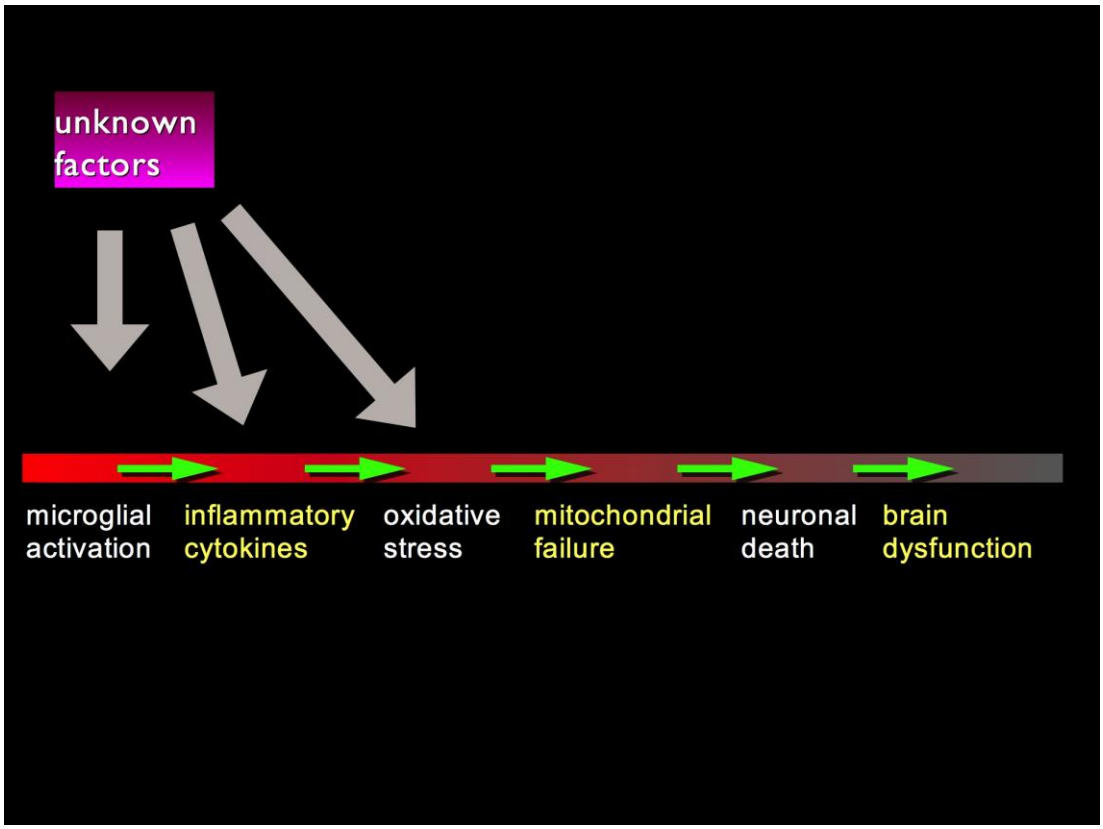

Figure 2: Microglial activation leads to brain dysfunction.

In the unique case of Alzheimer's disease, neurons called cholinergic neurons die off. This observation led to the so-called cholinergic hypothesis of Alzheimer's disease, which explained Alzheimer's as being caused by a reduction in levels of the neurotransmitter acetylcholine in a variety of areas.

Today, doctors have learned it is a little myopic to think that simply replenishing the lost

acetylcholine would be an effective treatment for Alzheimer's disease. And yet, that's where currently available pharmaceuticals for Alzheimer's focus. In a similar vein, if doctors find decreased dopamine in the brain – as happens in Parkinson's disease – then modern medicine's first line of defense is to replace the dopamine through drugs like levodopa, Requip (ropinorole hcl), and Mirapex (pramipexole). However, these replacement approaches ignore all of what happened to a person's brain and body before the disease. This is the difference between the reactive medicine approach and the functional medicine approach, which focuses on what causes illness with a view of a whole person's health and functioning in mind.

Currently, many in the medical field hold the view that there are unknown factors that increase inflammation and oxidative stress in all of these brain diseases. And with the functional medicine approach in mind, tackling a problem like Alzheimer's disease would lead a researcher back to the mitochondria, back to the energy producers in the cell.

Mitochondria work in a feed-forward loop, and any break in that loop will lead to damaged mitochondria and cell death. Acquired mitochondrial DNA damage – via an inherited mitochondrial DNA issue, or via free radials – will lead to cytochrome C activation. The cytochrome C activation then activates nuclear enzymes called caspase enzymes. Caspase enzymes, in turn, become the executioners of the cell: they mediate a process called apoptosis or cell death. In general, mitochondria determine the life and death of cells in the human body.

Mitochondrial dysfunctions are now a focus neurodegenerative disease, which means the search for new drugs will also be a search for ways of increasing mitochondrial function. It's also widely known that energy issues are paramount in neurodegenerative conditions. This makes sense because the brain is an energy sink. The brain of the average person sitting and actively listening takes up 25 percent of a person's energy expenditure in the body. It's the mitochondria that deliver the fuel for energy, for brain metabolism.

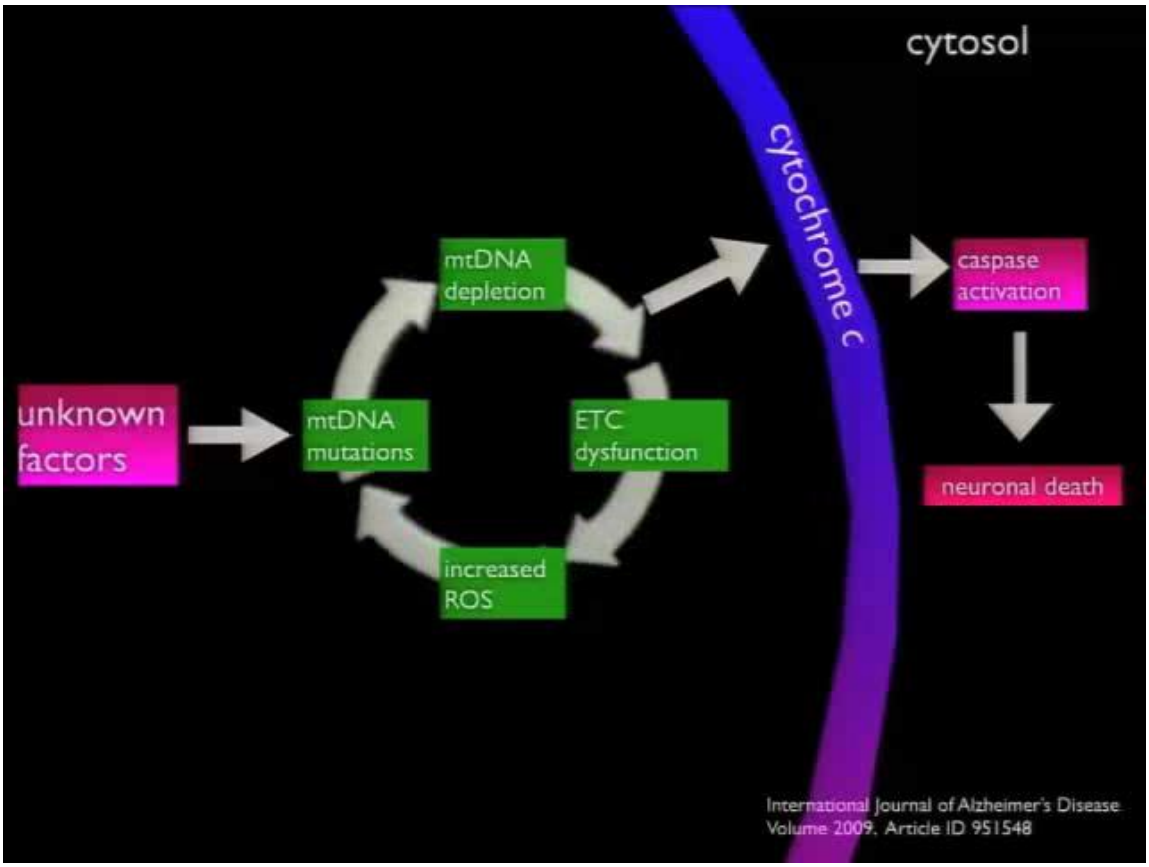

Figure 3: Mitochondrial damage can lead to neuronal death.

Chemicals, mitochondria and the brain

Oxidative phosphorylation is a key to how mitochondria deliver energy to the cell. This metabolic process works by transferring electrons through a series of steps called a chain. As the electrons transfer through the mitochondrial oxidative phosphorylation chain, energy is created. Certain environmental toxins can damage this process, with terrible consequences. For example, a street drug called MPTP was created in the 1980s in California. MPTP was supposed to be a synthetic form of the drug Demerol. Within a few days of taking it, individuals who injected the drug developed full-blown Parkinson's disease. The silver lining of the MPTP discovery was that it allowed research scientists to use MPTP to develop primate models for Parkinson's disease.

Another real-world toxin in Parkinson's is rotenone. Rotenone damages the transfer of electrons from Complex I to Complex II in the oxidative phosphorylation process – and rotenone is used experimentally to create Parkinson's in animals. But it is also the most

widely-used, topically applied pesticide in sheep and cattle in the world.

If mitochondria are damaged, of course, it's not just in the brain that the mitochondria will be dysfunctional, but throughout the body. A person with mitochondrial damage will have a holistic energy issue. For example, a typical Parkinson's patient has fibroblasts (a connective tissue cell) with significant mitochondrial dysfunction. By thinking of Parkinson's as a systemic disease, it becomes clear that whatever is driving Parkinson's is a body-wide problem. Parkinson's patients have dandruff, dry skin, liver issues and even constipation. From a holistic perspective, a doctor or a researcher concerned with Parkinson's should focus primarily on what's going on with the mitochondria: mitochondrial medicine.

Take the previous example of environmental toxins that damaged that transfer of electrons from Complex I to Complex II. That task is normally handled by an electron carrier called coenzyme Q10, or CoQ10. CoQ10's role to transfer the electron from Complex I to Complex II, is precisely where the breakdown takes place in Parkinson's. This is why these electron transfer disrupters cause Parkinson's disease in experimental animal models, and in humans.

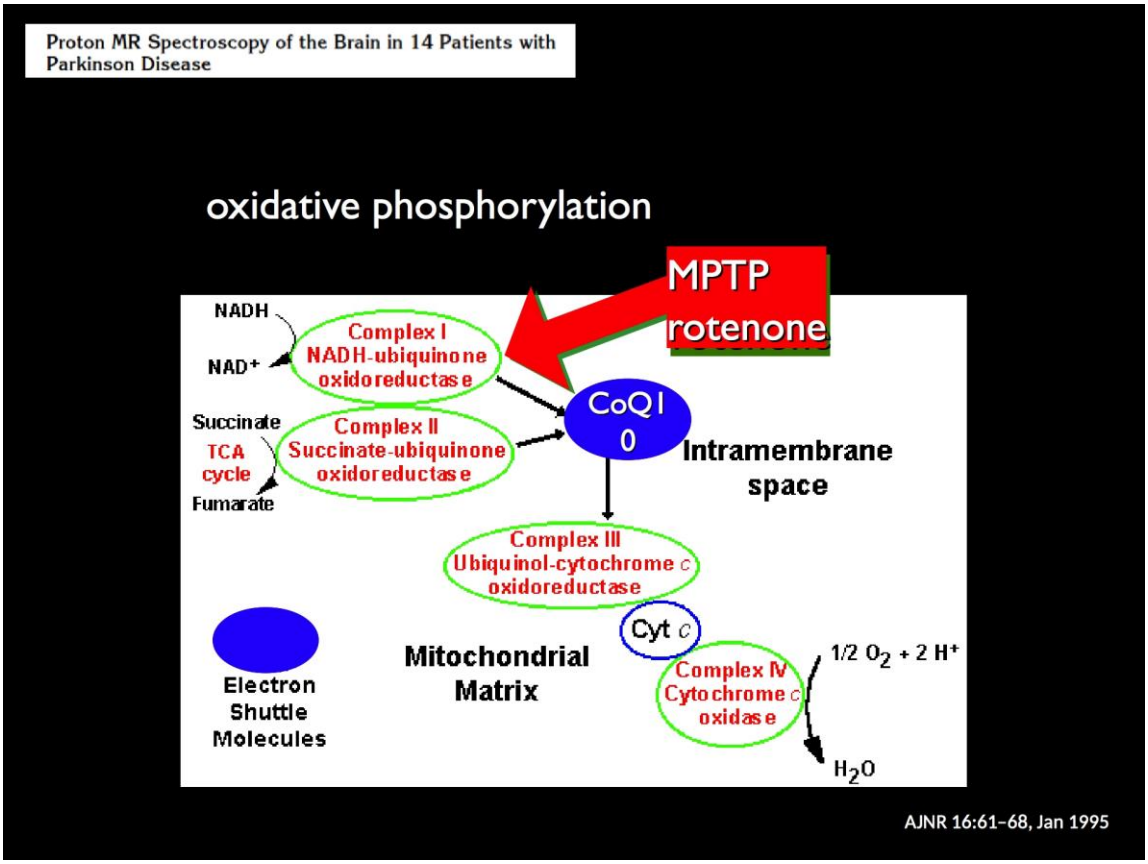

Figure 4: The oxidative phosphorylation process can be disrupted by MPTP.

A 2013 paper in the journal *Neurology* analyzed over 3,000 citations and found a significant increased risk of developing Parkinson's in individuals exposed to pesticides and herbicides. But some of the very same pesticides and herbicides – such as maneb/mancozeb – that are used in agriculture are also used in laboratories to create animal models of Parkinson's. In fact, maneb/mancozeb can be purchased online at Amazon, and is sold as treatments for home vegetable gardens.

All of these risks come back to the oxidative stress model, and the oxidative radicals that damage fat, protein, lipids, and DNA. Oxidative damage is the pathogenesis of Alzheimer's disease – so there is good reason to focus on antioxidants and agents used in combination to up-regulate defense mechanisms against oxidation in treatment.

What diet does to the body

Blood sugar effects on the brain

A look at the modern American diet can give some clues about what triggers oxidative stress. Sugar is a prime example. It's well known that blood sugar plays a role in determining a person's risk for developing dementia – an incurable disease that is affecting 5.4 million Americans.

A compelling paper published in August 2013 in the *New England Journal of Medicine* compared the fasting blood sugar levels (A1C) and cognitive abilities of a group of people over the course of seven years. By the end of the study, the researchers saw a dramatic correlation in risk for developing dementia based upon fasting blood sugar alone. This held true, even if the individual's blood sugar was at the lowest end of the high range, and still considered safe for diabetes. Of course, blood sugar is controlled by food, and that's why carbohydrates are so devastating to the brain.

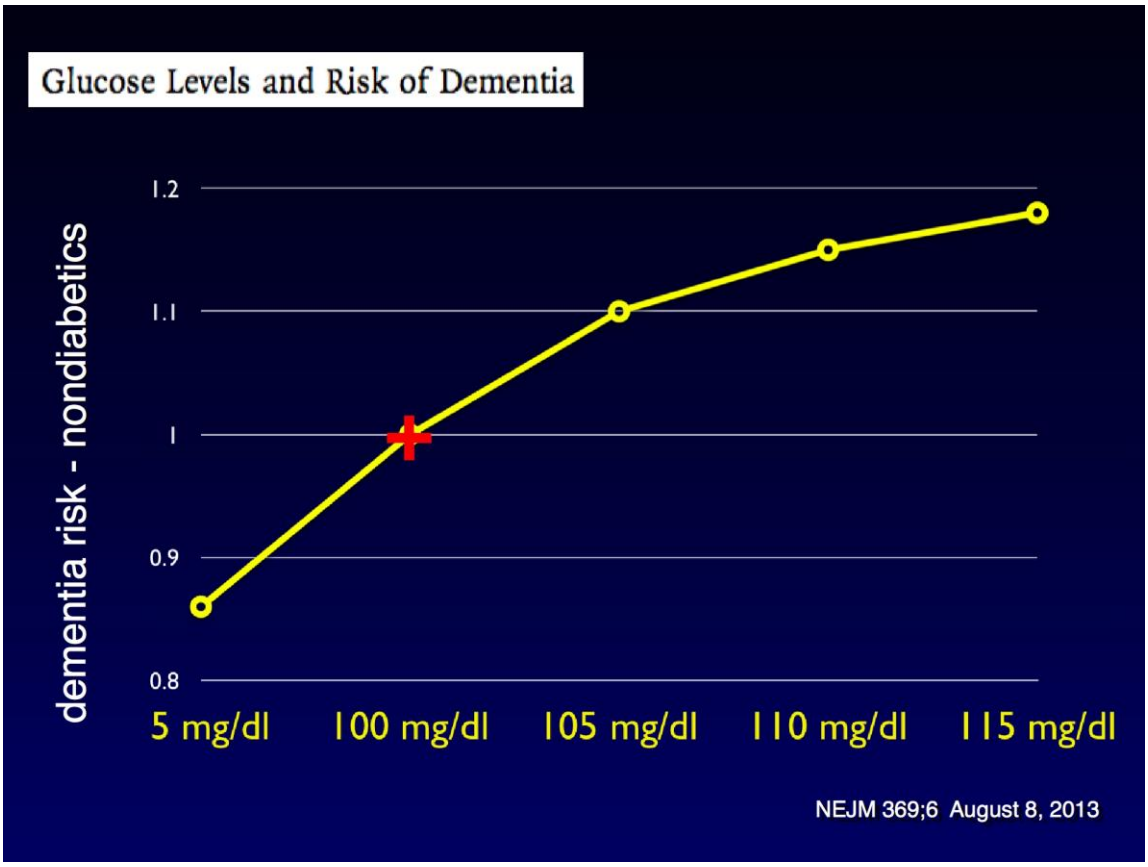

Figure 5: Dementia risk increases with high blood sugar on a continuum.

Higher levels of blood glucose are specifically toxic to memory, and will shrink the hippocampus, or so-called memory center of the brain. A November 2013 study published in the journal *Neurology* found a strong correlation between non-diabetic individuals, their average blood sugar and their delayed recall. The higher the hemoglobin A1C, the less recall these individuals had and the lower their learning ability.

One of the mechanisms that is causing this blood-sugar-brain connection is something called glycation of protein, or sugar binding to protein. When sugar binds to proteins, two negative things happen: inflammation increases, and oxidative stress increases. Imaging studies have even tracked the correlation between hemoglobin A1C, and the size of brain structures. High blood sugar can cause more dramatic annual brain shrinkage than the so-called Alzheimer's gene, APOE e4. And while people can't control their genetic destiny, it's good to remember that people can control their A1C with the foods they choose. Even with blood sugar levels in a normal range, lower blood sugar levels are better for long-term brain health with regard to memory function, as well as memory-relevant brain structures like the

hippocampus.

Given all these research, it's time to challenge the idea that unknown factors are influencing free radical mediated stress in brain diseases. When proteins are glycated, the amount of up-regulation of free radical production can be increased by as much as 50 fold. Bread, orange juice, and fruit are all so-called healthy choices that, when eaten in excess, can actually glycate proteins and cause free radicals. This reality has slowly gained public awareness towards why low carbohydrate diets are very important.

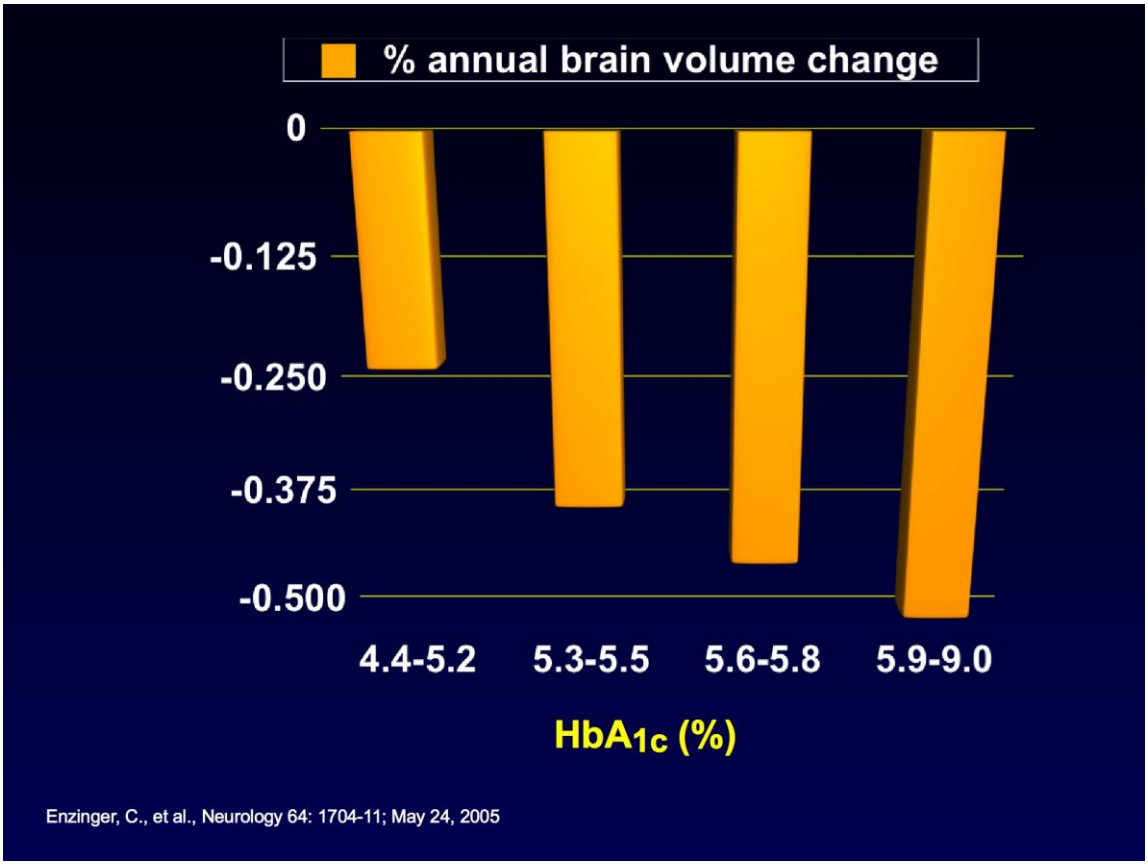

Figure 6: The brain loses volume faster as blood sugar (HbA1c) increases.

Back in 2002, a study was published in the *New England Journal of Medicine* that followed the effects of treating people with diabetes with metformin, a placebo, or diet and lifestyle changes. The study found that changing a person's lifestyle reduced their risk of death by an additional 50 percent compared to treatment with metformin.

This diet and lifestyle based influence on the risk of death then begs the question of treatment. Currently, metformin is a popular and effective treatment for reducing blood

sugar. However, lifestyle and prevention may have an even bigger impact. It may be time to look at food beyond the notion of fat, protein, carbohydrates – macronutrients – and the micronutrients of minerals and vitamins. Food is targeting our genome. It's information. The U.S. may have seen the highest increase in neurodegenerative conditions on the planet, but it is not because Americans are so genetically different from others in Europe and in Asia. It's because of the signals that the American diet is sending to the genome.

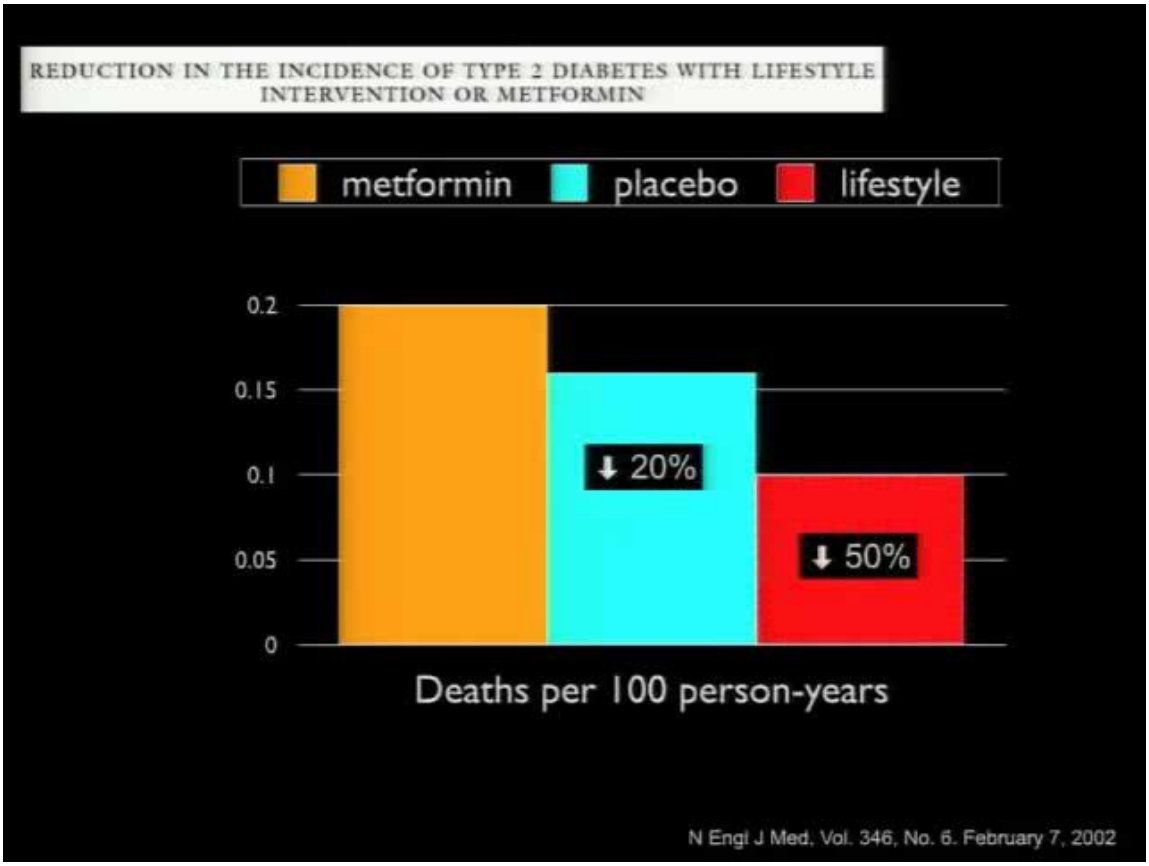

Figure 7: Lifestyle changes can greatly reduce death risk in diabetes patients.

A system-wide diet approach

Fat is a friend. Especially in the context of how food sends information to the genome. The average U.S. grocery store is full of chips and soda, yet at the same time the American public is worried about fructose, gluten and food sensitivity. Part of the problem may be the media and the medical establishment's treatment of diet and brain health as if it were a different relationship than diet and heart health, or bone health, or immune health.

Take, for example, a study by the Mayo Clinic published in 2012 in the *Journal of Alzheimer's Disease*. Researchers in the study analyzed the diets of a sample of elderly people and tracked their risk of developing dementia over time. They found that a person's relative dementia risk increased by 90 percent on a high-carbohydrate diet. But a high-fat diet, that included saturated fat, reduced dementia risk by 36 percent. Those who ate the most fat had a 44 percent risk reduction for dementia.

The benefits of a high-fat diet may seem more intuitive if the diet of early humans is taken into account. Before agriculture, there was a distinct lack of carbohydrate sources: no apple orchards, no wheat fields. Ancient humans' way of getting food was to chase an animal for three days until it dropped. Since there were no carbohydrates readily available, people powered their bodies with fat instead. Fat is an incredible endurance fuel.

Unfortunately, the American public was given the opposite diet advice in the late 1980s and early 1990s. Back then, low-fat diets or no-fat diets were touted as healthy. However, if someone cuts out fat from their diet, they will naturally eat carbohydrates to compensate. After the public got the low-fat message, the rates of diabetes in the U.S. went up three fold. And it's worth noting that diabetes doubles a person's risk for Alzheimer's disease.

Strangely enough, fat may also help people with their heart health. A two year comparison of low-fat, Mediterranean and high-fat diets published in 2008 in the *New England Journal of Medicine* found that high-fat diets resulted in greater weight loss, better cholesterol levels, better fasting insulin levels, better triglyceride levels and lower levels of inflammation markers. An inflammation marker affected by diet – C-Reactive protein – is also a marker for coronary artery disease and Alzheimer's disease.

There's no intuitive reason to suppose that a diet that is good for the cardiovascular system would be different than a healthy diet for the brain. One 2013 study in the journal of *Neurology, Neurosurgery and Psychiatry* investigated different diets among 522 elderly people without dementia. After six and a half years, the people on the higher-fat diets had the lowest cognitive declines, while the people on the low-fat diet had the greatest cognitive declines.

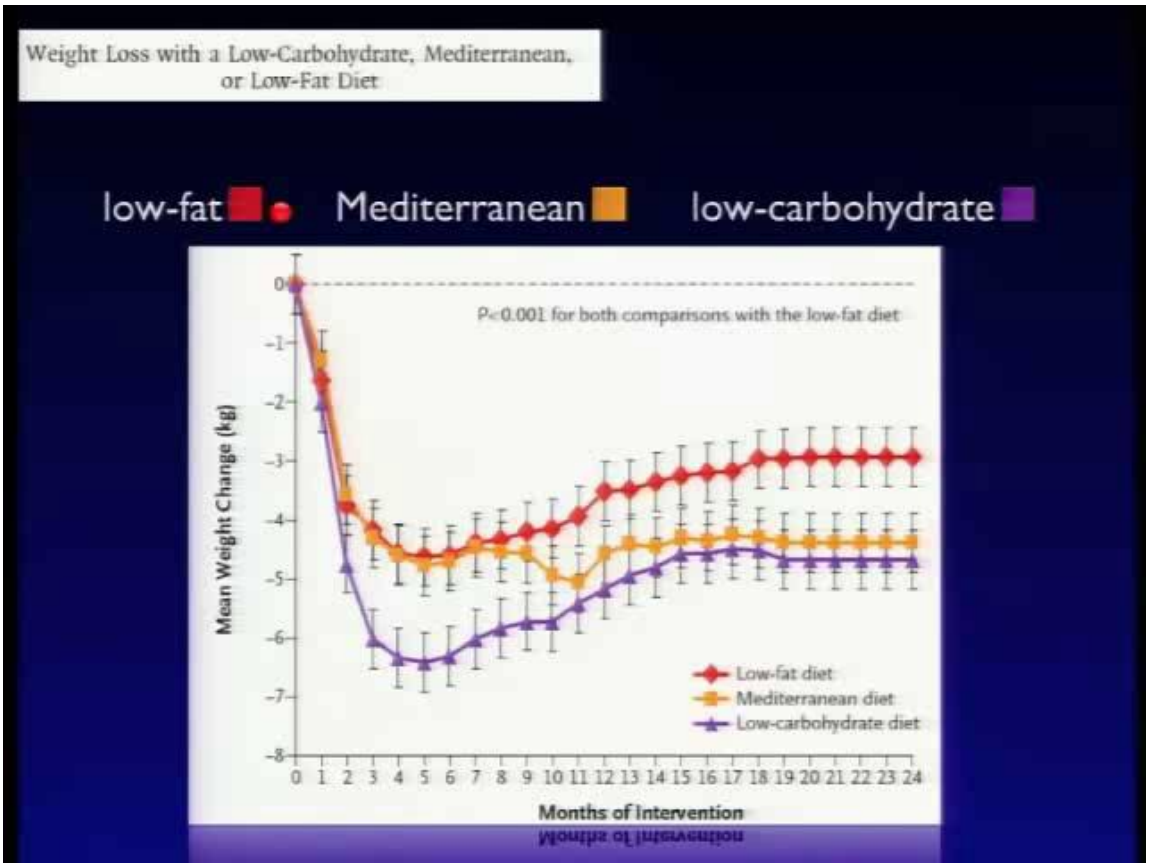

Figure 8: Low-fat diets are the least effective diet for weight loss over time.

Another 2013 study published in the *New England Journal of Medicine* found low-fat diets so harmful, the study had to be stopped early. The study, published in 2013, prescribed a Mediterranean diet, a standard low-fat diet or a high-fat diet to a group of more than 7,000 people. There was such a dramatic reduction (30 percent) in stroke or heart attacks in the group of people eating the higher-fat diets compared to the low-fat diets, that the researchers thought that it was unethical to finish the experiment. And yet, the old advice of eating a diet low in fat and cholesterol still permeates doctors' offices and grocery store advertisements.

The Food Pyramid put out by the USDA is a visualization of this carbohydrate-centric advice. The base of the pyramid seemingly encourages people to eat as many carbohydrates at they want, but implies the fat at the top – even olive oil – should be used as sparingly as possible.

Figure 9: A visual representation of the food pyramid.

The mechanism behind the protective effect of higher-fat diets might be antioxidative and anti-inflammatory. In other words, including more fat in a diet may counter oxidative stress and inflammation. On the other hand, the high-carbohydrate diet that is common to the U.S. may do the opposite.

One challenge to changing the modern, low-fat and high-carbohydrate diet is recognizing the source of all the sugar. No reasonable person would wash down breakfast with a can of cola and expect to call it healthy. A typical can of cola has 39 grams of carbohydrates. Yet, a 12 ounce glass of orange juice has 36 grams of carbs; that is equivalent to 9 teaspoons of pure sugar. Such a spike in carbohydrates will signal insulin to create fat through a known process called lipogenesis.

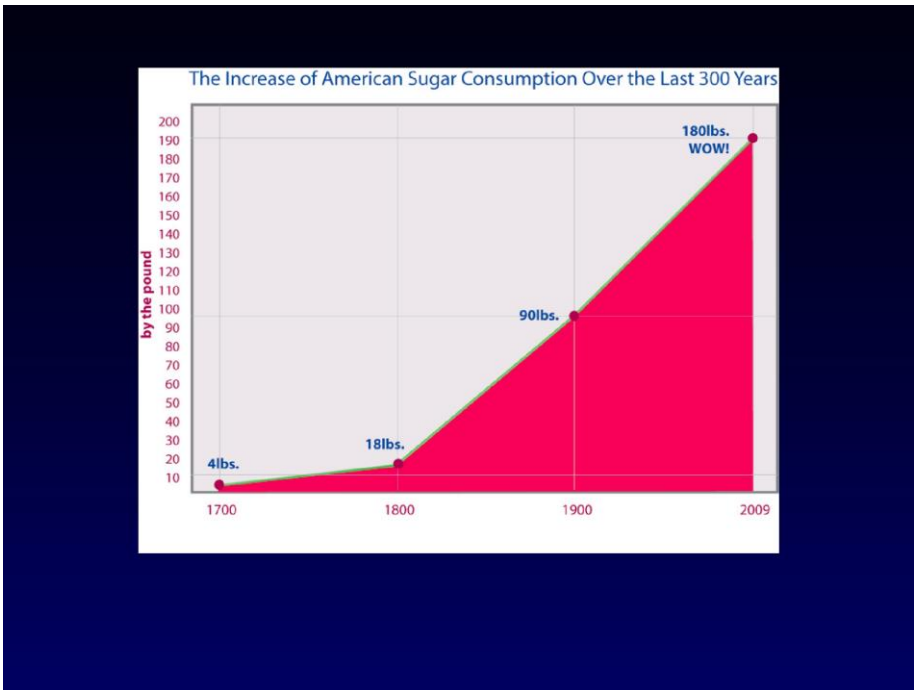

Figure 10: Sugar consumption in the U.S. has risen drastically.

The average annual per capita sugar consumption in the United Sates has risen from 18 pounds a year to over 100 pounds a year since the mid-1800s. Recent studies have confirmed the unhealthy effects of all this added sugar. A 2014 study in the J*ournal of the American Medical Association* followed nearly 12,000 people, and found those whose daily calories consisted of 25 percent added sugar had a threefold risk of cardiovascular death. The good news is that the mean percentage of daily calories from added sugar is now on the decline in the U.S.

Gluten and modern medicine

Gluten mediates inflammation

Food and digestion matter, even when an illness doesn't seem to be related to digestion at first. Aside from sugar, the link between diet and inflammation has garnered even greater attention in recent years by way of gluten. It's long been known that gluten – certain proteins found in wheat – is a culprit in gastrointestinal inflammation in celiac disease. But more clinicians are now documenting how gluten can induce body-wide inflammation in

individuals without celiac disease.

Dr. Alessio Fasano, who was honored with the Linus Pauling Award for his work in terms of gluten, revealed that gluten mediates inflammation through an interesting series of cascades. He demonstrated that when a person consumes gluten, gliadin (a component of gluten) can free itself when gluten is digested and can stimulate a receptor on enterocytes which then leads to the transcription of zonulin. The zonulin then becomes extracellular and binds to its receptor, which leads to the disassembly of the tight junction between enterocytes. This is an issue because the cells then separate and become "leaky." Gluten signals zonulin, and zonulin leads to leaky gut.

Furthermore, Dr. Fasano described that this mechanism occurs in 100 percent of humans, while only 1.6-1.8 percent will go on to develop celiac disease, and another 18-30 percent will become gluten sensitive. What is even more compelling is that once that junction has become disruptive, proteins from the digestion of not just of gluten but all of our foods can gain access to the bloodstream and then stimulate the immune system's macrophages and T-cells, up-regulating inflammation. Dr. Fasano has proven that this is happening in celiac disease and type 1 diabetes, and he postulates that this may also be a powerful mechanism in multiple sclerosis, asthma, and, possibly, gliomas. All this gluten-derived inflammation should not be ignored – especially considering the cornerstone of neurodegenerative conditions is inflammation.

Gluten's broader effect on the brain

Compelling research from Dr. Fasano has also revealed that this same gluten-zonulin inflammation is also disrupting the blood-brain barrier. It is possible not only to have a leaky gut, but also a leaky blood-brain barrier. In Dr. Fasano's 2011 study in *Physiological Reviews*, he found a strong correlation between zonulin levels and flare activity of multiple sclerosis. And gluten sensitivity alone can cause enough disruption across the blood-brain barrier to create visible changes in the white matter of the brain, according to a 2010 paper published by Dr. Marios Hadjivassiliou in the journal *The Lancet Neurology*.

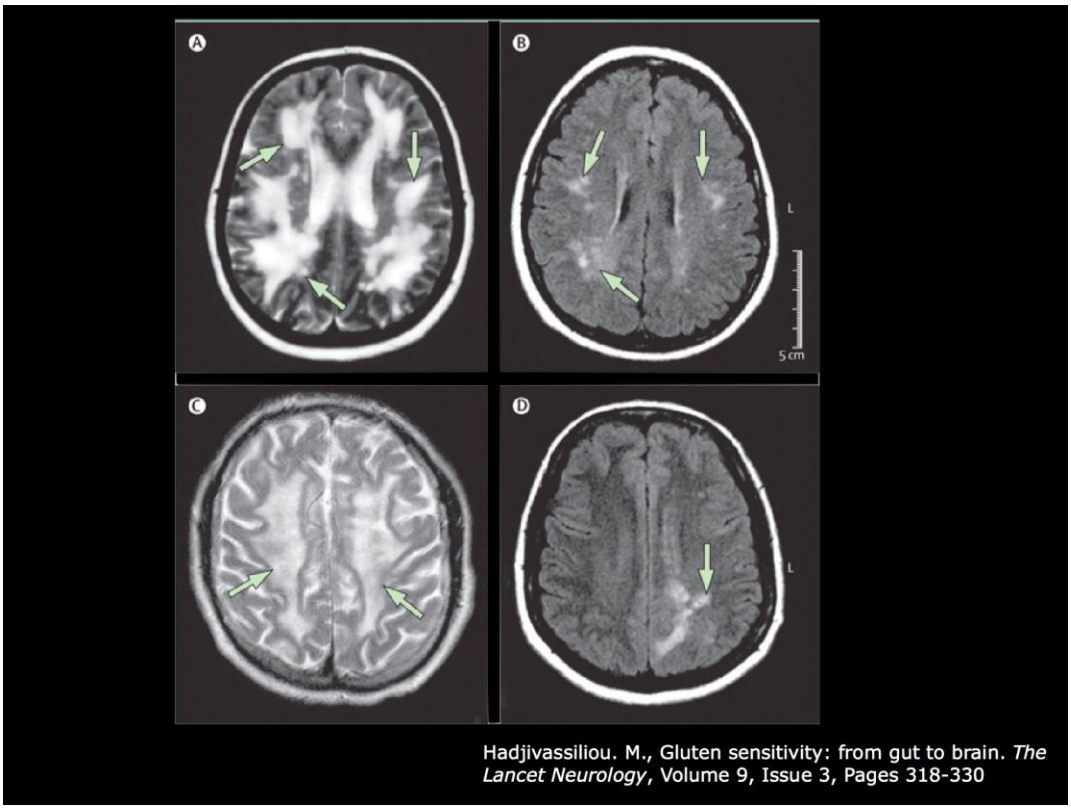

Figure 11: Imaging shows gluten sensitivity's effect on the brain.

All this recent evidence undermines the presumption that factors causing inflammation in human physiology are unknown. Gluten sensitivity can be a powerful player in terms of turning on this cascade of mitochondrial dysfunction, damaging mitochondria and, ultimately, leading to cellular death. It is certainly true that gluten sensitivity can cause the jejunal villi to become atrophic. But brain inflammation related to gluten sensitivity should also be acknowledged as a serious problem.

Dr. Hadjivassiliou and his team in England recently collaborated with Dr. Fasano and other experts to catalogue the variety of neurologic consequences of gluten sensitivity. The team found gluten sensitivity may contribute to abdominal pain, headache, "foggy mind," fatigue, depression and more. When diagnosing gluten sensitivity, extra-intestinal symptoms such as these should be strongly considered. It's now documented that gluten sensitivity up-regulates inflammation and that it can have manifestations throughout the body.

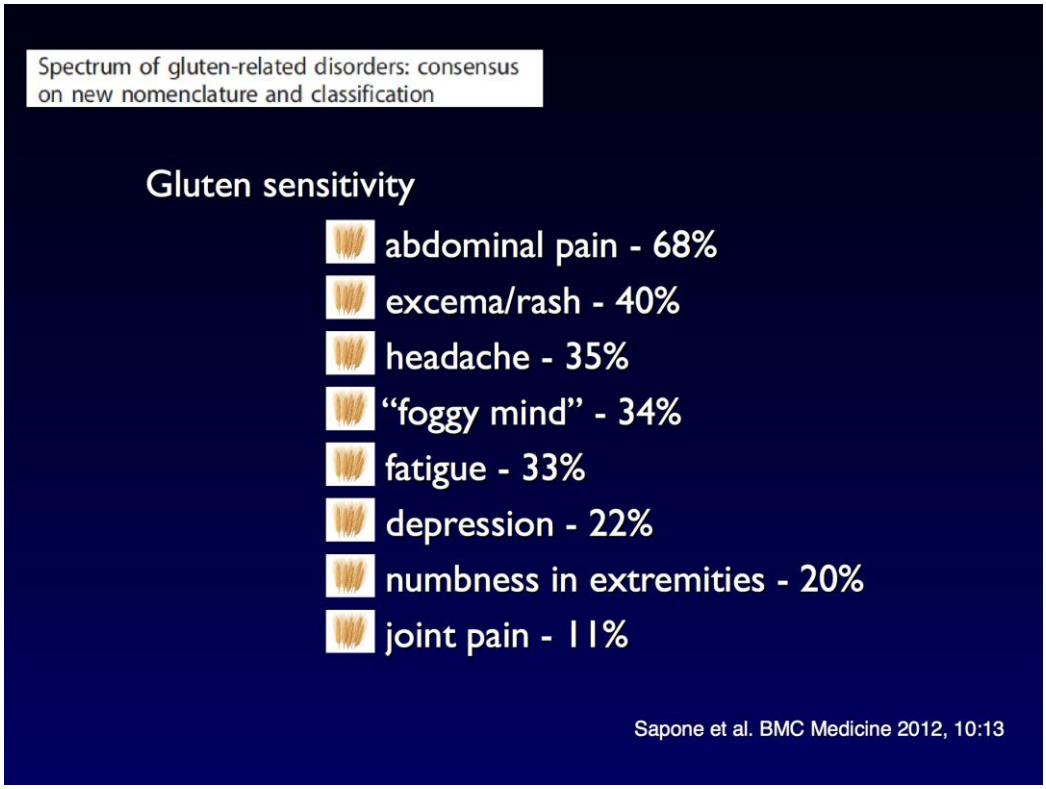

Figure 12: Gluten sensitivity can have body-wide effects.

In fact, in his 2010 *Lancet* study, Dr. Hadjivassiliou found most patients who present with neurologic manifestations of gluten sensitivity have no gastrointestinal symptoms. Other neurological presentations of gluten sensitivity may include peripheral neuropathy, encephalopathy, myopathy, myelopathy, and chorea movements.

A gluten-free diet for tremors

A few case studies of people with movement disorders related to gluten sensitivity have shown vast improvements with gluten free diets alone. Take for example, a 23-year-old man with a six month history of tremors and dystonia. He was first offered beta blockers and Botox injections in his arms and legs as treatments. But, interestingly, he also had bowel complaints and a past history of ADHD symptoms: both of which are commonly related to gluten sensitivity. Based upon his gastrointestinal issues and potential learning disability, some anti-gliadin antibodies tests were run, and were dramatically positive. Nine months of a gluten-free diet resulted in dramatic reductions in his tremor and dystonia.

In another case study, a 55-year-old woman had a five year history of progressive twitching of the left side of her face. She had undergone multiple treatments with Botox, and was diagnosed with a hemifacial spasm. She also suffered from migraines, hypothyroidism and iron deficiency – all clues to gluten sensitivity – as well as a vitamin D and B12 deficiency. Her MRI revealed she had a white matter lesion suggestive of multiple sclerosis. This woman also tested positive for gluten sensitivity and a variety of gluten-related markers. She was treated with glutamine, probiotics, vitamin D, and a gluten-free diet. After 32 days, her muscle twitching reduced significantly and she was able to return to essential life activities, including driving a car.

Conclusion

A deluge of new research has shown links between our modern high-carbohydrate, low-fat diet, and increasing rates of certain diseases. As neurodegenerative disorders rise, so too has sugar consumption in the Western world. Yet, new research has shown that healthy, fat-rich diets have a myriad of benefits to the brain on the macro-scale in brain function, and benefits on the micro-scale in terms of inflammation. Sugar's inflammatory effects may cause a disruption of healthy mitochondrial function that will sap energy from the brain, and can lead to body-wide ailments. Recent studies have documented blood sugar's effect on a wide collection of troubles from the size of the hippocampus, to diabetes, stroke and dementia risk.

Another diet-based source of inflammation is gluten sensitivity. Although the gluten-free diet is a booming billion dollar industry in the U.S., simply switching from carbohydrates to gluten-free carbohydrates will not solve the larger inflammatory diet issue. As with high blood sugar, new research into gluten-based inflammation suggests that what you eat may affect your whole system from gut, to brain, to nerves. Gluten-free diets have given hope to some people with neurological, immune and, of course, intestinal issues. Luckily, more diet-based interventions like these are starting to demonstrate the preventative power of a systemic approach to diet, inflammation and health.

Biography

David Perlmutter, MD, FACN, ABIHM is a Board-Certified Neurologist and Fellow of the American College of Nutrition. He received his M.D. degree from the University of Miami School of Medicine where he was awarded the Leonard G. Rowntree Research Award. After completing residency training in Neurology, Dr. Perlmutter entered private practice in Naples, Florida. Dr. Perlmutter is a frequent lecturer at symposia sponsored by such medical institutions as Columbia University, the University of Arizona, Scripps Institute, New York University, and Harvard University. He has contributed extensively to the world medical literature with publications appearing in The Journal of Neurosurgery, The Southern Medical Journal, Journal of Applied Nutrition, and Archives of Neurology. He is the author of: *The Better Brain Book*; *Raise a Smarter Child By Kindergarten*; *Power Up Your Brain;* New York Times #1`Bestseller, *Grain Brain*; and *Brain Maker*, also a New York Times bestseller. In 2002, Dr. Perlmutter was the recipient of the Linus Pauling Award for his innovative approaches to neurological disorders and in addition was awarded the Denham Harman Award for his pioneering work in the application of free radical science to clinical medicine. He is the recipient of the 2006 National Nutritional Foods Association Clinician of the Year Award, the Humanitarian of the Year award from the American College of Nutrition in, 2010, and the 2015 Media award from the American College of Nutrition.