ALZHEIMER'S DISEASE

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This paper deserves an acknowledgement at the outset. I would have been caught in the quagmire of confusing references and never have finished without **Dr. Mathieu Lalonde's** review of the first and then the final draft and his responses with tracking notes and two long emails with valuable references. In fact, I wanted him to author or even just co-author the article. That being impossible because of Mat's time-consuming and demanding post-doctoral fellowship at Harvard, plus his nutrition seminars and CrossFit workouts, I've quoted him liberally, used his well picked references, and set out to give my readers an introduction to some of the inroads scientists have been making in the pursuit of understanding the genesis of the pathophysiology of Alzheimer's Disease, now known as type 3 diabetes.

Mat obtained his Bachelor's degree in Science with a concentration in chemistry from the University of Ottawa and a Ph.D. in organic chemistry from Harvard University, where he is now pursuing post-doctoral studies in inorganic chemistry. He, along with Robb Wolf, are the bright lights in health, athletic performance, and nutrition. Mat not only has the background to understand the highly technical science literature, but he also has an incisively inquiring mind—a dynamite combination when coupled with his ability to make technical information understandable and available to us all. Mat's comment to this: "I only wish my colleagues were like-minded. They unfortunately think I'm wasting my time researching nutrition and exercising. All, save my Ph.D. advisor."

This is not an article about diet, something I've always avoided writing or even talking about, considering my ignorance of the topic and the tremendous responsibility that accompanies advising people on the life-altering subject of what to eat. However, herein is information from trusted sources that we can apply now to our lives. The destiny of the food we eat involves complicated cascades of events—there is usually no simple explanation. Understanding this, we will know to identify and seek truly qualified sources, lest we be led astray by the emotional hype of the less qualified. In fact, drop into most enlightening webinars on diet with Dr. Mathieu Lalonde:
http://www.paleodish.com/2010/06/08/my-interview-with-mat-lalonde/
http://life.nationalpost.com/2010/06/10/qa-mat-lalonde-discuss-the-paleo-diet/

Experts like Mat, Robb and Dr. Sears represent hope, as the young among us raise their children and prepare them and themselves for the future, and as we, the elders, approach and pass ages 60, 70, and 80. The role of diet in cognitive decline is only beginning to

build up steam in the scientific community, inspired by the huge flux of "baby boomers" into elderlyness. Given the dietary factors that have reduced the risk for cardiovascular disease, diabetes, and hypertension, there is hope of an application to Alzheimer's and other neurodegenerative diseases.

"I consult with Mathieu on a weekly basis and would recommend that if you are serious about your own health, longevity, and performance that you give yourself or a loved one a gift this year and register for a seminar with this amazing young scientist." (Comment by Pierre Augé on Robb Wolf's site.)

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PLAQUES AND TANGLES OF ALZHEIMER'S DISEASE

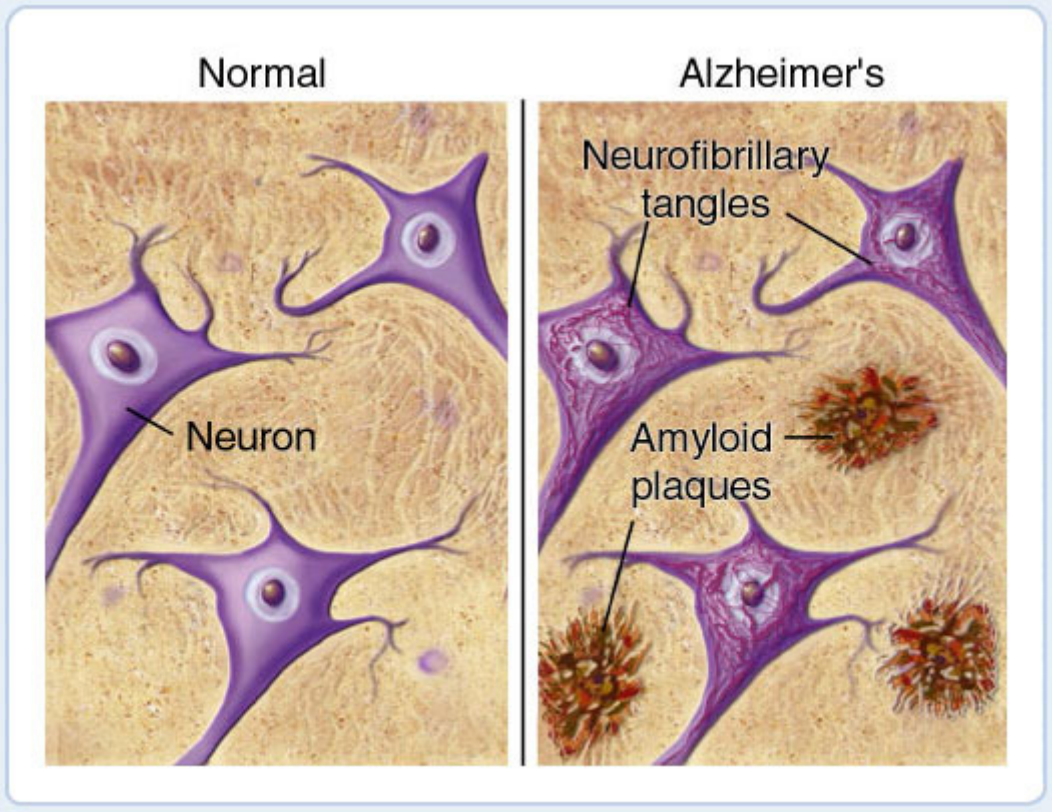

Fig. 1. The formation of amyloid (protein) plaques and neurofibrillary tangles are thought to contribute to the degradation of the neurons (nerve cells) in the brain and the subsequent symptoms of Alzheimer's disease. (From Alzheimer's Disease Research, a program of the American Health Association Foundation)

This dreaded disease initially manifests as a gradually progressive cognitive decline—loss of memory and language skills, and inability to attend to business and activities of daily living. Contributing events are numerous and complex, involving a multitude of variables presently under intense study. The hypothesis, still under debate, is that this destructive pattern is caused by the collapse and disintegration of microtubules

within nerve cells in the brain causing "tangles" and the formation of beta amyloid (protein) plaques between nerve cells, as illustrated in Fig. 1. This pattern is an inflammatory stimulus, which elicits an immune-inflammatory response.

VULNERABILITY OF THE BRAIN TO OXIDATIVE STRESS

The published papers from Professor D. Allan Butterfield.[1] [2] [3] are clear warnings that the brain is more susceptible to oxidative stress than are other organs because of its oxygen needs, consuming about one third of our inspired oxygen. Plus, it is rich in polyunsaturated fatty acids that are highly vulnerable to attack by free radicals. Such oxidative damage is compounded by the scarcity of antioxidant defense systems.[4]

Free radicals can arise from the homolytic cleavage of chemical bonds, which leaves a reactive unpaired electron in the outer shell of an atom; this initiates chain reactions and cell damage. The process is often mediated by oxygen, hence the term “reactive oxygen species” (ROS). Free radical oxidative damage to intracellular targets such as DNA or proteins is a major cause of neuron apoptosis related to Alzheimer's disease.[5] The results of studies conducted by Butterfield and Kanski strongly support the notion that intervention in Alzheimer's disease by brain accessible antioxidants "may provide a promising therapeutic strategy."[6]

ANTIOXIDANTS

Antioxidants are molecules that can inhibit oxidation of other molecules by giving up one of their own electrons and/or atoms to stabilize the free radical. Low levels of antioxidants or inhibition of enzymes involved in their synthesis and recycling causes oxidative stress that may critically damage cells. Adequate levels of antioxidants prevent free radicals from being formed or neutralize them before damage is done. This involves a complex network of multiple antioxidant enzymes and metabolites at work in our bodies to protect the cellular structure of our DNA, proteins and lipids.

Methionine

Methionine is a sulfur-containing essential amino acid and a powerful antioxidant, which inactivates free radicals. Because methionine is not synthesized in the body, it must be obtained from food sources such as red meat, fish, eggs, garlic, onions, yogurt and seeds.

Dr. Mat Lalonde was a huge help to me in understanding the dependence of this antioxidant on several enzymes involved in the synthesis of homocysteine to methionine and in the maintenance of methionine in its normal non-oxidized state–processes that fail in the Alzheimer patient.

Methionine synthase. Alzheimer patients have a malfunction of at least two enzymes, one of which is *methionine synthase*. Normally, this enzyme is involved in the synthesis of methionine from homocysteine. In patients with Alzheimer's disease this enzyme malfunctions and homocysteine levels become elevated due to lack of conversion to

methionine. The malfunction of *methionine synthase* is a two-edged sword in that not only is the antioxidant role of methionine lost because of low levels in the blood, but also the coexisting elevated homocysteine levels are a powerful risk factor for cardiovascular disease, which is part of the metabolic syndrome along with Alzheimer's disease.

Methionine sulfoxide reductase. Alzheimer patients also have low levels of *peptide methionine sulfoxide reductase*. This enzyme reduces the oxidized form of methionine back to regular methionine, essentially reversing the damage done by reactive oxygen species.[7] So, in Alzheimer's disease there is a lack of methionine due to poor diet and malfunctioning of the enzyme, methionine synthase. The methionine that is present is being oxidized by reactive oxygen species (free radicals) and is not re-converted to methionine due to the low levels of peptide methionine sulfoxide reductase.

Summary. Mat summarizes the methionine tangle for us: "The malfunction of methionine synthase, the high levels of reactive oxygen species, the low levels of peptide methionine sulfoxide reductase are all the result of the metabolic syndrome, which itself is caused primarily by excess fructose and linoleic acid consumption as well as the consumption of lectins, prolamine proteins (including gluten), phytic acid (phytates), and saponins.[8] Alzheimer's disease is now officially referred to as Type 3 diabetes for a reason."

Curcumin (Turmeric)

Spices and herbs often contain active phenolic substances with potent antioxidant, anti-inflammatory, and anti-cancer properties.[9] [10] [11] [12] Not the least of these is curcumin.

Curcumin is the principal curcuminoid of the Indian spice, turmeric, the lovely plant pictured here. This perennial of the ginger family has antioxidant, anti-inflammatory and anti-cancer properties. The Indian diet is also consistent in its use of sesame seeds, which provide the antioxidant, methionine, already discussed.

The polyphenolic antioxidant property of curcumin has the potential to inhibit the action of free radicals that damage cells via homolytic cleavage of carbon–hydrogen bonds of lipids in their membranes, which initiates the destructive free radical chain reaction.[13] [14] [15] [16]

Curcumin's anti-inflammatory properties and cancer-preventive activities have been consistently reported in vitro and in vivo models of tumor initiation and growth.[17] Dietary curcumin given to mice with Alzheimer's disease for 6 months resulted in a suppression of inflammation and oxidative damage in the brain and even reversed

cognitive deficits.[18] [19] As for its effect on cancer cells, curcumin is said to inhibit protein modification, thus interfering with cell growth in tumors.[20]

KNOW YOUR OMEGA 3 FATTY ACIDS

The three main types of omega 3 fatty acids are:

1) Alpha-linoleic acid (ALA) from plants and vegetable oils (flaxseed oil, canola oil, walnuts, macadamia nuts, etc).
2) Eicosapentaenoic acid (EPA) and
3) Docosahexaenoic acid (DHA). Sources for EPA and DHA are fish, fish oil, game meat, and grass-fed beef.

Dr. Lalonde pointed out serious errors in some publications, such as Cordain's "Paleo for Athletes", in which it is recommended that we eat walnuts and macadamia nuts and consume oils such as flaxseed oil and canola oil. The omega-3 from nut and plant sources (flaxseed oil and canola oil) is mainly ALA as opposed to the EPA and DHA that we should be consuming. The limited usefulness of ALA lies in the fact that very little of it can be extended to the more useful EPA and DHA which are required, amongst other things, for eicosanoid and docosanoid biosynthesis.

Recommendations from inaccurate sources spread quickly to innumerable Web sites and the ads on the Web are quick to tell you that ALA is transformed in our bodies into EPA and DHA. The advice is not good when the explanation doesn't go far enough, leaving us only half-way there. Mat sorts that puzzle out for us. There IS a conversion process of ALA to EPA and DHA, but it is "really inefficient", leaving the body with excess ALA which "spills over into pathways that synthesize bad hormones." So, how bad can it be to consume too much of ALA omega-3? Too much of the "wrong" omega-3 (ALA), compounded by an excess of omega-6 fatty acids and too much sugar plus the cerebral inflammation inherent in Alzheimer's disease itself, opens the door for insulin resistance* and metabolic syndromes.[21] [22] As you can see, human metabolism has intricate pathways; there's usually no simple answer. This is why we need to find trusted and competent sources who have the education and interest in nutrition that qualifies them to interpret this information for us.

THE SIRT1 GENE—BEATING THE PLAQUES

Leonard Guarent and associates at MIT have shown that the SIRT1 gene produces proteins called sirtuins that activate the ADAM10 gene to break up the peptides that form the plaques in the brains of patients with Alzheimer's disease. Additionally, activation by SIRT1 also induces a pathway known to repair neurological damage in the brain. There are two ways to activate this important gene: 1) resveratrol and 2) short-term fasting.

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* Insulin resistance is the inability of cells to respond to circulating insulin, resulting in an increase in blood glucose. In time, insulin resistance can lead to Type 2 diabetes, itself a risk factor for both Alzheimer's disease and heart disease.

Resveratrol. In addition to stimulating the SIRT1 gene, studies suggest that resveratrol influences adipose tissue mass in a way that may retard the development of obesity and its related morbidities.[23]

Resveratrol is a plant-derived phenolic found principally in red wine (global), skins of certain red grapes, cranberry juice and Spanish red grape juice. The amount of resveratrol found in grape skins also varies with the grape variety and cultivation, its geographic origin, exposure to fungal infection, and the amount of fermentation time a wine spends in contact with grape skins. Red wine contains between 0.2 and 5.8 mg/L depending on the type of grape. White wine contains much less resveratrol because it is fermented without the skin whereas red wine is fermented with the skins, allowing the wine to absorb the resveratrol. Ounce for ounce, peanuts have about half the amount of resveratrol as that found in red wine. Blueberries have about twice as much resveratrol as bilberries, and less than ten percent of the resveratrol of grapes. Cooking or heat processing of these berries will contribute to the degradation of resveratrol, reducing it by up to half.[24]

Short-term fasting and caloric restriction. The beneficial effects of mild stress on aging and longevity have been studied for many years in the form of caloric restriction and short-term fasting with the following conclusions.

1) Caloric restriction leads to retardation of the aging processes and to longer life in many organisms[25] and protects against Alzheimer's disease.[26 27]
2) High caloric intake and increase in body mass index during middle age have been associated with a decline of cognitive function in old age.[28]
3) Much like resveratrol, caloric restriction and intermittent fasting activate a wide variety of mechanisms,[29 30] including the SIRT1 gene and protein conservation,[31] reducing the incidence of age-related disorders.[32 33]

An important characteristic of intermittent fasting is that it can increase lifespan even when there is little or no overall decrease in caloric intake.[34] According to Walker et al[35] short-term fasting produces a rapid metabolic shift from lipid/cholesterol synthesis and fat storage to mobilization of fat and may improve conditions associated with metabolic syndrome. These findings indicate that SIRT1 activation is a viable strategy to combat Alzheimer's disease and perhaps other neurodegenerative diseases [36]—encouraging and exciting findings in the initial steps to a cure.

GLOSSARY

Lectins are proteins that bind carbohydrates and may be inflammatory and/or toxic due to their ability to bind to gut tissues, permeate the gut barrier, enter the bloodstream, and bioaccumulate in various organs. Whole grains, peanuts, kidney beans, and soybeans are high in lectins. Cow’s milk, tomatoes, nightshade vegetables (like potatoes) and some seafood also contain fairly high amounts.

Linoleic acid is an unsaturated omega-6 fatty acid found in some vegetable oils, such as soybean, rapeseed (canola), and flaxseed, and in walnuts.

Peptide methionine sulfoxide reductase. This enzyme is a repair mechanism for oxidatively damaged proteins.

Phytic acid can be found in most grains, seeds and beans. Rich sources of phytic acid are wheat bran and flaxseed (3 % phytic acid). Phytic acids have been shown to inhibit the absorption of minerals such as calcium, magnesium, iron, and zinc in the digestive tract. Phytic acid also inhibits digestive enzymes such as alpha-amylase, pepsin, trypsin, and chymotrypsin.

Prolamine proteins. Any of a class of simple proteins soluble in alcohol and usually having a high proline and glutamine content, found in the grains of cereal crops such as wheat, rye, barley, corn, and rice. Prolamine proteins are the causative agent of celiac disease and implicated in the leaky gut syndrome through stimulation of CXCR3 and zonulin secretion.

Zonulin is a protein that regulates intestinal permeability. It opens the spaces between cells allowing some substances to pass through while blocking the entrance for harmful bacteria and toxins.[37]

CXCR3 belongs to a family of molecules involved in the directed migration of immune cells.

Leaky gut syndrome is said to exist when the bowel lining has been damaged by toxins, poor diet, parasites, infection, or medications, such as antibiotics or NSAIDS. This damage involves increased permeability of the gut, allowing toxins to enter the circulation and interstitial areas.

Saponins are phytochemicals that can be found in large concentrations in nightshades (solanacea family of plants) and legumes. The best known sources of saponins are peas, soybeans, quillaja bark extract, as well as some herbs with names indicating foaming properties such as soapwort, soaproot, soapbark and soapberry. Saponins are involved in the leaky gut syndrome due to their ability to dissolve the gut membrane.

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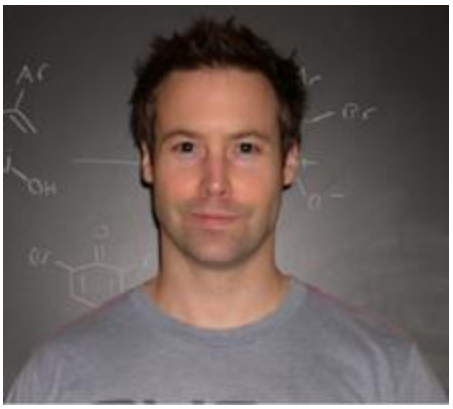
Thanks first of all goes to my CrossFit trainer, **Jim Baker**, who opened up the subject of Alzheimer's disease by introducing me to the Indian spice, turmeric. The picture of that lovely plant is for you, Jim.

Next stop was **Robb Wolf** who kicked off the subject by joining Dr. Mat Lalonde in pointing out the role of methionine. Can't wait for your new book, Robb!

Thank you, **Dr. Mathieu Lalonde,** for your help with this difficult subject. I'm looking forward to attending one of your seminars. I'll be the one taking copious notes.



Mathieu Lalonde, Ph.D, teacher

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