

# DOES DEMENTIA EXIST? DISPELLING THE MYTH

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*The great enemy of truth is very often not the lie—deliberate, contrived and dishonest—but the myth—persistent, persuasive, and unrealistic. Too often we hold fast to the clichés of our forebears. We subject all facts to a prefabricated set of interpretations. We enjoy the comfort of opinion without the discomfort of thought.*

—John F. Kennedy

Obesity is obvious. Just look around the American landscape. But memory loss and cognitive decline is invisible—and more fearsome. Alzheimer's disease will affect 30% (and some experts say 50%) of people over 85 years old, which is the fastest growing segment of the population. The prevalence of Alzheimer's is expected to increase 3-fold by 2050 affecting 14 million people, at an annual cost at \$83.9 billion to our healthcare system and society,<sup>1</sup> which doesn't even begin to account for the untold suffering on families and caregivers. It is now the seventh leading cause of death.<sup>2</sup>

With Alzheimer's we are facing a global problem. It is projected to increase 285% in North America, 534% in South America, 476% in Africa, and 497% in Asia by 2050.<sup>3</sup> Even small progress in preventing the disease and slowing its progression will have a profound impact on the personal and financial costs we will bear.

If we want to do something other than provide palliative care, we must ask certain questions. What is dementia? What causes it? Is it uniformly the same disease or the heterogeneous manifestation of multiple genetic and environmental insults? Can it be prevented? Can it be slowed, stopped, or even cured? And why are we seeing growths of epidemic proportions of the incidence of cognitive dysfunction, mild cognitive impairment (MCI), and dementia?

Conventionally dementia falls into 2 main categories—Alzheimer's and vascular dementia, with many other minor variations. Therapy is limited to 2 main categories of medication—acetylcholinesterase inhibitors and NMDA (N-methyl D-aspartate) receptor antagonists, neither of which addresses the causes of dementia and both of which are marginally effective (if at all) and have significant side effects. New treatments such as vaccines are on the horizon.

Emerging research indicates that inflammation, oxidative stress, insulin resistance, and mitochondrial dysfunction are key mediators of brain degeneration. But rarely is the question explored

as to why these processes occur. What are the proximal causes? Is there another clinical model for preventing, treating, and even reversing cognitive decline and dementia? Even more, mounting research suggests that loss of cognitive function is not a homogeneous process and that Alzheimer's or dementia is not a single disorder but a common clinical manifestation of disordered neuronal function arising from a multitude of genetic, environmental, and lifestyle factors unique to each individual. Even if large-scale system-based clinical trials are yet to be done—or difficult to do—if we can assemble existing data into safe lifestyle-based and nutritional interventions for optimizing brain function, then we might hold back the tsunami of broken brains and broken lives we face.

## HEALING THE MIND AND REVERSING DEMENTIA: IS IT POSSIBLE?

New research suggests that focusing on the “disease” called dementia and finding drugs to modify downstream effects of brain injury such as insufficiency of acetylcholine misses the opportunity to address the real problems. In fact, “dementia” does not exist but is simply a common collection of symptoms that explain nothing about the underlying etiology or pathophysiology. These include inflammation, oxidative stress, insulin resistance and other hormonal dysregulation, mitochondrial dysfunction, nutritional deficiency, and toxic injury. The question is not how to treat dementia, because it is not a single disorder, but how to find the underlying reasons for our broken brains and how to fix them.

The cognitive dysfunction we call dementia is simply the way the body expresses injury to a myriad of insults that can be quite different from person to person. No 2 “dementias” are exactly alike. But how do we apply molecular personalized genomic medicine to such a complex disorder?

The answer is quite simple. Ample science lays out the patterns of dysfunction in dementia and, to a great degree, most of the precipitating causes. Then our individual genetic differences and predispositions set us up for biological breakdown from the same few common insults—toxins such as mercury, digestive imbalances, nutritional deficiencies or excesses, stress, allergens, infections. These in turn, lead to the altered physiological processes we see in the “dementias”—inflammation, oxidative stress, mitochondrial dysfunction, and insulin resistance.

We have to think about individuals, not diseases. In medicine our differences (genetic predispositions, environmental exposures, diets, and stresses) are more important than our similarities. Sometimes the practice of medicine lags behind the science, and sometimes the practice gets ahead of the science. Genetic testing

puts us squarely in the middle of that dilemma.

We are at a crossroads where the old ideas we have about disease and diagnosis become less meaningful as we understand more and more about the importance of individual differences in determining illness. This is a time when personalized medicine will replace medicine based on diagnosis and disease. In fact, disease and diagnosis as we know it (ICD-9 classification of diseases) will soon be an obsolete concept, an artifact of medical history like bloodletting or phrenology (the art of diagnosis based on the shape of your skull, popular in the 19th century).

#### AN “N” OF 1: REVERSING DEMENTIA

As a medical student, I participated in a public health research project in a remote Nepalese village. In exchange for the villagers' help, we offered an improvised outdoor medical clinic. One man brought his mother to our clinic after carrying her on his back for 10 days through the Himalayas. I asked how we could help. He said his mother was blind. She had cataracts. There was nothing we could do.

That is how I felt about my patients with dementia until I met “George.” George presented with dementia. His story is an example of how treating a person—not a disease—leads to improved clinical outcomes; how environmental influences on genetic predispositions—mostly mercury exposure in this case—can lead to any number of diseases depending on individual genetic variations.

George presented with a diagnosis of dementia after a comprehensive neurological evaluation including neuropsychological testing, MRI (magnetic resonance imaging), MRA (magnetic resonance angiography), and SPECT (single-photon emission computerized tomography) scanning. When he came with his wife to see me, he could no longer manage his business affairs, had become increasingly unable to function at home, and had to withdraw from family and social relationships.

#### HOW THE ENVIRONMENT AFFECTS YOUR GENES: A CASE OF MERCURY POISONING

Chronic diseases, like Alzheimer's, cardiovascular disease, or cancer are usually multi-gene disorders. It is not 1 gene but the interaction between many genes, their variations or single nucleotide polymorphisms (SNPs), and the environment that puts someone at risk for a chronic disease such as dementia. That is why we will never find “the” gene for Alzheimer's—or heart disease, cancer, autism, or depression.

In the case of George, whose mind and life were evaporating, I looked deeply into his genes and the biochemistry his genes controlled and found places we could improve things. He was homozygous for apo E4, a high-risk gene for Alzheimer's disease<sup>4</sup> that also predisposes to dyslipidemia and impaired heavy metal detoxification from the brain.<sup>5</sup>

A 6-hour DMPS provocation challenge test for heavy metals\* revealed mercury of 350 mg/g creatinine (normal < 3 mg/g creatinine). Sources of mercury include vaporization of dental fillings or environmental exposures from tuna fish or air pollution.<sup>6</sup> George lived his life in an industrial area with large coal burning plants and had many dental amalgams.<sup>7</sup> Mercury toxicity is a potent neuro-

toxin linked to many neurological disorders including dementia.<sup>8</sup>

In one study of 465 patients with chronic mercury toxicity, 32% had severe fatigue, 88% had memory loss, and almost 30% had depression. These symptoms and mercury poisoning were much more common in people with the apo E4 gene. Removal of amalgam fillings combined with a mercury detoxification program resulted in significant symptom reduction.<sup>9</sup>

Other genes act synergistically with apo E4 to amplify risk. Common polymorphisms of genes regulating glutathione metabolism, the main detoxifier of metals in the body, such as glutathione-S-transferase (GST),<sup>10</sup> increase risk of cognitive impairment. Combinations of GST and apo E4 polymorphisms further increase risk for dementia.<sup>11</sup> George carried the GSTM1 null or absent SNP. Carriers of the null (or absent) polymorphisms for GST have higher total body burdens of mercury.<sup>12</sup> Genes load the gun, and the environment pulls the trigger.

George had an elevated homocysteine and was homozygous for methylene tetrahydrofolate reductase (MTHFR),<sup>13</sup> which impairs methylation and increases homocysteine, which can double the risk of dementia.<sup>14</sup> Disruptions of 2 key interdependent, interconnected biochemical cycles are at the root of the physiological dysfunction we see in most chronic diseases. These are the methylation and trans-sulfuration (glutathione metabolism) cycles. They are necessary for proper detoxification and redox balance, as well as modulation of immune response, control of gene expression, membrane function, and more. Polymorphisms in any of the enzymes facilitating these cycles may increase the risk of chronic disease, particularly neurologic and psychiatric disorders such as dementia, autism, ADHD, and depression. Adequate concentrations and active forms of nutrient cofactors involved in these cycles, especially methylcobalamin (B12), 5-methyl-tetrahydrofolate (5-MTHF), and pyridoxine (B6), as well as adequate dietary sources of sulfur are essential for proper function of the methylation and sulfation cycles.

Lastly, George had a polymorphism of cholesterol ester transfer protein (CETP). This gene limits HDL reverse transport of cholesterol and increases risk of hyperlipidemia. CETP polymorphisms act synergistically with apo E4 to increase the risk of dementia.<sup>15</sup>

For George, those SNPs (apo E4, GSTM1, MTHFR, CETP) acted synergistically to increase his risk and made him in one way or another susceptible to environmental insults from mercury overload, nutritional deficiencies of folate or B<sub>12</sub>, and dietary influences on cholesterol and insulin sensitivity. Other studies show similar polymorphisms in autism<sup>16</sup> and depression.<sup>17</sup> In fact, these may be simply different manifestations across the age spectrum of the same “disease.” The genetics, biochemistry, and physiology of these conditions overlap and arise from common roots. What is critical to remember is that these genes are highly regulated and their expression modified by nutrient and lifestyle inputs.

\*Blood levels of mercury only reflect recent exposure from pollution or fish consumption, but a provocation test identifies total body burden of mercury. Studies have found that using DMPS increases mercury excretion from 3- to 107-fold. The chelating agents or drugs, DMPS and DMSA, are both used to treat heavy metal toxicity.

## PERSONALIZED MEDICINE: A CURRENT REALITY OR FUTURE POSSIBILITY?

Based on George's unique genotype and his phenotypic expression (elevated body burden of mercury, hyperlipidemia, insulin resistance, hyperhomocysteinemia, low glutathione, and impaired detoxification), a therapeutic plan was developed to address his entire systemic dysfunction. George also had a 30-year history of irritable and inflammatory bowel diseases, which has been linked to dementia and other neuropathologies.<sup>18</sup>

The single gene, single disease, single drug model is inappropriate for complex multi-gene systemic disorders with common manifestations but differing etiologies such as dementia. The components of his therapeutic plan were design to remove toxic triggers (mercury, poor diet, dysbiosis), while optimizing nutrient-regulated gene expression. Doing just one thing wouldn't help George. Treatment required addressing all the imbalances, the causative factors, and their effects systematically.

Treatment included careful mercury detoxification including safe amalgam removal and chelation.<sup>19</sup> Phytonutrients and nutrients that upregulate glutathione, including cruciferous vegetables such as kale, watercress, and cilantro; herbs such as milk thistle; nutrients such as selenium and zinc, were added to his diet. His hyperlipidemia and insulin resistance were managed with a low glycemic load, plant-based high-fiber whole foods, organic diet, and exercise.

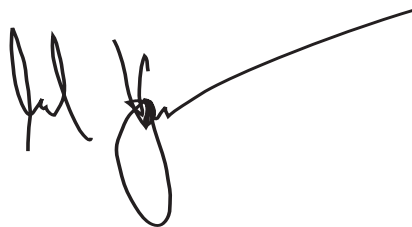
To further improve his genetic limitations in methylation and sulfation, he was treated with high doses of MTHF (methyl-tetrahydrofolate),<sup>20</sup> methylcobalamin,<sup>21</sup> and B<sub>6</sub>. To address his gut inflammation, food allergens were eliminated, small bowel bacterial overgrowth was treated, and enzymes and probiotics were replaced. Additional basic nutritional support, including a multivitamin and omega 3 fatty acids,<sup>22</sup> was provided.

After a year of aggressive therapy that was matched to his quirky genes and biochemistry—not his diagnosis—George had a remarkable and dramatic recovery. Before I saw him, he could not manage his business nor did his grandchildren want to be around him. After matching his treatment to his genes, he was again to function able, and his grandchildren loved being with him.

Although this area of genetic testing and nutrigenomics is new and more research is needed to help us refine our understanding and treatment, there are ways to look through new doors into an entirely new era of medicine—one that no longer focuses on the disease but on the person and his or her uniqueness. Widespread gene testing is not ready for primetime, but it can be a helpful guide in understanding the origins and the risks of some chronic illnesses. But we have to recognize that it is the interplay of many genes interacting with the environment that determines our health. What we do know is that there is no single gene for Alzheimer's—or autism, depression, heart disease, or cancer. In fact, those diseases, as single homogeneous, uniform conditions, do not exist. We must give up that myth.

Instead, there are common variations in the symphony of our gene patterns that are integral to many chronic diseases. These patterns vary from person to person and are highly influenced by diet, stress, infections, allergens, and toxins.

The time has come to focus on systems approaches to complex systems disorders. Treatment based on mechanism, genetics, biochemistry, and physiology will supplant diagnosis-based treatment. Clinicians can begin to navigate with a different map for the territory of illness than the one we received in our training and in the process can become re-enchanted with medicine and the possibility of healing where there was none.



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