THE RELATIONSHIP OF THE TOXIC EFFECTS OF MERCURY TO EXACERABATION OF THE MEDICAL CONDITION CLASSIFIED AS ALZHEIMER'S DISEASE

By

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Abstract: Mercury(II), when exposed to normal brain tissue homogenates, is capable of causing many of the same biochemical aberrancies found in Alzheimer's diseased (AD) brain. Also, rats exposed to mercury vapor generate similar effects in their brain tissues. Specifically, the rapid inactivation of tubulin, creatine kinase and glutamine synthetase occurs on the addition of low micromolar levels of mercury(II) or exposure to mercury vapor. Further, mercury(II) exposure to neurons in culture is also capable of producing three of the widely accepted pathological hallmarks of AD, elevated amyloid protein, hyper-phosphorylation of Tau, and neurofibillary tangles. This occurs after the rapid inhibition of tubulin and creatine kinase. I propose that mercury, and other toxicants that have enhanced specificity for thiol-reactive enzymes, such as tubulin and creatine kinase, are the etiological source of AD. This hypothesis is supported by the genetic susceptibility expressed through the APO-E gene family. Specifically, a reduction of APO-E gene types carrying cysteines decreases the ability to remove mercury and other thiol-reactive toxicants from the cerebrospinal fluid. This increases brain exposure to thiol-reactive toxicants and the risk of AD.

RATIONALE FOR THE HYPOTHESIS:

AD is a disease of unknown etiology. However, it is widely accepted that most AD is not directly genetically inherited and that some external vector, such as a toxicant exposure or an infection, must be involved for the disease to progress into a clinically observable condition. In the USA the rate of AD is very similar for rural versus urban peoples and it does not vary appreciably from state to state. Therefore, if a toxicant is involved then this toxicant must be of a very personal nature, like what we eat or what is placed into our bodies through other sources such as dental fillings, vaccines, etc. The involvement of infectious agents such as bacteria, virus or yeasts; while possible at this time, seem not to be directly involved. This is based on the huge amount of National Institutes of Health (USA) and other world-wide funds spent on AD to identify the causal factors and they have not identified a microbial vector. If an infectious agent were involved (like in AIDS and polio) it seems as if it would have been identified by now.

For any toxicant, or class of toxicants, to be proposed as involved in the etiology of AD they must be available equally to individuals living in markedly different locations. They must explain the genetic susceptibility concept of AD. Further, under experimental conditions the toxicants must cause the exacerbation of the many biochemical aberrancies found in AD brain. In my opinion, mercury and mercury containing compounds from dental amalgams, vaccines, other medicinals and preservatives used in paints, seed grains, etc. fill this requirement. Mercury and organic mercurials are neurotoxicants. Further,

the enzyme inhibitory effects of mercury are synergistically enhanced by exposures to other toxicants such as lead and cadmium (smokers). Even the simultaneous presence of EDTA (ethylene-diamine-tetraacetic acid, a common food additive) or metal binding antibiotics such as tetracycline can enhance mercury toxicity. Therefore, any determination of a safe level of mercury exposure using rats in a cage being feed carefully monitored food and water is not reliable for determination of a "safe level of exposure to mercury" for humans. The fact is science does not know what the combined toxic effects of many toxicants or enhancers of toxicity would be.

Therefore, thiol-reactive toxicants such as mercury, cadmium, lead and certain organics are rational suggestions as being exacerbating factors for AD, or possibly even causal. However, mercury is the one toxicant that has been shown to reproduce many of the biochemical aberrancies and diagnostic hallmarks of AD and mercury exposure is readily available to most humans. I propose that exposure to mercury is the major toxic factor involved in AD and that simultaneous exposures to other toxicants or factors enhance the toxicity of mercury and hasten the onset of AD, especially in those individuals who are genetically susceptible.

RESEARCH REVIEW AND RESULTS:

Research regarding Alzheimer's disease (AD) done in our laboratory in the late 1980s was directed towards detecting aberrancies in the nucleotide binding proteins of AD post-mortem brain versus age-matched, non-demented control brain samples. Basic to all of our findings was the following observation. Two very important brain nucleotide binding proteins, tubulin, and creatine kinase (CK), showed greatly diminished activity and nucleotide binding ability. Further, they were abnormally partitioned into the particulate fraction versus the soluble fraction of AD brain tissue (1,2). It is critical to understand that both tubulin and CK are found primarily in the soluble fraction of a normal brain homogenate. However, both are almost totally located in the particulate fraction after separation of the soluble and particulate fractions by simple centrifugation. Yet, both proteins appear of normal size and unmodified on reducing gel electrophoresis. This indicates that both intact tubulin and CK have formed crosslinks with other proteins that are insoluble under physiological conditions. Yet, these crosslinks are readily disrupted by the common dithiolthreitol reduction procedure used before gel electrophoresis.

What tubulin and CK have in common is that both have a very reactive sulfhydryl in their nucleotide binding sites that, if modified, inhibits their biological activity (14, 15). Mercury has a very high affinity for sulfhydryls and has been proven to be a potent inhibitor of both of these proteins biological activity. Also, mercury is divalent and can form crosslinks between soluble proteins like tubulin and CK. For example;

$$\text{Protein-A-SH} + \text{Protein-B-SH} + Hg^{2+} \Rightarrow \text{Protein-A-S-Hg-S-Protein-B} + 2\ H^{+}.$$

This chemistry would allow the formation of aggregates that would abnormally appear in the particulate fraction. The massive amounts of dithiolthreitol used in reducing gels could chelate and remove mercury from the proteins resulting in their solubilization as observed.

Both tubulin and CK are proteins that bind the nucleotides GTP (guanosine-5'-triphosphate) and ATP (adenosine-5'-triphosphate), respectively. We use a

"photoaffinity labeling" technology to determine the availability of these binding sites before and after addition of mercury or other toxicants (21). Using this technology our laboratory demonstrated that both tubulin and CK had diminished biological activity in AD brain compared to age-matched controls. Since AD is not directly a genetically inherited disease we searched for possible toxicants that might mimic the specific findings observed in AD brain. Our first finding was simple and straight-forward. After testing numerous heavy metals we observed that only mercury(II) (i.e. Hg^{2+}) could mimic this effect in homogenates of normal brain at concentrations that might be expected to be found in brain (3,4). The observation was that Hg^{2+} at very low micromolar levels (≅ 1 micromolar) could rapidly, selectively and totally abolish the GTP binding activity of tubulin ($M_r = 55{,}000$ daltons) without any noticeable effect on other GTP binding proteins protein(s) at an M_r of about 42,000 daltons, (contains actin) that are also present in both control and AD brain. Therefore, addition of mercury, and only mercury, to control brain homogenates gave a GTP binding profile that was identical to that observed in AD brain (4,5,6). Further, recent results in our laboratory have shown that the addition of Hg^{2+} to control brain homogenates not only caused the decrease in nucleotide interaction but could also support the abnormal partitioning of tubulin into the particulate fraction as observed in AD brain (7). This was especially effective in the presence of other divalent metals, such as zinc, which is elevated in AD brain.

The next set of experiments was to determine if mercury vapor, the form that escapes from dental amalgams, could mimic the effect in rats exposed to such vapor for various periods of time (5). Rats are different from humans in that their cells can synthesize vitamin C whereas humans have to ingest vitamin C. Vitamin C is thought to be somewhat protective against heavy metal toxicity and other oxidative stresses. However, we observed that the tubulin in the brains of rats exposed to mercury vapor lost between 41 and 75 percent of the nucleotide binding capability demonstrating a similarity to the aberrancy observed in AD brain (5).

There is an "excito-toxic" amino acid hypothesis for the cause of AD wherein excito-toxic glutmate builds up in brain tissue causing neuronal death. The activity of mercury sensitive glutamine synthetase (GS) was measured in AD brain and the amount of GS in the cerebrospinal fluid of AD versus control patients was determined. GS was found it to be inhibited in AD brain and elevated in cerebrospinal fluid (12, 22). It has also been predicted by two groups that the elevation of GS in the cerebrospinal fluid of AD patients has potential as a diagnostic aid for AD (12,16). However, it is reasonable to conclude that brain GS would be rapidly inhibited by Hg^{2+} from mercury vapor. This inhibition would cause a rise in glutamate based neurotoxicity and could cause the lysis of astroglial cells. The measurement of GS in cerebrospinal fluid is most likely a measure of glial cell toxicity and death in several central nervous system diseases.

The fact that mercury has inhibitory effects on tubulin, CK and GS and that these proteins are proven to be aberrantly inhibited in AD does not conclusively prove that mercury exposure causes AD. However, it definitely proves that chronic, daily exposure to mercury would at least exacerbate the clinical conditions of AD based on the ability of low doses of mercury to inhibit the same enzymes known to be inhibited in AD brain. Is such an exposure to mercury likely? The answer is yes. Dental amalgams, or "silver fillings" as organized dentistry calls them, are approximately 50% mercury by weight and

it is quite easy to demonstrate that mercury vapors readily emit from these fillings. This has been demonstrated by several studies, one showing mercury released at 43.4 micrograms/cm^2/day for two years (9). This was confirmed by a recent NIH study indicating that individuals with an average number of amalgam fillings have about 4.5 times the blood/urine mercury levels as controls without amalgams (20). This confirms and earlier study where urinary mercury levels dropped by a factor of 5 after the removal of amalgam fillings where the conclusion was that mercury from dental amalgams exceeds that from food, air and fluids (23). Further, studies in our laboratory have shown that soaking of amalgams in distilled water created a solution that also caused rapid inhibition of brain tubulin and creatine kinase.

Any hypothesis of the etiology of AD must consider information on genetic susceptibility. The best known genetic risk factor for AD is the correlation of APO-E genotypes to the age of onset of AD (24). Individuals can inherit any combination of the alleles APO-E2, E3 or E4. Individuals inheriting APO-E2 or combinations of APO-E2 and E3 are much less likely to get early onset AD than are individuals who have inherited APO-E4 genes. Also, APO-E2 appears to be more protective than APO-E3 against early onset AD. Therefore, it is necessary that the mechanism of mercury toxicity contain an explainable relationship for the APO-E the genetic susceptibility. This is accomplished in a straight-forward manner by considering the basic structural difference between these three alleles. Simply put, the protective APO-E2 has two sulfhydryls (cysteines) that can bind mercury or other heavy metals that APO-E4 lacks. For example, in APO-E3, one of APO-E2 cysteines is replaced by an arginine and in APO-E4, both of the APO-E2 cysteines are replaced by arginines. Therefore, lack of protection against early onset AD follows loss of mercury binding sulfhydryls from APO-E proteins (6).

The protection provided by APO-E2 is reasonable when considering the nature and biochemical assignment of APO-E proteins. APO-E proteins are involved in cholesterol transport and all three alleles do this reasonably well. However, APO-E is classified as a "housekeeping protein". That is, in contrast to tubulin, GS and CK, which are meant to stay inside of cells where they are synthesized, APO-E is meant to leave the brain cells carrying damaged cholesterol through the cerebrol spinal fluid (CSF), across the blood-brain barrier into the blood where it is removed by the liver. It fits into the hypothesis that while APO-E2 or E3 are leaving the brain cells and traversing the CSF they likely bind and remove mercury, other heavy metals or other sulfhydryl reactive toxins that may have made it into the central nervous system (6). APO-E4 cannot as effectively bind mercury and therefore does not provide the protective parameters that APO-E2 and E3 have. It is interesting to note that the second highest level of APO-E protein in the body is in the CSF that bathes and protects the brain.

There has been considerable debate concerning whether or not mercury reaches levels in the brain and other tissues that could be considered toxic or harmful (24,25). The determination of the levels of mercury toxicity that could cause neurological disease has been done using animals, such as rats, under tightly controlled laboratory conditions where the diet is carefully monitored to exclude other toxicants. Also, any rat that becomes ill or infected by microbial sources is removed from the study. However, humans do not live under such restricted conditions. For example, heavy metal imbalances in AD brains have been reported numerous times. Cigarette smokers are

exposed to excess cadmium (Cd) and lead (Pb) toxicity is not that uncommon in the inter-city environment or for those exposed to leaded gasoline fumes for many years. Our laboratory has shown that one can add various metals to human brain homogenates to levels that alone do not affect nucleotide binding to tubulin, yet the very presence of these metals potentiate the toxicity of mercury. That is, the presence of Zn^{2+} and Cd^{2+}, at non-toxic levels, decrease the amount of Hg^{2+} required for 50% inhibition of tubulin or creatine kinase viability. When we compare the toxicity of Hg^{2+} in brain homogenates as described above (refs. 3 & 4) the addition of 0, 10 and 20 micromolar Zn^{2+} increases the inhibition of GTP binding to tubulin from 4% to 50% and 76%, respectively (7,13). In other words, mercury is much more toxic in the presence of other metals that compete with mercury for the binding sites on protective biomolecules (e.g., APO-E2 & E3, glutathione, metallo-thionine, etc.). This observation probably explains some observations on the toxicity of solutions in which dental amalgams have been soaked.

Through the same rationale, illnesses that lower our metabolic energy levels also lower our ability to synthesize the reducing equivalents that allow our body to bind and dispose of excess mercury. Mercury is known to inhibit the metabolic processes in mitochondria that produce ATP and NADH by inhibiting the enzymes of the citric acid cycle and the electron transport system. These nucleotides are absolutely required for both the synthesis of reduced glutathione (GSH) and to reduce glutathione after it is oxidized. Glutathione in the reduced state is the major biomolecule involved in the natural removal of mercury from the body.

A recent publication supports our contention that mercury from dental amalgams poses a major threat to the exacerbation of AD. Olivieri et al. demonstrated that exposure of neuroblastoma cells to sub-lethal doses (36×10^{-9} molar) of Hg^{2+} caused a rapid drop in GSH, an increased secretion of β–amyloid protein and an increased phosphorylation of the microtubulin protein Tau (17). The latter two of these biochemical changes are uniquely observed in AD brain tissues and are widely considered to be diagnostic, pathological markers of the disease. β-amyloid protein makes up the 'amyloid plaques' that was one of the first diagnostic markers reported for AD brain pathology. A very strong component of AD researchers believe that amyloid protein is the cause of AD. Therefore, mercury exposure at nanomolar levels causes neuroblastoma cells to produce a protein that is believed to be involved directly in AD. This lead the authors of this paper to conclude that mercury would have to be consider as causal for AD (17).

Further, the recent report of the response of neurons in culture rapidly forming neurofibillary tangles on exposure to extremely low levels of mercury, by a process involving loss of microtublin structure, completes the picture that mercury is capable of causing the formation of the two major diagnostic hallmarks of AD in neuronal cultures (18). An impressive video accompanying this publication and available on the world wide web shows the addition of 2 microliters of 10^{-7}M mercury to a 2 milliliter solution bathing neurons caused a rapid stripping of the tubulin from the neurofibrils leaving them bare. The bare neurofibrils could then wind and aggregate forming neurofibrillary tangles (NFTs) indistinguishable from those observed in AD brain and used pathologically as a diagnostic marker for AD. The final mercury concentration of 10^{-10}M in these experiments is roughly 100 to 1000 times lower than the 10^{-7}M levels normally found in

human brain of individuals with amalgam fillings. The majority of the mercury in brain is likely bound by protective proteins or selenium and not free to cause neuronal damage.

However, these two recent publications supports the initial contention that mercury first rapidly inhibits enzymes like tubulin, creatine kinase and glutamine synthetase and dramatically affects metabolism and membrane structure. This leads to the formation of NFTs, a diagnostic marker for AD. The exposure of the neurofibrils by the stripping of tubulin exposes the microtubular associated protein Tau to an aberrant situation leading to Tau's increased phosphorylation state as observed in AD brain tissue. After this occurs the cells respond to the cytotoxicity by producing and secreting amyloid protein, that forms the amyloid plaques observed on brain pathology and used to substantiate the AD diagnosis. To the point, neurofibillary tangles, hyper-phosphorylated Tau, and amyloid plaques are the result of neuronal toxicity and death in AD, they are not the cause. The cause is exposure to environmental toxicants like mercury that attack enzymes with the most reactive thiols groups.

Wataha et al. (8) reported that extracts of the amalgam material (trade name, Dispersalloy) "was severely cytotoxic when Zn release was greatest, but less toxic between 48 and 72 hours as Zn release decreased". In our laboratory we soaked amalgam fillings in distilled water and then tested the resulting solution for toxicity. The results were obvious, the water was now extremely toxic and when added to brain homogenates dramatically inhibited the viability of tubulin and creatine kinase, exactly as observed when we added mercury cation. Zn is an essential metal needed for health and many times recommended by physicians to be taken in supplemental form. It is my opinion that the increased toxicity was not caused by direct Zn toxic effects. Rather, enhanced toxicity was due to the Zn potentiated toxicity of mercury caused by Zn^{2+} occupying biomolecule chelation sites resulting in a higher concentration of free Hg^{2+} capable of inhibiting the activity of critical nucleotide binding proteins such as tubulin and CK. The bottom line is that mercury toxicity is enhanced by the presence of other heavy metals and both are released from dental amalgams. Additionally, when one considers the toxicity of a certain body level of mercury it is somewhat meaningless unless the body level of other heavy metals is also considered.

This raises the question of how much mercury is released from amalgams under similar conditions. Chew et al. (9) tested the "long term dissolution of mercury from a non-mercury-releasing amlagam (trade name Composil)". Their results demonstrated "that the overall mean release of mercury was 43.5 +/-3.2 micrograms/cm^2/24hr, and the amount of mercury released remained fairly constant during the duration of the experiment (2 years)". In my opinion, this is not an insignificant amount of mercury exposure if one considers the number of years a 70 year old individual living today may have been exposed. Additionally, this is the level released without galvanism, excess heat, or pressure from chewing, all factors that increase mercury release from amalgams.

Many recent literature and popular press reports state that the presence of periodontal disease raises the risk factor or exacerbates the condition of several other seemingly unrelated diseases such as stroke, low birth weight babies, cardiovascular disease (See October 1996 issue of Periodontology). The anerobic bacteria of periodontal disease produce hydrogen sulfide (H_2S) and methyl thiol (CH_3SH) from cysteine and methionine, respectively. This accounts for the "bad breath" many individuals have.

However, in a mouth that produces H_2S, CH_3SH (from periodontal disease) and Hg^o (from amalgam fillings) the very likely production of their reaction products, HgS (mercury sulfide), CH_3S-Hg-Cl (methyl-thiol mercury chloride) and CH_3S-Hg-S-CH_3 (Dimethylthiol mercury) has to occur. This is simple, un-refutable chemistry whose presence is supported by easily observable amalgam tattoos. These tattoos are purple gum tissue surrounding certain teeth where the gum and tooth meet and caused by HgS as determined by mercury analysis of such tissue. HgS is one of the most stable forms of mercury compounds and is the mineral form of mercury, called cinnabar, from which mercury is mined from the earth). All of these compounds are classified as extremely toxic and the latter compound, dimethylthiol-mercury is very hydrophobic and it solubility similar to dimethyl-mercury. Dimethyl-mercury was the compound that was made famouns in the press where only a small amount spilled on the latex gloves of a Dartmouth University chemistry professor caused severe medical problems and finally death 10 months later. Logic implys that anyone with periodonatal disease, anaerobic bacterial infected teeth and mercury containing fillings would be exposed daily to these very toxic compounds. In our laboratory we synthesized the two methylthiol-mercury compounds and tested them. They are extremely cytotoxic at 1 micromolar or less levels and are potent, irreversible inhibitors of a number of important mammalian enzymes, including tubulin and CK.

Idiopathic cardiomyopathy

To determine if toxic teeth could have an effect on the enzymes/proteins of human brain we have done the following study. Several very toxic teeth were incubated for 1 hour in distilled water. Aliquots of these solutions were then added to control human brain homogenates and the resulting samples tested for enzyme viability. The result showed that several of the solutions, but not all, in which toxic teeth had been incubated inhibited the viability of the same enzymes that are found to be inhibited in AD brain. Therefore, depending on the type of anerobic bacterial infection in avital teeth it is possible to have a toxicant production that would exacerbate the condition classified as AD.

In summary, the data on the effects of mercury on the nucleotide binding properties and the abnormal partitioning of two very important brain nucleotide binding proteins first suggested that mercury must be considered as a contributor to the condition classified as AD. This is strongly supported by the recent finds that nanomolar levels of mercury causes neuroblastoma cells to secrete β-amyloid protein and increase phosphorylation of the microtubulin associated protein Tau, both major biochemical observations related to AD. Also, neurons in culture exposed to mercury cation at the 10^{-7} to 10^{-10} M levels have conclusively been shown to rapidly lose organized tubulin that surrounds the neurofibrils resulting in the formation of neurofibillary tangles that are indistinguishable from those observed in AD brain and used as a diagnostic marker of the disease(18). Consideration of mercury as an exacerbating factor is especially relevant when mercury is present in combination with other heavy metals such as zinc (Zn) cadmium (Cd) and lead (Pb). It has been reported that combining an LD-1 of lead with an LD-1 of mercury in rats gave an LD of 100 (19). Bluntly, the determination of safe body levels of mercury by using animal data where the animals have not been exposed to other heavy metals is no longer justifiable. Mercury is much more toxic to individuals

with other heavy metal exposures. As I have been sent numerous lab reports on levels of elements in the hair and other tissues of suspected mercury toxic patients I have noticed that many have exceedingly high Pb, Cd, Cu, Zn, etc. levels. It is my opinion that one of the major questions left to be answered concerning the toxic effects of mercury is "does the combination of mercury with different heavy metals lead to different clinical observations of toxicity?" There can be no doubt that the elevated levels of other heavy metals increases the toxicity of mercury. Further, the reaction of oral mercury from amalgams and the reaction of this mercury with toxic thiols produced by periodontal disease bacteria very likely enhances the toxicity of the mercury being released. This makes any claim regarding the determination of safe levels of mercury as obtained under controlled conditions (e.g. in a system where other heavy metals are excluded) very suspect when discussing toxic mercury effects in the uncontrolled environment that humans are exposed to.

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27.

At 10:07 AM 6/1/01 -0700, you wrote:
>Dear Doctors Haley and Pendergrass,
>
>I've aquired and read your studies on Hg from amalgam
>fillings and a possible link to Alzheimer's disease.
>I've been researching causal factors in AD and have
>never seen anything approaching the evidence you've
>established for Hg. All the more shocking that I only
>found out about it via PubMed searches and not any of
>the myriad AD texts and publications I've read. My
>Mother has severe AD and her total teeth mass is about
>50% mercury amalgam.
>
>It occurred to me that I'd seen research on damage to
>the olfactory nerve in the nasal cavity as a
>very-early indicator of AD. On its face, the olfactory
>nerve seems a likely avenue for Hg vapor from amalgams
>to directly access the brain, particularly due to the
>affinity of Hg to nerve tissue. This avenue would be
>much more direct than via lungs... blood...
>
>In combination with your research showing non-AD brain
>tissue will test positive for AD afer Hg exposure, and
>the resent studies showing Hg promotes beta-amyloid
>and tau phosphorylation, the evidence is arguably
>overwhelming for an Hg-AD link, especially when
>measured relative to any other possible toxicant.
>
>Here are just a few of the studies showing that
>olfactory impairment is an early marker of AD. Thank
>you for your research and efforts to make your
>findings known!
>
>Ian Goddard
>
>==
>Am J Psychiatry 2000 Sep;157(9):1399-405
>
>Olfactory deficits in patients with mild cognitive
>impairment predict Alzheimer's disease at follow-up.
>
>Devanand DP, Michaels-Marston KS, Liu X, Pelton GH,
>Padilla M, Marder K, Bell K, Stern Y, Mayeux R.
>
>New York State Psychiatric Institute, New York, NY
>10032, USA.
>
>OBJECTIVE: This study evaluated the predictive utility
>of olfactory identification deficits in patients with
>mild cognitive impairment for follow-up diagnosis of
>probable Alzheimer's disease. METHOD: Ninety
>outpatients with mild cognitive impairment were
>examined at 6-month intervals. Matched healthy
>comparison subjects (N=45) were examined annually. The
>University of Pennsylvania Smell Identification Test

>was given at baseline. RESULTS: Olfaction scores were
>lower in patients with mild cognitive impairment than
>in healthy comparison subjects. Seventy-seven patients
>were followed up; 19 were diagnosed with Alzheimer's
>disease by 2 years. Patients with low olfaction scores
>(< or =34 of 40), and patients with low olfaction
>scores who reported no subjective problems smelling,
>were more likely to develop Alzheimer's disease than
>other patients. In a Cox proportional hazards model
>adjusted for age, sex, modified Mini-Mental State
>score, and education, low olfaction scores did not
>predict time until development of Alzheimer's disease,
>but low olfaction scores accompanied by lack of
>awareness of olfactory deficits predicted time to
>development of Alzheimer's disease. This effect
>remained when attention or memory measures replaced
>modified Mini-Mental State score in the model. In
>patients with high Mini-Mental State scores (> or =27
>of 30), low olfaction with lack of awareness remained
>a significant predictor of Alzheimer's disease.
>Olfaction scores of 30-35 showed moderate to strong
>sensitivity and specificity for diagnosis of
>Alzheimer's disease at follow-up. CONCLUSIONS: In
>patients with mild cognitive impairment, olfactory
>identification deficits, particularly with lack of
>awareness of olfactory deficits, may have clinical
>utility as an early diagnostic marker for Alzheimer's
>disease.
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>http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list
• _uids=10964854&dopt=Abstract
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>Neuroreport 2001 Feb 12,;12(2):285-8
>
>Olfactory centres in Alzheimer's disease: olfactory
>bulb is involved in early
>Braak's stages.
>
>Kovacs T, Cairns NJ, Lantos PL.
>
>Department of Neuropathology, Institute of Psychiatry,
>London, UK.
>
>In Alzheimer's disease (AD), neurofibrillary tangles
>spread from the entorhinal cortex to the limbic
>system, then to neocortical areas, according to the
>Braak's stages. Olfaction is impaired in early stages
>of AD. The aim of this study was to describe the
>pathology of the cortical olfactory centres in
>relation to Braak's stages determining the earliest
>site of pathology. We examined 15 control and 15 AD
>cases. The primary olfactory cortices were involved in
>more advanced Braak's stages, while olfactory bulbs
>were damaged in very early (i.e. Braak's stage 0 or 1)

>stages. These results are supporting the fact that
>olfaction might be an early marker in AD and argues
>against the hypothesis that AD pathology is spreading
>through the olfactory system.
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>http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list
• _uids=11209936&dopt=Abstract
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>Int J Geriatr Psychiatry 2001 May;16(5):513-7
>
>Olfactory identification is impaired in clinic-based
>patients with vascular
>dementia and senile dementia of Alzheimer type.
>
>Gray AJ, Staples V, Murren K, Dhariwal A, Bentham P.
>
>Senior Registrar, Worcestershire Community Healthcare
>NHS Trust, UK.
>
>AIMS: It is now well established that there are
>abnormalities in the sense of smell in patients
>suffering from Alzheimer’s disease (AD). They have
>both raised olfactory thresholds and impaired odour
>identification. The situation in vascular dementia is
>unclear. We used the University of Pennsylvania Smell
>Identification Test (UPSIT), a 40-item, forced choice,
>cued, ‘scratch-and-sniff’ test, to examine olfactory
>identification in vascular dementia and to determine
>whether it would differentiate the disorder from AD
>and normal elderly. METHODS: We investigated three
>matched subject groups: 13 people having a Cambridge
>Examination for Mental Disorders in the Elderly
>(CAMDEX) diagnosis of definite senile dementia of
>Alzheimer type, 13 having a CAMDEX diagnosis of
>definite vascular dementia and 13 non-cognitively
>impaired controls. The subjects were then tested with
>the UPSIT in their own home by an independent blind
>researcher to see if the test could distinguish the
>different diagnostic groups in this setting. RESULTS:
>The median UPSIT score was 30 (out of a maximum
>of 40) for controls, 12 for the vascular group and 15
>for the AD group. The difference was significant (p =
>0.05) between both demented groups and the normal
>controls. Similarly there was a significant difference
>in the UPSIT score between the AD group and controls
>(p = 0.001) and between the vascular dementia group
>and controls (p = 0.001), but there was no significant
>difference between the AD group and the vascular
>dementia group. The UPSIT score correlated strongly
>with the degree of cognitive impairment as measured by
>the CAMCOG (r(s) = 0.683, p = 0.01) CONCLUSIONS:
>Patients with vascular dementia had a similar degree
>of olfactory impairment to those with AD. The UPSIT
>successfully differentiated between dementia patients
>and normal elderly British subjects tested in their

>own homes. The UPSIT did not differentiate between
>those with AD and vascular dementia. Copyright 2001
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>
>http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list