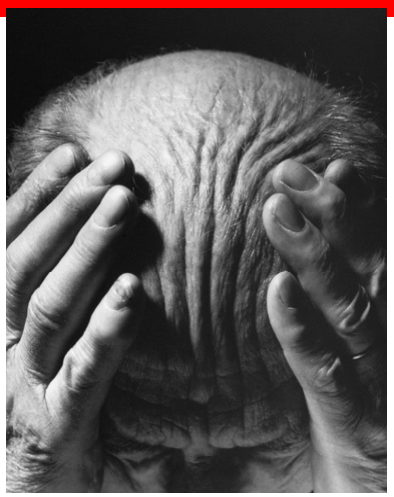
Biochemical factors in Alzheimer's disease: prevention and treatments

William Shaw Ph.D.
The Great Plains Laboratory, Inc



Aging (Milano) 2001 Jun;13(3):143-62 Alzheimer's disease: insights from epidemiology. McDowell I.

- Roughly 7% of the population aged 65 and over has AD.
- Approximately 50% of the population over 85 has AD
- Clinical course of the disease is well established and mortality rates rise with increasing levels of cognitive deficit.
- Four risk factors for AD are firmly established: increasing age, the presence of the apolipoproteinE-epsilon-4 allele, familial aggregation of cases, and Down's syndrome.

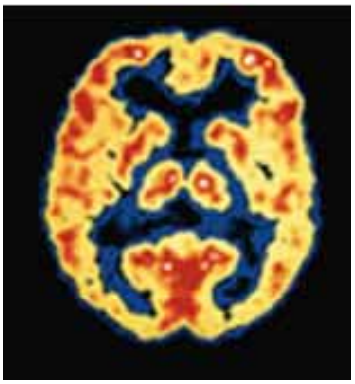
Aging (Milano) 2001 Jun;13(3):143-62 Alzheimer's disease: insights from epidemiology. McDowell I.

- Women generally appear at higher risk than men, as do people with lower levels of education;
- Depression is probably prodromal
- Head injury is an established risk factor and may interact with the apolipoprotein E gene;
- Several occupational exposures appear hazardous, and exposure to aluminum in the water supply confers excess risk.
- Hypertension and other vascular symptoms appear to predispose to AD, which is now seen as nosologically closer to vascular dementia than was previously believed.

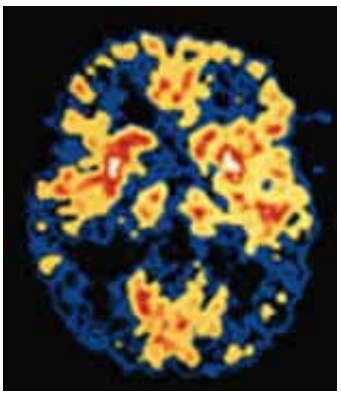
Aging (Milano) 2001 Jun;13(3):143-62 Alzheimer's disease: insights from epidemiology. McDowell I.

- The use of non-steroidal anti-inflammatory drugs to treat arthritis is associated with a reduced risk of AD, as is estrogen use by post-menopausal women.
- Physical activity appears beneficial, as does a diet with high levels of vitamins B6, B12 and folate.
- Red wine in moderate quantities appears protective (Resveratrol?).

PET Scans For Glucose Uptake

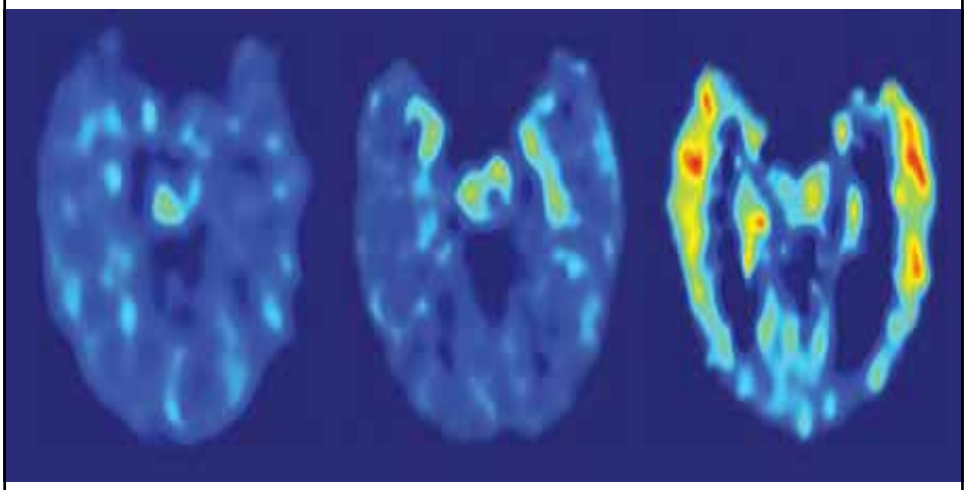


NORMAL BRAIN



ALZHEIMER'S BRAIN

Brain scans for abnormal protein deposits

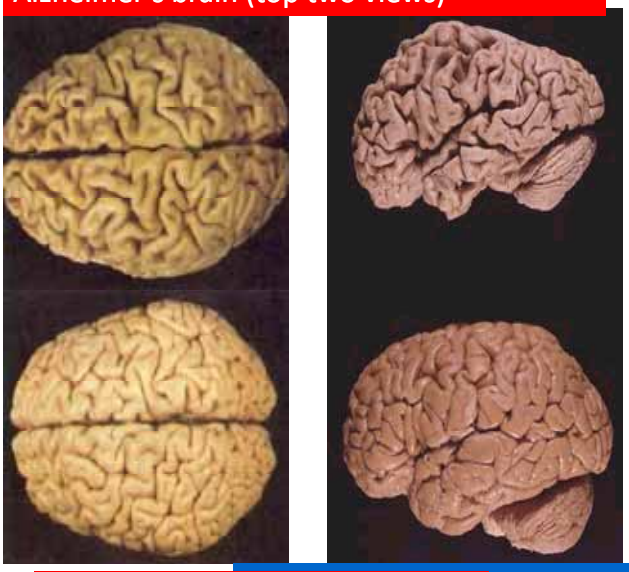


Normal

Mild cognitive impairment

Alzheimer's

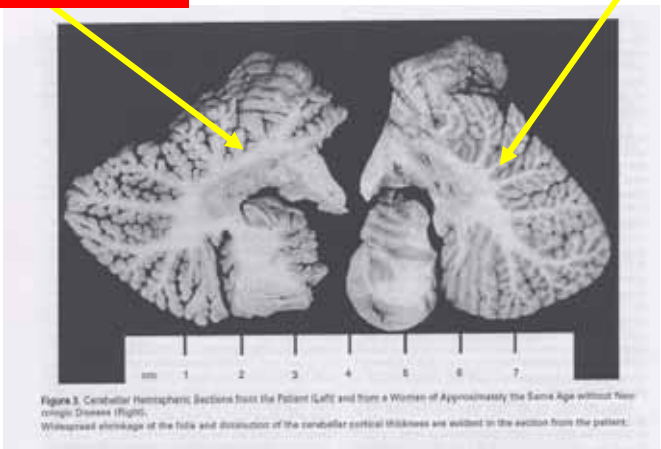
Alzheimer's brain (top two views)



Normal brain (bottom two views)

Mercury spill victim

Control



Toxic metals in hair of a 5 year old with autism

POTENTIALLY TOXIC ELEMENTS

TOXIC ELEMENTS	RESULT µg/g	REFERENCE RANGE	PERCENTILE 68th 95th
Aluminum	19	< 8.0	
Antimony	0.16	< 0.066	
Arsenic	0.21	< 0.08	
Beryllium	< 0.01	< 0.02	
Bismuth	4.4	< 0.13	
Cadmium	0.31	< 0.15	
Lead	18	< 1.0	
Mercury	12	< 0.4	
Platinum	< 0.003	< 0.005	
Thallium	< 0.001	< 0.01	
Thorium	< 0.001	< 0.005	
Uranium	0.015	< 0.06	
Nickel	0.69	< 0.4	
Silver	0.17	< 0.2	
Tin	0.84	< 0.3	
Titanium	1.4	< 1.0	
Total Toxic Representation			

The Fetal Basis of Amyloidogenesis: Exposure to Lead and Latent Overexpression of Amyloid Precursor Protein and -Amyloid in the Aging Brain.The Journal of Neuroscience, January 26, 2005, 25(4):823-829

- Rats exposed neonatally to low levels of lead have increased amyloid deposits in their brains in old age, implicating early lead exposure in the causation of Alzheimer's disease.
- The exposure permanently alters the behavior of the APP gene, which produces the amyloid peptide.
- Exposure in old age to the same lead level, however, did not produce the effect.
- These results suggest Alzheimer's may be one of an increasing number of adult diseases caused by early child exposure to heavy metals.

Does inorganic mercury play a role in Alzheimer's disease? A systematic review and an integrated molecular mechanism. J Alzheimers Dis. 2010;22(2):357-74. Mutter J

- Two reviewers extracted relevant data independent of each other from 1041 references
- 106 studies fulfilled the inclusion criteria.
- 32 studies out of 40 testing memory in individuals exposed to inorganic mercury, found significant memory deficits.
- Autopsy studies found increased mercury levels in brain tissues of AD patients.
- In vitro models showed that inorganic mercury reproduces all pathological changes seen in AD, and in animals inorganic mercury produced changes that are similar to those seen in AD.

McLachlan DR, Kruck TP, Lukiw WJ, Krishnan SS
Would decreased aluminum ingestion reduce the incidence of Alzheimer's disease? CMAJ 1991 Oct 1;145(7):793-804

- **Mounting evidence that implicates aluminum as a toxic environmental factor**
- Laboratory studies of the effects of intracerebral aluminum on the cognitive and memory performance of animals,
- Biochemical studies,
- Epidemiologic studies
- Slowing of the progress of the disease with the use of an agent that removes aluminum from the body

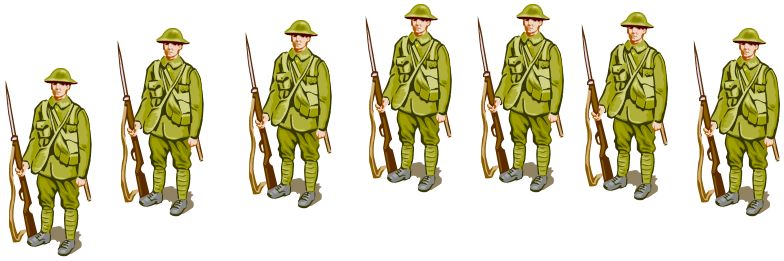
Hum Toxicol 1988 May;7(3):259-62
Comparative effects of several chelating agents on the toxicity,distribution and excretion of aluminium.
Domingo JL, Gomez M, Llobet JM, Corbella J. Laboratory of Toxicology and Biochemistry, School of Medicine, Reus,Spain.

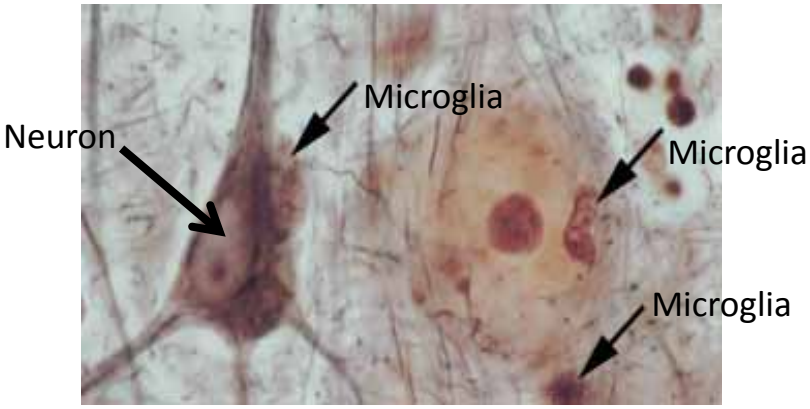
- Malic acid and deferoxamine mesylate (DFOA)were the most effective agents in increasing the urinary excretion of aluminum.

Domingo J et al. Citric, malic, and succinic acids as possible alternatives to deferoxamine in aluminum toxicity. Clin Tox 26: 67-79,1988.

	Treatment June 1996	With Sept 1996	magnesium malate May 1997
Hair aluminum values	26 ppm	18 ppm	2.3 ppm

Case studies of Alzheimer's disease reversal

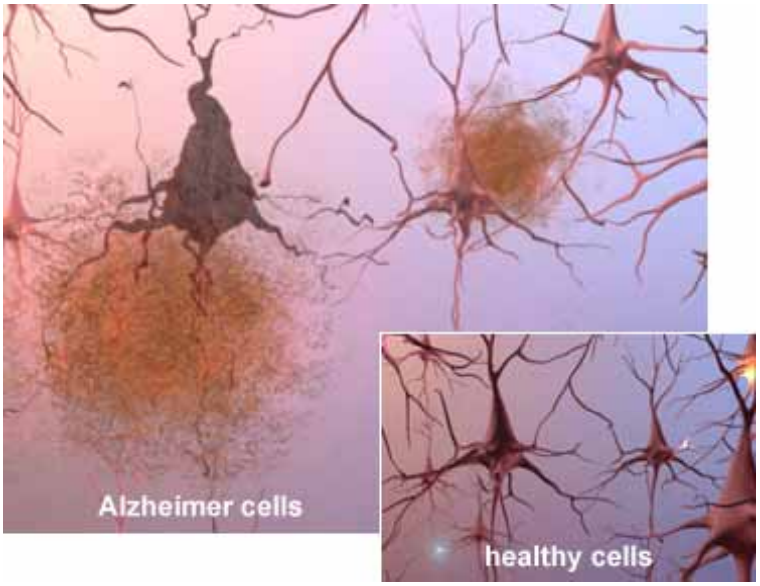


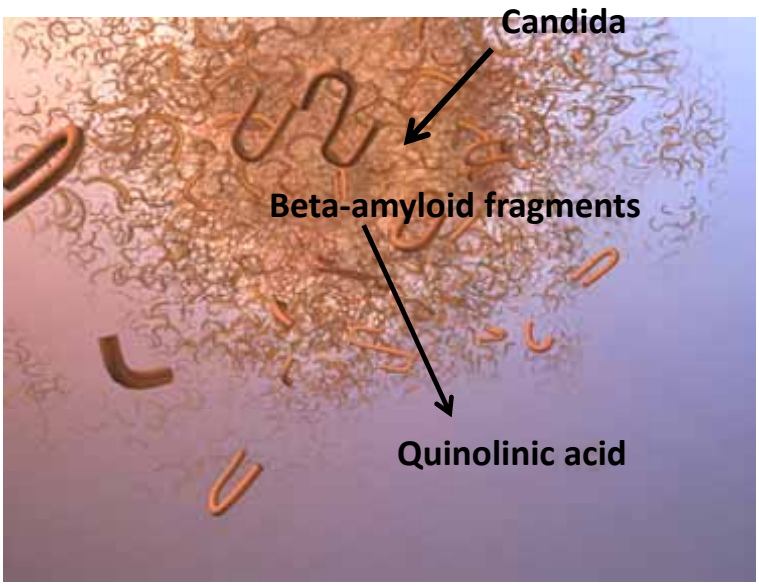


A photo from one of Alois Alzheimer's first patients, showing a large neuron (dark brown cell, left) with an enlarged microglia clinging to the top right of its cell body. The light beige circle is made of amyloid protein with a darkened plaque at its center. Manuel Graeber (Neurogenetics, 1:73-80, 1997)

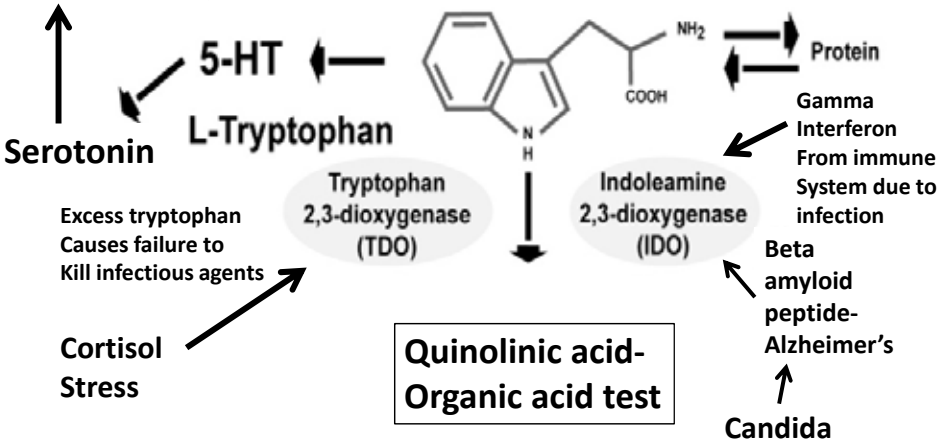
Implications of the kynurenine pathway and quinolinic acid in Alzheimer's disease. Guillemin Gilles J. ; Brew Bruce
J. Adv Exp Med Biol. 2003;527:167-76

- Amyloid beta (Aβ 1-42), a cleavage product of amyloid precursor protein, induces production of quinolinate, in neurotoxic concentrations, by macrophages and, more importantly, microglia
- Quinolinate measured in organic acid test
- Senile plaques in Alzheimer's disease are associated with evidence of chronic local inflammation (especially activated microglia)
- Found to be anti-Candida compound. Candida trigger for Alzheimer's?
- Major aspect of quinolinate toxicity is lipid peroxidation and markers of lipid peroxidation are found in Alzheimer's disease





5-HIAA-organic acid test



Kills cells containing bacteria, viruses, parasites. May also damage infectious organisms themselves IDO causes drastic reduction in tryptophan for protein synthesis needed by infected cells and infectious organisms-tryptophan at very low levels

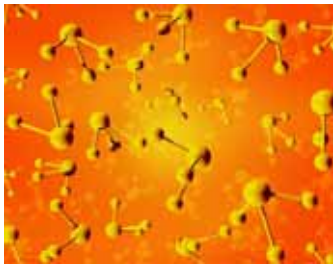
Low normal tryptophan metabolite 5-HIAA

Neurotransmitter Metabolites			
30 Homovanillic (HVA)	0.80 - 3.6		2.1
31 Vanillylmandelic (VMA)	0.46 - 3.7		2.2
32 5-Hydroxyindoleacetic (5-HIAA)	≤ 4.3		0.37
33 Quinolinic	0.85 - 3.9		2.5
34 Kynurenic	0.17 - 2.2	H	2.3
35 Quinolinic / 5-HIAA Ratio	0.42 - 2.0	H	6.8
36 Quinolinic / Kynurenic Ratio	0.82 - 3.6		1.1

Normal quinolinic acid but very high ratio indicates excessive conversion of tryptophan to quinolinic

Convenient Alzheimer's screening test- sketch of clock

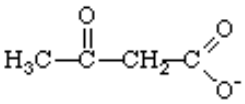
- Scores only 14 of 30 on MMSE, needs 16 to qualify
- Doctor asks him to draw a clock – consistent with moderately severe Alzheimer's



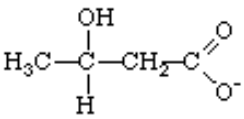
Medium chain triglycerides converted in liver to

Ketones

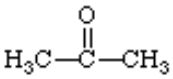
Ketone Bodies



Acetoacetate



D-β-Hydroxybutyrate

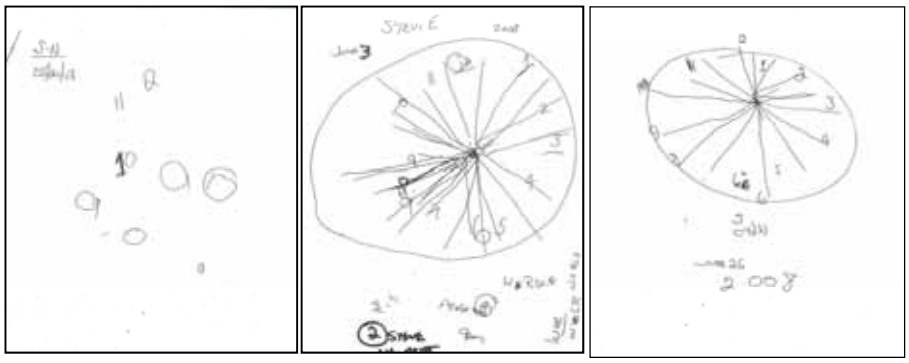


Acetone

First Days after Coconut Oil Intervention Dr. Mary Newport, November 2009

- Begins daily consumption of coconut oil
  - Measured dose at breakfast, cooking and other coconut containing foods for dinner
- More alert - Personality and sense of humor resurface
- Steve says the “light switch came back on” and the “fog lifted”
- Facial tremor disappears
- Intention tremor infrequent

Dr. Mary Newport, November 2009



DAY BEFORE COCONUT OIL | 14 DAYS ON COCONUT OIL | 37 DAYS ON COCONUT OIL

Expanded Coconut Oil Intake, Dr. Mary Newport, November 2009

- As a result of levels with coconut oil also used measured amounts at lunch and dinner
- Mixing coconut oil and MCT oil
- Substituting foods with MCTs for others:
  - Goat's milk and cheese for cow's milk and cheese
  - Coconut milk for other liquids in cooking

Between 2 - 4 months after Intervention, Dr. Mary Newport, November 2009

- Visual disturbance resolves
- Normalization of gait – able to run again
- Completes household and gardening tasks with minimal to no supervision and without distraction
- Wears both shoes and keeps pairs together
- His ability to initiate and continue a course of conversation improves
- Recognizes family members that he couldn't recall one year earlier
- Family says he no longer looks lost, conversation makes sense

Between 4 -10 Months After Intervention

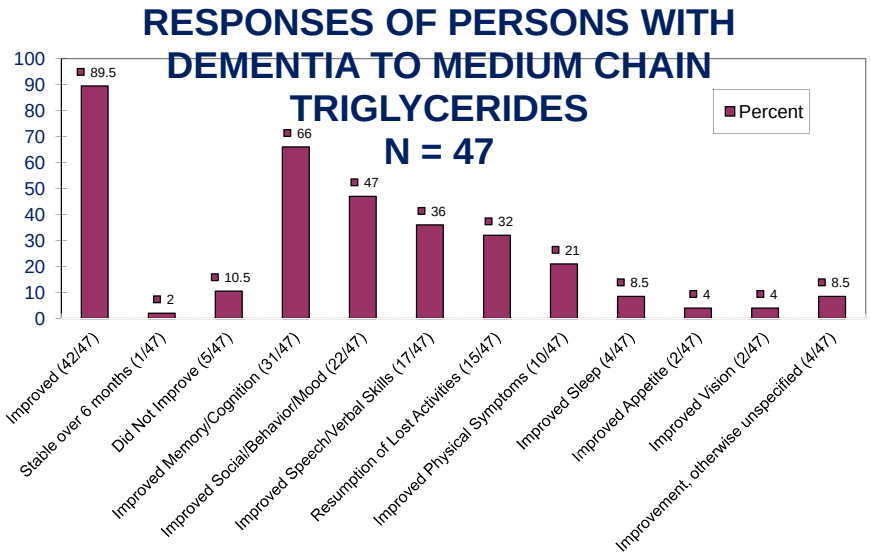
- Conversational skills continue to improve
- Reading comprehension improves
- Short term and recent memory improves
- Stops having episodes of near syncope
- No longer depressed – Says, "I have my life back."
- Wants to do more with his life - volunteers in hospital warehouse
- Vacuums, cuts grass and weeds gardens again (instead of taking equipment apart!)

Getting the Message Out

- Family confirms Steve has improved
- Article: "What If There Was a Cure for Alzheimer's Disease and No One Knew?" July 2008
  - Sent letters to high profile persons to investigate MCT oil studies and make public aware
  - Chicago ICAD conference
  - Grass roots method/internet
  - St Petersburg Times article October 2008
  - Website: www.coconutketones.com
  - Legislators March 2009

Diseases With Decreased Glucose Uptake into Brain/Nerve Cells

- Alzheimer's disease
- Parkinson's disease
- Multiple sclerosis
- Huntington's chorea
- ALS/Lou Gehrig's disease
- Duchenne muscular dystrophy
- Some forms of autism
- Down's syndrome – develop Alzheimer's disease by ages 30-40
- Acute brain injury, accompanied by lack of oxygen
- Type I and Type II diabetes



47 individuals there were 25 males, 20 females, 1 unknown
30 of 47 reported age with range of 55 to 94 years old (average 76.8.)
29 used coconut oil only, 3 MCT oil only and16 a combination of coconut oil and MCT oil

Other Reported Improvements, Dr. Mary Newport, November 2009

- Parkinson's disease
- Multiple sclerosis
- Improved blood sugars in type II diabetes
- Down's syndrome
- Bipolar disorder
- Glaucoma
- Macular degeneration
- Cognition in elderly dog

Coconut Oil Equivalents, Dr. Mary Newport, November 2009

- Coconut oil - 1 tablespoon = 15 cc or ml
  - Coconut Milk (undiluted) – 4 ½ tablespoons
  - Coconut meat – 2" x 2" x ½" piece
  - Coconut grated – 1/3 cup
  - Coconut oil capsules (1 gm) – 14 capsules

START SLOW, Dr. Mary Newport, November 2009

- Common effect – Diarrhea
  - Begin with 1 teaspoon and increase slowly
  - Start on a day when you don't have to go somewhere immediately!
  - Take with other food
  - Can take it slowly during meal over 20-30 minutes
  - Some foods may help retain oil – cottage cheese
  - Try grated coconut or coconut milk as alternative for part of "dose"

Food Ideas, Dr. Mary Newport, November 2009

- Use coconut oil instead of butter on toast, English muffins, bagels, grits, corn on the cob, potatoes or sweet potatoes.
- Add coconut oil or coconut milk to your favorite smoothie recipe.
- Mix coconut oil into:
  - Oatmeal or other hot cereal.
  - Rice, vegetables, noodles, pasta.
  - Half and half with salad dressings.
  - Soup, chili or spaghetti sauce.

Food Ideas, Dr. Mary Newport, November 2009

- Use a measured amount of coconut oil to stir fry or sauté any of your favorite dishes.
- Purchase or make coconut macaroons made from all natural products.
- Make Coconut oil "fudge"
- Eat a 2" x 2" square of raw coconut for a snack to provide 15 grams of oil.
- Add flaked or grated coconut to hot or cold cereal, yogurt, fruit or vegetable salads

Why not use just MCT oil?

- Many other fatty acids of all chain lengths in coconut oil that may serve special purpose:
  - Supports thyroid
  - Anti-microbial properties – kills certain viruses and bacteria that some research implicates in Alzheimer's and Parkinson's
    - Herpes viruses
    - Helicobacter pylori
  - May be other factors in the "whole" oil that benefit Alzheimer's and other diseases

KETOGENIC DIET, Dr. Mary Newport, November 2009

- History
  - Fasting used as treatment for seizures and epilepsy in biblical times and middle ages
  - Early 1900's - NY Pediatrician Rawle Geyelin successfully fasted children to control seizures (15 day fast) – 18% were helped
  - 1921 – Wilder proposed that benefits of fasting (increase in ketone bodies) could be produced by diet rich in fats and low in carbohydrates - - "ketogenic diet"

KETOGENIC DIET, Dr. Mary Newport, November 2009

- History (continued):
  - 1924 – Peterman reports effectiveness of diet from Mayo Clinic – 51% seizure free after 2 ½ years on diet
    - 1 gram protein per kg body weight
    - 10-15 grams/day carbohydrate
    - Remainder of calories as fat
    - Total calories Basal Metabolic Rate + 50%
  - Identical to ketogenic diet used today – some variations exist – including MCT oil version – half of calories are MCT oil

Ketone Effects, Dr. Mary Newport, November 2009

- Presence of ketone in circulation, even at low levels increases cerebral blood flow by as much as 40%
- Ketones used within mitochondria to drive the chain reaction that produces ATP
- Reduces generation of free radicals and at same time increases the scavengers of free radicals linked to the NADP system, such as glutathione.
- Activates anti-inflammatory mechanisms

Neurology October 19, 2010;75(16):1402-3

- Blood samples from more than 270 individuals who showed no evidence of dementia.
- They tested for levels of vitamin B12 and for levels of homocysteine, an amino acid that has been linked to an increased risk of Alzheimer's disease,
- Tracked the study participants for seven years.
- Each unit increase in vitamin B12 reduced the risk of developing Alzheimer's by 2 percent.

The Best Kept Secret for Avoiding Alzheimer's... Posted By Dr. Mercola | November 19 2010

- 2-year long clinical trial was the largest to date to investigate the effect of B vitamins on mild cognitive impairment (MCI)
- About half of individuals over 70 progress to Alzheimer's after 5 years
- 800 micrograms (mcg) folic acid -- US RDA is 400 mcg/day
- 500 mcg B12 (cyanocobalamin) – US RDA is only 2.4 mcg/day
- 20 mg B6 (pyridoxine hydrochloride) -- US RDA 1.3-1.5 mg/day
- In this study, the participants who received the vitamin supplements had half the rate of brain atrophy (shrinkage) associated with dementia, compared to those who did not receive supplementation.
- Those with the lowest B12 levels had a 6-fold greater rate of brain volume loss compared with those who had the highest levels!

Freed DM, Kandel E. Long-term occupational exposure and diagnosis of dementia. Neurotoxicology 1988;9(3):391–400.

- Serum levels of tetrachlorethylene, dry cleaning solvent (745 parts per billion) were approximately 15 times that seen in a normal population.
- Man worked as a dry cleaner for over 30 years and was subsequently diagnosed with probable Alzheimer's Disease.

Kukull WA, et al. Solvent exposure as a risk factor for Alzheimer's disease: a case-control study. Am J Epidemiol 1995;141(11):1059–79

- 139 individuals diagnosed with Alzheimer's disease and 243 controls
- History of exposure to one or more solvent groups (benzene and toluene, phenols and alcohols, and ketones plus other solvents) resulted in an adjusted Alzheimer's Disease odds ratio of 2.3 for both sexes
- For men the odds ratio increased to 6.0 (95% CI, 2.1–17.2).

Obese People Have Severe Brain Degeneration
Paul Thompson, senior author of the study and a UCLA professor of neurology.

- Obese people had lost brain tissue in:
- Frontal and temporal lobes, areas of the brain critical for planning and memory,
- Anterior cingulate gyrus (attention and executive functions)
- Hippocampus (long-term memory)
- Basal ganglia (movement)
- Overweight people showed brain loss in the basal ganglia, the corona radiata, white matter comprised of axons, and the parietal lobe (sensory lobe).
- "The brains of obese people looked 16 years older than the brains of those who were lean, and in overweight people looked 8 years older,"

Rachel A. Whitmer of the Division of Research at Kaiser Permanente in Oakland, Calif. By DENISE GRADY
http://www.nytimes.com/2006/07/17/health/17alzheimer.html

- Based on the records of 22,852 patients with Type 2 diabetes who were followed for 8 years.
- Glycosylated hemoglobin, a blood test that reflects blood sugar levels for the previous two months.
- Normal is 7 or lower.
- Risk of dementia rose when the level reached 10.
- Those with readings from 10 to 11.9 had 13 percent more risk than people with levels below 10.
- From 12 to 14.9, the risk was 24 percent higher.
- Over 15, it jumped to 83 percent higher

IgG food allergies a major factor in obesity and Alzheimer risk?

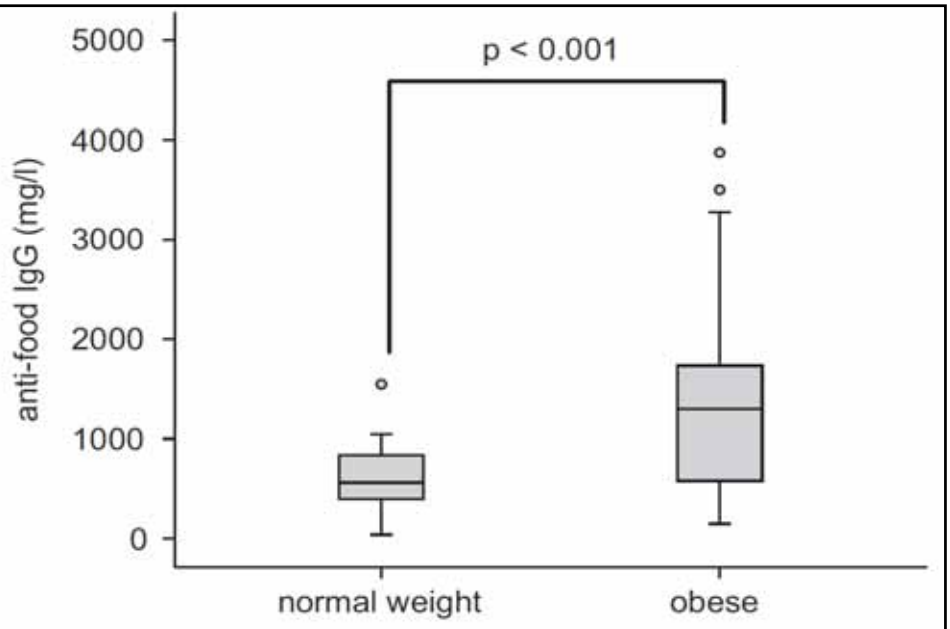
Article

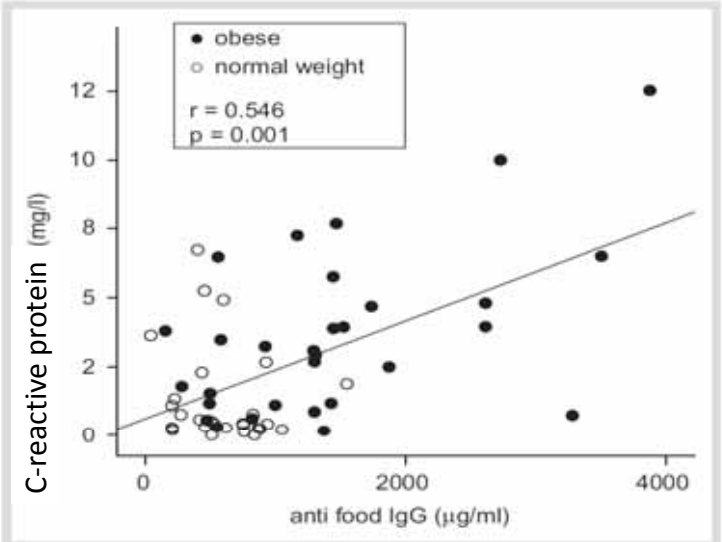
IgG Antibodies Against Food Antigens are Correlated with Inflammation and Intima Media Thickness in Obese Juveniles

Published online: 2007
Exp Clin Endocrinol Diabetes

Author M. Wilders-Truschnig[1], H. Mangge[1], C. Lieners[2], H-J. Gruber[1], C. Mayer[1], W. März[1]

Affiliation [1] Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University Graz, Austria
[2] Laboratoires Réunis Junglinster, Luxembourg





American Journal of Clinical Nutrition April 2005;81(4):897-902 .Silica and Alzheimer's.

- During the first phase of the study, researchers found women who had normal or higher mental function at the start had a higher daily intake of silica.
- This link remained significant, statistically, even after taking age, location, income, education level and history of stroke into account.
- The second phase, which followed up with women from a particular city seven years later, revealed women who developed Alzheimer's were almost three times more likely to have a significantly reduced daily intake of silica than those who didn't have it.

Incidence of Alzheimer's disease in Down syndrome

- **Virtually all persons with DS have features of Alzheimer's disease in the central nervous system by age 35**
- **70% of people with DS live to 40 or over**
- **85% of people with DS over 35 yr.had one or more signs of dementia**
- **Deposition of amyloid A4 in brain of DS as much as 50 yr earlier than normals**

Genes on chromosome 21 that may contribute to symptoms of DS

- Ribosomal RNA 4
- Amyloid beta precursor protein-Alzheimer's disease
- Superoxide dismutase
- Interferon alpha receptor
- Interferon gamma receptor
- Cystathionine beta synthetase-amino acid metabolism
- Phosphofructokinase-sugar metabolism
- CD 18-regulation of white blood cells
- Collagen type VI,alpha1 and alpha 2

Antioxidants in Down syndrome

Superoxide-made in white blood cells to kill Candida and bacteria such as Staphylococcus

$O_2^{\cdot -}$ → H_2O_2 **Hydrogen peroxide**

SOD,Cu,Zn Superoxide Dismutase

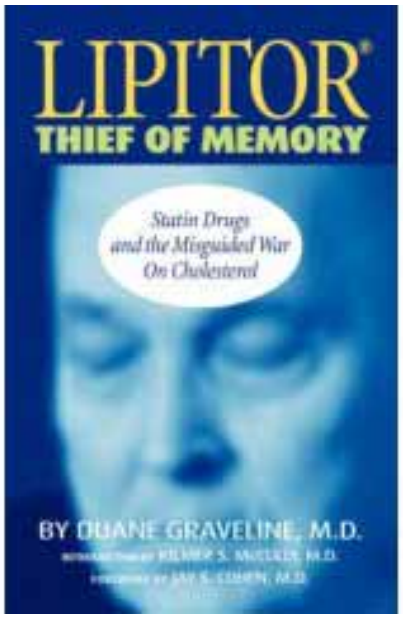
1.5X higher in DS tissues

Decreased $O_2^{\cdot -}$

Increased H_2O_2

Why is the brain more susceptible to oxidative damage?

- **High amounts of unsaturated fatty acids present in brain phospholipids**
- **Low amounts of antioxidants**
- **20% or more of total body oxygen intake but only 2% of body weight**
- **High amounts of iron present**
- **Low amounts of iron binding proteins**



Duane Graveline MD MPH
Former USAF Flight Surgeon
Former NASA Astronaut

Interview with Dr. Graveline

The first episode happened after I had been prescribed Lipitor® for my modestly elevated cholesterol. I had returned from my usual morning walk in the woods when my wife noticed me walking aimlessly in our driveway as if I were lost. I did not recognize her and refused to enter our home. I reluctantly accepted cookies and milk and somehow she got me into the car to see my family doctor and neurologist. Memory back after stopping drug.

Interview with Dr. Graveline

Hours after taking Lipitor® again, my wife found me in the greenhouse with that "gone" look in my eyes again. This time, during the 12 hour episode, I regressed all the way back to my teen years with precise recall for all my high school friends and events.

Characterization of the Lipid Profile in Dementia and Depression in the Elderly Nikolaos Dimopoulos,et al Geriatr Psychiatry Neurol 2007 vol. 20 138-144

- The study population consisted of 3 groups: A) 37 subjects with dementia, B) 33 subjects with depression, and C) 33 controls.
- All individuals were screened with the Mini-Mental State Examination (MMSE), the Geriatric Depression Scale (GDS), and an evaluation of their psychiatric state.
- Groups A and B had significantly lower levels of total plasma cholesterol and HDL cholesterol than group C ($P < .01$).
- The results of this study suggest that an association does exist between the plasma concentration of cholesterol and HDL-C and depression and/or cognitive impairment.

PAPER

Serum lipids and memory in a population based cohort of middle age women

V W Henderson, J R Guthrie, L Dennerstein

J Neurol Neurosurg Psychiatry 2003;74:1530–1535

See end of article for authors' affiliations

Correspondence to: V W Henderson, Donald W Reynolds Center on Aging, University of Arkansas for Medical Sciences, 4301 W. Markham Street, # 810, Little Rock, Arkansas 72205 USA; vhenderson@uams.edu

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Objective: To assess the relation between serum lipids and memory in a healthy middle age cohort of women.
Methods: For 326 women in the Melbourne Women's Midlife Health Project aged 52–63 years, serum lipids were measured annually, and memory was assessed during the eighth annual visit.
Results: There was a small but significant association between current low density lipoprotein cholesterol (LDL-C) concentrations and memory; for total cholesterol (TC) the association approached significance. Better memory was associated with positive changes in TC and LDL-C based on lipid measurements three years, but not six years, earlier. Memory performance was lowest among women in the lowest quartile of current LDL-C values and among women whose LDL-C levels declined over the previous three years. High density lipoprotein cholesterol (HDL-C) and triglyceride concentrations were unassociated with memory. The association between memory and TC and LDL-C was primarily related to immediate recall and not delayed recall performance on the word list task. Low cholesterol has been linked with depression, but lipid measures and self-rated mood were unrelated.
Conclusions: Higher serum concentrations of LDL-C, and relatively recent increases in TC and LDL-C concentrations, are associated with better memory in healthy middle age women. Possible cognitive effects of cholesterol reduction should be considered in future studies of lipid lowering agents.

Serum Cholesterol and Cognitive Performance in the Framingham Heart Study. P. K. ELIAS,PhD, et al Psychosomatic Medicine 67:24–30 (2005)

- 789 men and 1,105 women evaluated for relationship between total cholesterol and cognitive performance
- Found that those who had the lowest total cholesterol (200 mg/dL) performed more poorly on tests of word similarities, word fluency and attention and concentration ability than patients with higher cholesterol levels.
- Lowest scores were on those less than 180 mg/dL

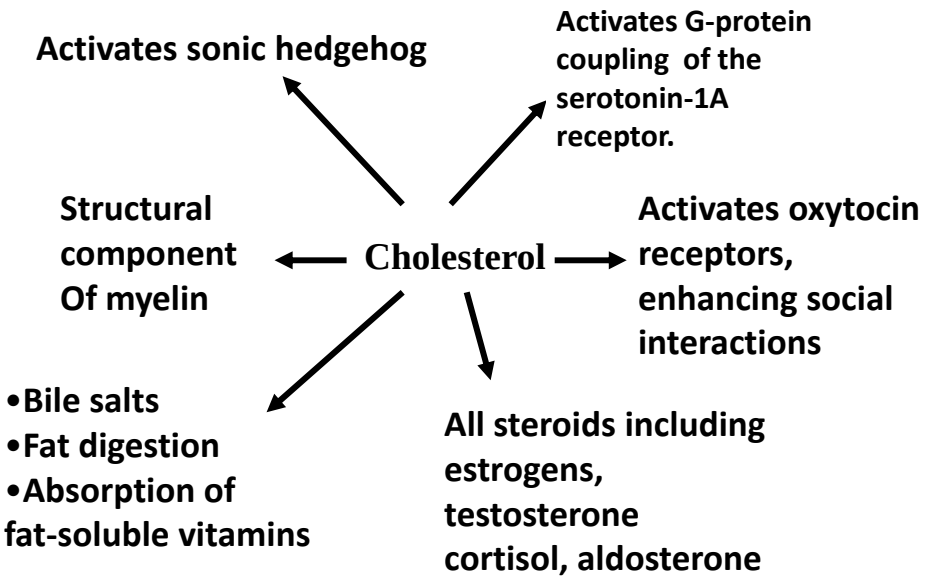
Neurobiol Dis. 2009 May;34(2):212-20. Epub 2009 Jan 21. Aneuploidy in the normal, Alzheimer's disease and ataxia-telangiectasia (AT) brain: differential expression and pathological meaning. Iourov IY, et al

- The overall proportion of aneuploid cells in the brain of AT individuals was estimated at approximately 20-50%. ,
- A dramatic 10-fold increase of chromosome 21-specific aneuploidy (both hypoploidy and hyperploidy) was detected in the AD cerebral cortex (6-15% versus 0.8-1.8% in control).
- These data indicate neural aneuploidy to be a newly identified feature of neurodegenerative diseases, similar to other devastative disorders hallmarked by aneuploidy such as chromosome syndromes and cancer.

Experimental Cell Research Volume 300, 2004, P 109-120 Cholesterol is essential for mitosis progression and its deficiency induces polyploid cell formation C Fernándeza

- Prolonged cholesterol starvation inhibited cytokinesis and caused the formation of polyploid cells, which were multinucleated (cells which have more than one nucleus per cell and are implicated in tumor formation) and had other abnormalities.
- Supplementing with cholesterol completely abolished these adverse effects, demonstrating they were specifically due to cholesterol deficiency.

Central role of cholesterol in brain



Summary of cholesterol benefits

- Cholesterol is an essential nutrient, although humans can make some
- Deficiency of cholesterol is associated with preterm delivery, abnormally small head size
- Low cholesterol leads to increased infections and higher incidence of many psychiatric diseases and social ills
- Optimum cholesterol appears to be between 160-240 mg/dL blood serum
- Cholesterol < 160 mg/dL associated with increased mortality and increased risk of psychiatric disorders, neurological disorders, infectious diseases, and cancer

Testing for Alzheimer's disease

- Hair metals or urine after chelation challenge
- IgG food allergy
- Organic acids- Candida, nutritional deficiencies, B12, B6, biotin, pantothenic acid, vitamin C, quinolinic acid (neurotoxic marker for inflammation),pyroglutamic for glutathione deficiency
- Cholesterol-optimum is between 200-240 mg/dL (USA units)
- Homocysteine
- Hemoglobin A1C
- Apolipoprotein E- 4 allele genotype-

Supplements associated with memory enhancement in peer reviewed articles

- Phosphatidyl serine
- Omega 3 fatty acids
- Vitamin E
- Cholesterol
- B-vitamins at multiples 2-250 X RDA values
- Lipoic acid
- Water high in silica-enhances aluminum elimination
- Lithium- nutritional levels, not pharmaceutical
- MCT oil, coconut oil, coconut