Alzheimer's -- hypothesis for an *attractive* cause, diagnosis of likelihood, and prevention

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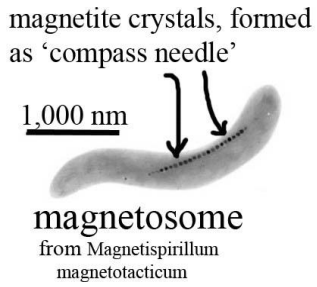
SUMMARY

A hypothesis of the cause of Alzheimer's is presented, and, if validated, can lead to several means of prevention, though not cured. The hypothesis is based upon a natural and generally painless process, *programmed cell death*, or ***apoptosis***, whose purpose in all humans is to guard against many potentially negative consequences that otherwise occur naturally (e.g., certain cancers). The apoptotic rate normally increases steadily with age with everyone having a different rate. Under normal conditions, apoptosis does not appear, by itself, to cause Alzheimer's, though a higher rate of apoptosis is definitely associated with not only Alzheimer's but Parkinson's and other neurodegenerative diseases. When brain cells die, enzymes (microglia, et al) are directed to dissolve the complex components of brain cells.

Present in all brain cells are prokaryotic organelles, called '*magnetosomes*,' discovered in humans less than two decades ago. [Magnetosomes act as magnetic compass needles for potential use by most animals in magnetotaxis, or magnetic navigation, though their *functional* use would place them in stereo pairs in ears or such organs and not in brain cells.] At their functional core are a few dozen biogenic, naturally magnetic, cubic crystals of magnetite 30 nanometers in diameter, that defy the chemical actions of the enzymes to dissolve them. Such magnetite cubes would, therefore, be freed-up from their magnetosome housing and probably accumulate in clumps in the brain. The older one gets and/or the higher the rate of apoptosis, the more crystals or clumps are present, thus important for individuals over age 60 or so.



A) One causative scenario, magnetic binding of essential nutrients: ferritin is an iron compound and essential nutrient for brain cells. It would magnetically bind to these liberated clumps of magnetite crystals. Deprived of ferritin, other brain cells would also die, releasing yet more clumps of magnetite. If one already has a naturally high rate of apoptosis, this 'ferritin high-jacking-by-magnetite' would result in exponential brain cell death, i.e., a chain-reaction, effectively an inflection point in the otherwise linear increasing rate of apoptosis. It has been noted in tens of scientific papers (some cited below) that the brains of cadavers of persons who die from Alzheimer's always exhibit *anomalous concentrations of ferritin and 'unexplained' presence of cubic crystals of magnetite*.

B) Another causative scenario, oppressive presence of material: the rate of apoptosis can be approximated by this expression, $A_r = R \times 10^9$, where A_r =rate of cell death per day and R=age of individual in years. In other words, at 50 years of age, an individual loses, on average, 50 billion brain cells per day. One of the properties of magnetite is that it is very inert and thus resistant to the attempts of enzymes to rid the brain of it, so that, once formed, stays forever. As an individual ages, the accumulation in the brain of these crystals of magnetite could be so oppressive, so as to be seen by the 'protective' principals of apoptosis as a danger to the host's health, and thus increasing the rate of cell death by acting as a trigger to release a protein *Clq* or *prions*, in response to the overwhelming intrusive presence of these clumps.

A simple test on living persons with suspected Alzheimer's and a control group can be tested using magnetometers on both sides of the skull to measure a symmetric magnetic background from such clumps; apply a short session of an external, cross-skull magnetic field gradient (coil with electric

current; then, repeat the magnetic field measurements. There should then be a different magnetic field for each side due to the magnetic clumps of magnetite being slightly shifted to one side by the gradient from the applied magnetic field. The relative asymmetry, perhaps expressed as a ratio, would be larger for persons due to more magnetite crystals from a higher lifetime rate of apoptosis. While it may seem that this ratio may be an analog of the apoptotic rate, it may very well be something far more complex, involving many other factors. Gathering such 'ratio' data from many suspected AD and non-suspected, age-corrected, persons would create a table of these ratios. A most important observation would, of course, be a correlation between a higher ratio and those suspected of having Alzheimer's AND maybe for age-corrected, but with high-ratios persons not *yet* suspect (perhaps, even tens of years before). Such an indicator, if proven valid through other tests, would greatly support this hypothesis. It might just provide strong evidence for the 'trigger', i.e., the specific driving mechanism, that many researchers have been seeking that eventually leads to the next stages of uncontrolled brain cell death and Alzheimer's disease.

Furthermore, if such an indicator is proven, it paves the way for various means for evaluation, that is, a high rate capable of inducing Alzheimer's; medium or low rate, not likely to get Alzheimer's (but more likely, cancer). Knowing the cause of a disease is usually the most critical step in finding a cure or means of prevention. While the former may not be likely, therapies for prevention may be possible, if the above cause is validated.

For persons who exhibit anomalously high apoptotic rate, apply a much higher magnetic gradient and much longer time. Then, immediately do one of the two steps. For a simple, non-invasive means, use small neodymium-boron-magnets subcutaneously to sequester a significant amount of these magnetite clumps. Another, minimally invasive, but more effective treatment for high apoptotic rate persons would be to utilize a syringe with a probe equipped with a small or nano-sized electro-magnetized rod at the tip to attract the sequestered clumps which are then drawn into the syringe for removal. Such persons with high ratios, susceptible to ongoing production of clumps, should repeat such tests in, say, five years for another session, since they will have proven to be more likely to be subject to AD than persons of average apoptotic rate. The most significant arguments ***against*** the efficacy of these suggested prevention therapies is that the brain, with its many distinctly separate regions, may not allow movement of magnetic particles from an externally-applied magnetic gradient, as is commonly done today for medical research applications in the thorax and abdomen.

Another means, if magnetic binding of ferritin is the proven factor: use a drug to supplant ferritin, a form of iron, other than ferritin, that could be administered that is metabolically suitable for brain cells but that does not exhibit magnetic properties in the presence of a magnet.

For diagnostic purposes, it may be possible to measure and differentiate between distributed and clumped magnetite in AD patients and a control group using a pico-Tesla cesium magnetometer or SQUID magnetometer, perhaps, in a magnetically-clean room. Further, if the above results prove valid, a clinical trial would involve many persons as above, say, at 50 years old, maybe even 40.

SELECTED BACKGROUND

Alzheimer's disease (AD) affects over 5 million persons in the U.S. alone. It has so far defied attempts by medical researchers to explain its origin. Without a full understanding of the underlying mechanism, it will be difficult to derive therapies, develop medication or implement prevention strategies for AD.

Magnetosomes are present in many if not all animal species. Present in a unique prokaryotic organelle inherited from bacteria more than a billion years ago, these magnetosomes contain crystals of the mineral *magnetite*. These crystals, when configured, constitute the magneto-responsive

element that forms the 'magnetic compass' needle that, under certain conditions, assists some species of animals to navigate using the earth's magnetic field. (See, for example, R.B. Frankel, R.P. Blakemore, and R.S. Wolfe, Magnetite (1979) in Freshwater Magnetic Bacteria. Science 203, 1355-1357)

Magnetite, in its inorganic form is a common mineral comprised of ferrous and ferric oxide, Fe_3O_4. It is vary hard, relatively *inert*–and *ferrimagnetic* in the presence of an ambient magnetic field. These last two characteristics (and the differences between inorganic and biogenic forms) are critical in the proposed hypothesis. Magnetite is a very common accessory mineral in granitic and volcanic rocks and is sometimes mined as iron ore. Dipping a common magnet in the water at the seashore or the bank of a stream will attract small grains of magnetite. These grains, weakly magnetic in the presence of an ambient field, are not in themselves, magnetic. That is, they are not permanently magnetized. Magnetic domains, microscopic regions several tens of nanometers (nm) in size, comprise ferrimagnetic material. They are randomly oriented and require external ambient magnetic fields to exhibit their magnetic behavior.

In bacteria and higher order animals, magnetite is formed by biological processes and is called *biogenic magnetite – forming 30 to 40 nm cubic crystals each comprised of a single magnetic domain*. Therefore, unlike inorganic magnetite crystals, these crystals are permanently and fully magnetized when formed. In order for these crystals to act as a compass needle and produce sufficient torque to sense the ambient earth's magnetic field, tens of such crystals are lined up with their magnetized vectors all aligned, constrained against clumping, by a cyto-scaffold to keep the crystals aligned. This line of magnetite crystals is then attached via cytoskeleton ligatures to the external bi-layer lipid protein membrane, the whole unit representing a single magnetosome, or magnetic compass 'needle' whether in humans, insects or bacteria. **(**See, for example, Kirschvink, JL, et al (1992) Magnetite biomineralization in the human brain. Proc. Natl. Acad. Sci., USA, 89: 7683-7687)

As brains cells die, various enzymes dissolve cells or other non-functioning materials—including the lipid protein, the cytoskeleton and scaffolding. But, biogenic or inorganic magnetite such as found in the environment, survives millions of years: resisting acids, ultraviolet and mechanical abrasion. Therefore, biogenic magnetite crystals from tens of millions of cells, liberated from their protective membranes, should form clumps and resist the actions of any natural enzyme to dissolve them or remove them from the body. Their magnetic properties will then act, even at a distance, on molecules of ferritin being delivered to brain cells.

Brain tissue collected from AD cadavers always contain anomalous amounts of iron*, though the iron compounds are not always specified. Under the subject hypothesis, it should contain small amounts of magnetite and considerably more concomitant ferritin. In fact, such evidence has been widely observed, but without accompanying explanation. (See excerpts of abstracts from these papers below.) Another recent paper**, intended to investigate whether use of cell phones was responsible for brain tumors, offered a surprising, unintended result, namely, that high frequency electromagnetic fields (EMF), simulating use of cell phones, actually kept the Alzheimer's-bred transgenic mice from exhibiting AD, compared to the control group. One explanation for this surprising find could be that such EMF interferes with the ability of magnetite crystals to attract ferritin, as ferritin is paramagnetic, and is substantially affected by the RF energy of the cell phones, thus preventing the magnetic highjacking of ferritin by magnetite clumps. *Dobson J, (2004) Magnetic iron compounds in neurological disorders. Ann. NY Acad Sci, Mar; 1012:183-92. **Arendash, GW, et al Electromagnetic field treatment protects against and reverses cognitive impairment in Alzheimer's disease mice. J Alzheimer Dis (2010) Jan;19(1):191-210.

Based upon the above, our working hypothesis is: *at a certain rate of brain cell death what was linear becomes exponential, rapidly destroying critical regions of brain tissue, thereby defining early or mid-stage Alzheimer's disease.* A variant of this could be related to brain tumors or Parkinson's Disease.

Assume that the subject hypothesis herein is proven valid, particularly the requirement that one must exhibit a greater than normal rate of programmed cell death to initiate the *exponential* phase whereby magnetite captures ferritin and/or excessive crowding of these magnetite debris triggers the increase in the apoptotic rate. If so, this higher basic rate of apoptosis that fosters the AD-related exponential phase might be a trait associated with amyloid beta and/or tau tangles in the entorhinal cortex. In other words, amyloid beta, as a cause of AD, could be its association with a higher rate of apoptosis that allows the above magnetite-triggered scenario described herein.

Consider this numerical example for the process: Assume that for the above magnetite-induced chain reaction, the threshold is 5,000 brain cell deaths per day, a BCD of 5,000/day (numbers and description are merely placeholders for purposes of example). A 60 year-old person not genetically predisposed for AD exhibits a BCD rate of 2,000/day, increasing at a rate of 50 BCD/day/year. At 100 years old, this person will still only have a BCD of 4000, and not symptomatic of AD. Another 60-year-old person with no AD symptoms but carrying the Apo E4, has the same BCD of 2,000 as the above non-AD person, but with a *rate of change* of BCD of 200/day/year (due to something associated with the Apo E4, tau or other known AD indicator). This person, will, by 75, attain a BCD of 5,000 and thus exhibit symptoms of AD.

[Patents have been filed for much of the above as it applies to diagnoses and therapy for neurodegenerative diseases.]

Excerpts from abstracts citing magnetite and ferritin in the brains of deceased Alzheimer's patients

links to all papers
http://dl.dropbox.com/u/6088957/Links%20to%20magnetite%2C%20ferritin%20in%20AD.pdf)

A study of the magnetic properties of superior temporal gyrus brain tissue from 11 Alzheimer's disease (AD) and 11 age-matched control subjects demonstrates an exponential correlation between the concentrations of the Fe;{2+}-ion-containing iron oxide, magnetite (Fe{3}O{4}), and the fraction of those particles that are smaller than 20 nm in diameter. These data provide circumstantial evidence in favor of their genesis within the 8 nm diameter cores of the iron storage protein ferritin. **We also show, for the first time, that the total concentration of biogenic magnetite is generally higher in the AD brain (in some cases as much as 15 times greater than controls)** . . .
Pankhurst Q, Hautot D, Khan N, Dobson J Increased levels of magnetic iron compounds in Alzheimer's disease. J Alzheimers Dis. (2008) Feb;13(1):49-52.
(http://www.ncbi.nlm.nih.gov/pubmed/18334756?ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DefaultReportPanel.Pubmed_RVDocSum)
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There is a well-established link between iron overload in the brain and pathology associated with neurodegeneration in a variety of disorders such as Alzheimer's (AD), Parkinson's (PD) and Huntington's (HD) diseases [1]. This association was first discovered in AD by Goodman in 1953 [2], where, in addition to abnormally high concentrations of iron in autopsy brain tissue, **iron has also been shown to accumulate at sites of brain pathology such as senile plaques** [3]. However, since this discovery, progress in understanding the origin, role and nature of iron compounds associated with neurodegeneration has been slow. Here we report, **for the first time, the location and characterisation of iron compounds in human AD brain tissue sections. Iron fluorescence was mapped over a frontal-lobe tissue section from an Alzheimer's patient, and anomalous iron concentrations were identified** . . .**Concentrations of ferritin and magnetite, a magnetic iron oxide potentially indicating disrupted brain-iron metabolism, were evident.** These results demonstrate a practical means of correlating iron compounds and disease pathology in-situ and have clear implications for disease pathogenesis and potential therapies

Collingwood JF, et al In situ characterization and mapping of iron compounds in Alzheimer's disease tissue. J Alzheimers Dis. (2005) Aug;7(4):267-72
(http://www.ncbi.nlm.nih.gov/pubmed/16131727?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DiscoveryPanel.Pubmed_Discovery_RA&linkpos=1&log$=relatedarticles&logdbfrom=pubmed)
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Elevated iron levels are associated with many types of neurodegenerative disease, such as Alzheimer's, Parkinson's and Huntington's diseases. However, these elevated iron levels do not necessarily correlate with elevated levels of the iron storage or transport proteins, ferritin and transferrin. As such, little is known about the form of this excess iron. It has recently been proposed that some of the excess iron in neurodegenerative tissue may be in the form of the magnetic iron oxide magnetite (Fe(3)O(4)). We demonstrate, for the first time to our knowledge, using highly sensitive superconducting quantum interference device (SQUID) magnetometry, that the **concentrations of magnetite are found to be significantly higher in three samples of Alzheimer's disease tissue than in three age- and sex-matched controls.** These results have implications, not only for disease progression, but also for possible early diagnosis.

Hautot D, Pankhurst QA, Khan N, Dobson J. Preliminary evaluation of nanoscale biogenic magnetite in Alzheimer's disease brain tissue. Proc Biol Sci. (2003) Aug 7;270 Suppl 1:S62-4.
http://www.ncbi.nlm.nih.gov/pubmed/12952638?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DiscoveryPanel.Pubmed_Discovery_RA&linkpos=2&log$=relatedarticles&logdbfrom=pubmed
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Previous studies of the structure of core nanocrystals of ferritin (Ft) in the brains of patients with Alzheimer's disease (AD) have shown differences in the mineral compound in comparison with physiological Ft. Both Ft cores have a polyphasic composition but whereas the major phase in physiological Ft is hexagonal ferric iron oxide (ferrihydrite), the major phases in brain AD Ft are two cubic mixed ferric-ferrous iron oxides (magnetite and wÃ¼stite). cytes. Ft was particularly abundant in myelinated axons in association with oligodendrocyte processes. **These findings provide new arguments to support the hypothesis of a dysfunction of ferritin, Ft, (with eventual degradation to hemosiderin (Hm) in AD resulting in an increase of toxic brain ferrous ions that may contribute to the production of free radicals that induce both cellular oxidative stress and aged-related myelin breakdown associated with cognitive decline and AD**

Quintana C, et al Study of the localization of iron, ferritin, and hemosiderin in Alzheimer's disease hippocampus by analytical microscopy at the subcellular level. J Struct Biol. 2006 Jan;153(1):42-54. Epub (2005) Dec 1
(http://www.ncbi.nlm.nih.gov/pubmed/16364657?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_DiscoveryPanel.Pubmed_Discovery_RA&linkpos=3&log$=relatedarticles&logdbfrom=pubmed)
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One of the characteristics of many neurodegenerative diseases is the disruption of normal iron homeostasis in the brain. Recent experimental work indicates that nanoscale magnetic biominerals **(primarily magnetite and maghemite) may be associated with senile plaques and tau filaments found in brain tissue affected by these diseases.** These findings have important implications for our understanding of the role of iron in neurodegenerative disease as well as profound implications for their causes. In addition, the presence of biogenic magnetite in affected tissue should also provide improved mechanisms for early detection through the modification of MRI pulse sequences.

Dobson J Nanoscale biogenic iron oxides and neurodegenerative disease. FEBS Lett. (2001) May 4;496(1):1-5
(http://www.ncbi.nlm.nih.gov/pubmed/11343696?dopt=abstractplus)
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Mammalian cellular iron is stored inside the multisubunit protein ferritin, normally taking the structure of a ferrihydrite-like mineral core. **It has been suggested that biogenic magnetite, which has been detected in the brain and may be related to neurodegenerative diseases such as Alzheimer's and Parkinson's diseases, could initially form in ferritin. Indeed, as ferritin is present in the brain, the ferrihydrite core could be a precursor for biogenic magnetite formation--particularly in cases where the normal functioning of the ferritin protein is disrupted.**

Gossuin Y, et al. Looking for biogenic magnetite in brain ferritin using NMR relaxometry. NMR Biomed. (2005) Nov;18(7):469-72. (http://www.ncbi.nlm.nih.gov/pubmed/16177954?dopt=AbstractPlus)
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Oxidant-mediated damage is suspected to be involved in the pathogenesis of several neurodegenerative disorders. Iron promotes conversion of hydrogen peroxide to hydroxyl radical and, thus, may contribute to oxidant stress. We measured iron and its transport protein transferrin in caudate, putamen, globus pallidus, substantia nigra, and frontal cortex of subjects with Alzheimer's disease (n = 14) and Parkinson's disease (n = 14), and in younger adult (n = 8) and elderly (n = 8) normal controls. Although there were no differences between control groups with regard to concentrations of iron and transferrin, **iron was significantly increased ($p < 0.05$) in Alzheimer's disease globus pallidus and frontal cortex** and Parkinson's disease globus pallidus, and transferrin was significantly increased in Alzheimer's disease frontal cortex, compared with elderly controls. . . .(Pearson's correlation coefficient) in elderly controls than in Alzheimer's and Parkinson's disease. **The altered relationship between iron and transferrin provides further evidence that a disturbance in iron metabolism may be involved in both disorders.**

Loeffler DA, et al Transferrin and iron in normal, Alzheimer's disease, and Parkinson's disease brain regions. J Neurochem. (1995) Aug;65(2):710-24 (http://www.ncbi.nlm.nih.gov/pubmed/7616227?dopt=AbstractPlus)

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The magnetic properties of human hippocampal tissue from 23 subjects (15 epilepsy patients and eight cadavers with no neuropathology) were analysed and tissue concentrations of magnetic material were calculated. The biogenic iron oxide magnetite (Fe(3)O(4)) is the dominant source of magnetisation in the tissue. Analysis of the group as a whole revealed no significant trend towards either increasing or decreasing magnetite concentration with age. **Separate analysis of male and female subjects, however, reveals a trend towards increasing magnetite concentration with age in males.** This trend is not seen in females and may have implications for iron metabolism and neurological disorders associated with disruptions in normal iron homeostasis.

Dobson J. Investigation of age-related variations in biogenic magnetite levels in the human hippocampus. Exp Brain Res. (2002) May;144(1):122-6. Epub 2002 Mar 12.
(http://www.ncbi.nlm.nih.gov/pubmed/11976766?dopt=AbstractPlus)

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The amount of loosely bound iron was measured in frontal cortex and cerebellum from autopsy brain samples from Alzheimer's patients and from non-demented, age matched controls. **It was found that the amount of total iron and of ferric iron in Alzheimer's brain tissues was significantly higher compared to control samples in both regions studied.** Neither the ferrous nor the ferrous to ferric ratio were found to be changed. **Since it is the loosely bound iron that is responsible for free radical reactions in vivo, these results are consistent with an increased free radical burden in Alzheimer's disease** that leads to the progressive neurodegeneration seen in this disorder.

Kala SV, Hasinoff BB, Richardson JS. Brain samples from Alzheimer's patients have elevated levels of loosely bound iron. Int J Neurosci. (1996) Sep;86(3-4):263-9.
(http://www.ncbi.nlm.nih.gov/pubmed/8884397?dopt=AbstractPlus)

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Ferritin is the primary iron storage protein in the brain. It consists of a 12nm diameter spherical protein shell with an 8nm cavity capable of storing up to 4500 iron atoms in the form of ferrihydrite. Ferrihydrite is superparamagnetic at body temperature and it exists in varying degrees of crystallinity in the human body. In addition to ferritin, biomineralization of ferrimagnetic magnetite is known to occur in a number of organisms including animals [e.g. 1]. Recent investigations have revealed the presence of biogenic magnetite in human brain tissue as well [2,3,4,5]. **The presence of magnetite in the brain has been established using a variety of magnetic and electron microscopic techniques. In addition, anomalous concentrations of iron are known to be associated with virtually all neurodegenerative diseases, however, since this relationship was first discovered 50 years ago, very little progress has been made in understanding their composition, origin or role in disease processes.**

Goodman, L Alzheimer's disease - a clinicopathologic analysis of 23 cases with a theory on pathogenesis. J. Nerv. Ment. Dis. (1953) 118: 97-130