ENVIRONMENTAL TOXINS AND NEURODEGENERATIVE DISEASE: what does the academic evidence show?

Rachel Nicoll PhD

A few words on the handout

- I have tried to show human studies where possible, covering the development, progression or mortality of AD, PD, ALS and MS…
- ..and their association with air pollution (indoor and outdoor), POPs, pesticides, foods and their contaminants, toxic metals, ionising and non-ionising radiation.
- There is evidence for some association between virtually all toxin categories and virtually all the 4 conditions.
- But there are also a number of studies showing no association – so the evidence is not clear. More on this at the end.
- And the absence of studies may just mean that I have not found any or that a study has not been carried out yet; don’t assume no association!

Some questions to be answered

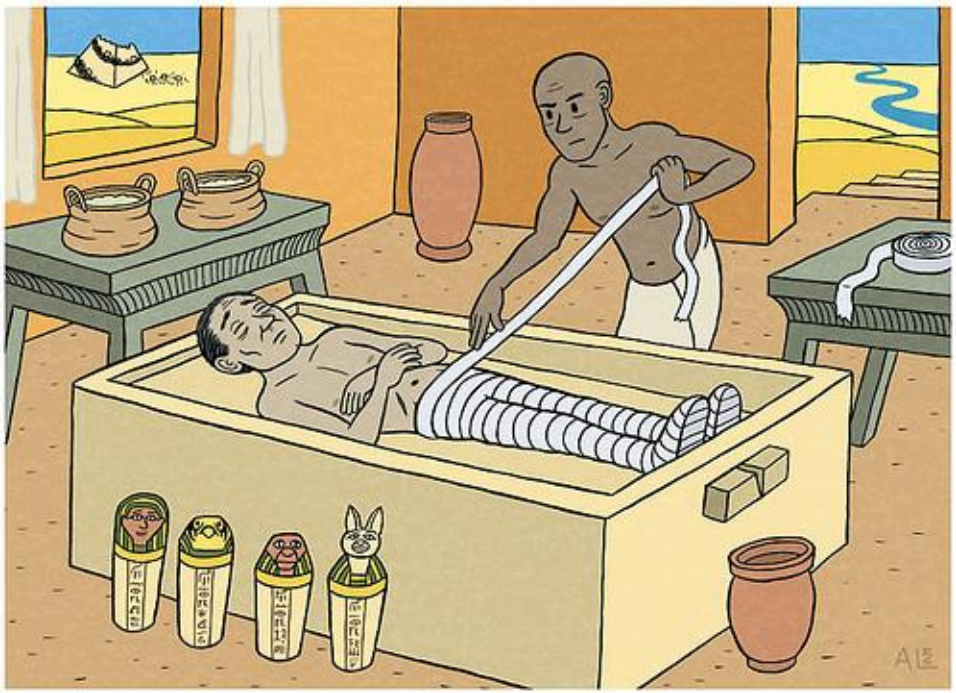
- What are the common toxins that could lead to neurodegenerative disease?
- How common are they?
- Which toxin (or category of toxins) is the most dangerous for the brain?
- What are the main mechanisms of effect and are they the same for each toxin?
- Can the body adapt to toxins?
- How can we avoid them?
- How can we test for them?
- How can we get rid of them from the body and brain?

Air pollution: BBC News March 2018: MPs warn of 'poisonous air' emergency costing £20bn a year

External air pollution

- It's relatively easy to measure ambient air pollution and correlate with hospital admissions.
- Diesel exhaust is the main culprit, with mainly PM and NO2, which can penetrate the BBB.
- Very clear links with pollution levels and PD hospital admissions and MS relapses in humans and AD development in animals.
- Most external air pollution enters the brain directly by inhalation; particulates have been found in AD plaques.
- A series of studies on air pollution (particularly PM) in Mexico City has shown early AD and PD development in the brains of children and young adults. Carrying the Apo ε4 allele exacerbates the risk.

Internal air pollution: Formaldehyde



Now found in:

- Building materials, esp. composite wood products
- Insulation materials
- Furniture and fittings
- Home office equipment
- Glue
- Permanent press fabrics
- Paints, lacquers, varnish
- Floor finishes
- Smoking
- Paper products
- The ‘new car’ smell

Internal air pollution: Formaldehyde

- Clear links between formaldehyde (FA) and AD and PD development in animals, inducing tau hyper-phosphorylation, DNA damage and apoptosis.
- In humans, urinary, breath and blood FA predicts cognitive decline, AD, PD and ALS.
- Occupational exposure strongly associated with ALS.
- FA is produced naturally in human cells, but in very small quantities.
- Natural cellular levels may be raised by excessive methylation, inducing PD-like changes.

Internal air pollution: Solvents

- Toluene: paint thinner, cement, glue, recreational inhalant.
- Association between PD and toluene occupational exposure or residential proximity to industrial works; in rats, low dose exposure leads to depletion of striatal dopamine stores.
- Trichloroethelene (TCE) was once used as an anaesthetic and more recently in dry cleaning fluid.
- Occupational exposure to TCE a risk factor for PD. TCE reduced dopaminergic neurons by 50% in rodents.
- Association between AD and other solvents: cleaning materials, toiletries, after-shave, nail varnish remover, anything with an aroma and many things that don't have one!

Internal air pollution: Smoking

- Smoking is associated with ALS and MS development.
- Smoking associated with dementia – but only in non-carriers of ApoE 4.
- Several studies have shown smoking to be protective against PD. Basically, scientists still don't really know why!
- Nicotine-based treatments now being trialled to reduce PD symptoms.

Nevertheless, it would still be a good idea to give up!

‘To cease smoking is the easiest thing I ever did. I ought to know, I’ve done it a thousand times.’
Mark Twain

Persistent organic pollutants (POPs)

- Perfluoroalkyl substances found in drinking water, non-stick cookware, water-repellent clothing, stain resistant fabrics, cosmetics and firefighting foams.
- Associated with AD and PD mortality.
- Blood levels of polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs) were associated with increased ALS risk.
- PCBs found in many foods, insulating materials, old electrical equipment, office products and pesticides; PBDEs are flame retardants.
- PCBs found in post mortem brains of PD patients. In rodent brains, presence of PCBs was associated with a dose-dependent decrease in striatal dopamine transporter levels.

Bisphenol A (BPA)

- Many uses but especially plastic water bottles - only glass bottles are safe!
- But maternal BPA exposure predicts adult PD development in humans and predicts MS development in mice.

Pesticides

- Well-known association between PD and pesticides. Studies are mainly of occupational exposure but residential exposure is also now showing a strong association.
- Interestingly, the risk is higher if protective clothing is used.
- Pesticide-induced PD can begin *in utero* with progressive neurotoxicity of the nigrostriatal dopamine system in rats.
- Meta-analyses found significantly higher AD and ALS risk.
- Just because a pesticide is banned, don't assume your patients have not been exposed: immigration from non-ban countries and long half-life.

Increased PD risk for sheep farmers

BRIDGE – MEDICINES AND PESTICIDES

Toward pesticidovigilance

Can lessons from pharmaceutical monitoring help to improve pesticide regulation?

By **Alice M. Milner**[1] *and* **Ian L. Boyd**[2]

Agricultural pesticides are an important component of intensive agriculture and, therefore, of global food production. In the European Union, ~500 active substances used in pesticides are approved, including insecticides, fungicides, herbicides, and plant growth regulators. When used at industrial scales, pesticides can harm the environment (*1*), but there is a trade-off between this effect and the need to produce food. Recent uncertainties about the health and environmental effects of glyphosate herbicide and neonicotinoid insecticides underline the need for regulation to be sensitive to this trade-off (*2*, *3*). Better regulation is needed to control how pesticides are used and affect the environment at a landscape scale.

Important insights into how pesticides can be better regulated come from the regulation and monitoring of pharmaceuticals. In particular, antibiotics provide some intriguing parallels with pesticides. Society depends on pesticides in a similar way to how it relies on antibiotics. Both have been manufactured and supplied to market demand with little care taken to consider whether this is sensible. Both are often used prophylactically or as therapies of first resort, when sparing use would be more appropriate. Both are vulnerable to loss of efficacy because of resistance in

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PHOTO: INCPOSTERCO/ISTOCKPHOTO

The current assumption underlying pesticide regulation—that chemicals that pass a battery of tests in the laboratory or in field trials are environmentally benign when they are used at industrial scales—is false.

Milner AM, Boyd IL, Science, 2017; 357: 1232

Foods: trans fats

- Trans fats intake is associated with AD and ALS incidence.
- Trans fats are incorporated into neuron cell membranes, altering cellular communication and increasing production of Aβ peptides.

Food contaminants: nitrosamines

- Nitrosamines are found in processed foods and are produced by high temperature cooking, particularly frying. They are more commonly associated with cancer but….
- Animal studies show that early exposure was associated with later neurodegeneration.
- '…exposure to nitrosamines plays a critical role in the pathogenesis of major insulin resistance diseases including T2DM, NASH, and AD' (de la Monte et al)

Sugars and artificial sweeteners

- Intake of beverages naturally and artificially sweetened (including by HFCS) associated with increased AD incidence, as well as lower brain volume and poorer memory score, markers of pre-clinical AD. This included daily fruit juice intake.
- This finding for beverages does not mean that sweet foods are not a risk factor, but they are notoriously difficult to assess, in contrast to beverages.

Toxic metals

- Aluminium: AD, PD, ALS, MS
- Arsenic: AD, PD, ALS, MS
- Cadmium: AD, PD, ALS, MS
- Cobalt: AD, ALS
- Copper: AD, PD, ALS, MS
- Iron: AD, PD, ALS
- Lead: AD, PD, ALS
- Manganese: AD, PD, ALS
- Mercury: AD, PD, ALS, MS
- Selenium: AD, PD, ALS
- Zinc: AD, PD, ALS

Safe levels?

- There is no safe level of exposure to the toxic metals listed.
- But there is a therapeutic dosage for Cu, Fe, Mn, Se and Zn.
- Even Hg once had a therapeutic role as an antimicrobial (vaccines and syphilis)!

Why metals may be more damaging than other toxins

- Toxic metals inhibit absorption of nutrient minerals.
- 'Nature abhors a vacuum'! Toxic metals may replace deficient minerals in tissue structures, particularly bones and joints, so weakening them (e.g. lead frequently replaces calcium in bone).
- Toxic metals can replace deficient zinc at enzyme binding sites, causing alteration of thousands of enzymes. How many of the population are zinc-deficient?
- Certain minerals can replace others in cells, e.g aluminium can replace deficient magnesium. How many of the population are magnesium-deficient?
- All metals can be neurotoxins, can pass through the BBB as nanoparticles and several have been found in the brain in post mortem, particularly aluminium and mercury but also manganese and iron.
- Most substances are biodegradable by natural processes. However, no metal is biodegradable; metals can only change form by attaching to or separating from other molecules. *

Iron and AD

- A 2017 study reported that iron distribution in the frontal cortex was not affected by normal ageing but in AD patients, iron accumulated in plaques and activated microglia and in the most severe cases, along myelinated fibres. Iron levels correlated with the amount of amyloid plaque and tau pathology (Van Duijn S, J Alzheimer's Dis, 2017).
- A meta-analysis showed that AD patients had lower serum Fe but Fe was significantly higher in 8 different brain regions. Where serum Fe is lower in AD, serum Zn is lower as well. (Tao Y, J Alzheimer's Dis, 2014; Li DD, Front Aging Neurosci, 2017)
- High CSF ferritin reduced the time from pre-clinical AD to full-blown AD by 8 years (Ayton S, J Neurol Neurosurg Psychiatry, 2017).

Iron: not just a problem in AD

- In PD, iron is higher in the substantia nigra and correlates with severity of motor symptoms and dopaminergic neurodegeneration, (Kristinsson J, Neuropsychiatr Dis Treat, 2012; Martin-Bastida A, Eur J Neurol, 2017).
- Studies are divided over whether serum Fe is higher or lower in PD patients (but is not in reference range).
- The combination of dopamine and iron generated ROS, which resulted in protein misfolding in PD (Arrequin S, J Inorg Biochem, 2009).
- Substantia nigra Fe content is associated with 'freezing of gait' in PD (Naduthota RM, J Neurol Sci, 2017).
- Dietary non-haem iron, but not haem iron, was associated with a 30% increase in PD risk; with low vitamin C intakes risk was increased to 90% (Powers KM, Parkinsonism Relat Disord, 2009; Logroscino G, Am J Epidemiol, 2008).
- Iron metabolism may also be dysregulated in ALS, with serum ferritin elevated in patients (Qureshi M, Open Neurol J, 2008).

Other points to consider about Fe

- An interesting animal study showed that maternal iron deficiency altered the AD-related genes in neonates, which persisted, even with iron repletion, and led on to AD-like conditions. This suggests that in these initially deficient animals, iron repletion prompts ‘excess’ iron to be transported to the brain for storage.
- A 2001 US study showed that 3% of the elderly were iron-deficient but 13% had iron overload.
- We know that excess brain iron has pathogenic properties because iron chelators can improve symptoms of AD and PD.

Risk of excess iron in practice

- Beware foods fortified with iron (unless menstruating): fortified foods contain inorganic iron (ferrous sulphate, aka rust).
- Check iron content of multis or prescriptions; may be ferrous sulphate and/or too high.
- Those on a gluten-free diet may also be at risk of iron overload since the fibre and phytate content of grains can usefully inhibit non-haem iron absorption.

Other potentially beneficial minerals

- Occupational exposure to industrial Cu, Mn or Zn associated with PD. But no evidence that dietary intake of Zn can cause a problem. Mostly it is the reverse.
- Blood Cu levels significantly higher in AD patients, Mn and Zn levels lower in AD and PD; Cu may be higher or lower in PD.
- Plasma and CSF Se associated with AD and PD development. In post mortem studies, elevated brain Se is found in Aβ plaques and NFTs.
- CSF Cu, Mn and Se were significantly higher in ALS patients.
- Are elevated blood/CFS/brain levels of minerals cause or effect?

Additional points on Se and Mn

- Diet: higher Se intake was associated with AD development.
- The most dangerous forms of Se appears to be the inorganic selenite and selenate, often found in drinking water.
- Even permitted levels in drinking water were associated with >5 times risk for ALS and ALS mortality in Italy.
- In vitro studies showed that organic and inorganic Se treatment of neuroblastoma cells increased apoptosis through generation of ROS/RNS, despite Se raising glutathione levels.
- Excess brain Mn or occupational/residential exposure can produce manganism, with PD-like symptoms.

Additional points on zinc

- Note that Cu and Zn compete for absorption from the GIT, so low Zn may mean elevated Cu. Zn is required for insulin synthesis and signalling and both are required for CuZnSOD production.
- Low Zn seems to increase susceptibility to all toxins. It also induces inflammation and oxidative stress, reduces DNA repair and promotes insulin resistance *(more on this in a minute!)*.
- Zinc treatment can reduce cognitive decline, mechanism unknown.

What the Alzheimer's Association has to say about toxic metals

Under 'Alzheimer's Myths':

- **Drinking out of aluminium cans or cooking in aluminium pots can lead to AD.** Studies have failed to confirm any role for aluminium in causing AD. Experts don't believe that everyday sources of aluminium pose any threat.
- **Silver dental fillings increase risk of Alzheimer's disease.** According to the best available scientific evidence, there is no relationship between silver dental fillings and Alzheimer's.

Ionising radiation

- In mice, ionising radiation simulating radiotherapy affected PD pathways and increased tau hyper-phosphorylation in neurons (Shukla S, J Proteome Res, 2015; Li L, J Neurochem, 2014).
- MS patients had received significantly higher diagnostic or therapeutic radiation, particularly skull X-rays or brain CT scans (Motamed MR, Med J Islam Repub Iran, 2014).
- UV radiation seems particularly to affect PD development. , through depletion of Parkin, causing dopaminergic cell death (Zhu Z, Oncotarget, 2017).
- A French study of >69,000 PD patients found a quadratic association with UVB. Under age 70, UVB is protective but over age 70 it is a risk factor for PD (Kravietz A, Environ Res, 2017).
- Both low gestational UVB exposure and higher adult exposure are risk factors for MS. Implications, since Vitamin D beneficial for MS? (Saiedi SL, Mult Scler Int, 2017; McDowell TY, Neuroepidemiology, 2010).

Non-ionising radiation

- EU 2016 Guidelines acknowledge that long-term exposure to certain RF EMFs (e.g. WiFi, mobiles) is a risk factor for AD and recommend reducing or eliminating all sources of high EMF exposure at home, in the workplace, schools, hospitals etc.
- 'There is increasing evidence that EMF exposure has a major impact on the oxidative and nitrosative regulation capacity in affected individuals, particularly through the adverse effects of peroxynitrite - as in many multisystem illnesses.'
- Pulsed EMFs (as in mobile phones) induce overexpression of Aβ in rats and in human neuroglioma cells (Jiang DP, Arch Med Res, 2013; Del Giudice E, Neurosci Lett, 2007).
- Meta-analysis: occupational ELF-EMF exposure associated with ALS and with PD mortality (Zhou H, PLoS One, 2012; Brouwer M, Occup Environ Med, 2015).

Where does the UK government stand on mobile phones?

- UK Health and Safety Executive, 2018: recognises that mobile phones can pose a danger to health……
- …..but only to prevent the possibility of a spark being generated that might ignite flammable materials.

Toxin interactions

- After years of testing just one chemical at a time, scientists are now looking at two at a time. This is a small step forward….
- Examples include:
  - PM2.5 and formaldehyde had no effect singly in inducing brain changes but the combination induced AD-like pathogenic changes.
  - Exposure to single pesticides (paraquat and maneb) had no effect but the combination significantly increased PD pathology, including mitochondrial degeneration.

Some common and specific mechanisms

- Generation of ROS/RNS inducing damage, oxidised lipids and brain inflammation.
- DNA damage: single and double strand breaks
- Neuronal mitochondrial damage, reduction in membrane potential and cell signalling ability and inhibition of the electron transport chain, reducing ATP production.
- Binding to and interfering with cell membranes or binding to DNA as adducts, where they inhibit normal functioning.
- Ionising radiation: heating effect
- Pesticides: Inhibition of acetylcholinesterase, decreased tyrosine hydroxylase, apoptosis of dopaminergic neurons
- Metals: Decreased metallothioneins (proteins which can bind toxic metals); displacement of nutrient metals by binding-site competition; increased cell membrane, GIT and BBB permeability.

TOXIN AVOIDANCE

It’s all in the handout!

Testing for toxins

- A detailed exposure history will give the best clue (diet, occupation, residence etc)
- For metals (*Biolab or Genova*):
  - Blood test: only recent exposure
  - Urine test: only recent exposure
  - Hair analysis: exposure in previous 2-3 months
  - Urine challenge test with DMSA chelating agent: flushes metals out of tissues. No prescription necessary for DMSA but use with extreme caution.
- Urine tests from Great Plains (*through Biolab*)
  - Non-metal chemical profile: 172 toxins
  - Glyphosate
  - Mycotox profile: 7 mycotoxins from 4 mould species
- Fat biopsy for lipophilic toxins
- Blood brain barrier permeability: https://www.cyrexlabs.com/

Toxin removal

- Note that removal of toxins may not make the patient any better, but generally patients can never recover until the toxins are removed.
- It's hardly worth getting a toxin out of the body unless the avoidance measures are in place.
- Detoxing the body

Special measures to detox the brain

- Ensure sufficient good, sound sleep – the brain uses this time to remove toxins and debris through activation of the glymphatic system.
- Anaesthesia does an equally good job, producing a 60% increase in the rate of β-amyloid clearance (Nedergaard M, Science, 2013).
- The glymphatic system uses the cells' mitochondria to remove cellular waste from the brain in CSF (cf: lymph). So ensure mitochondrial function is optimized as well.
- Fasting helps remove lipophilic toxins from adipose tissue. Fasting for at least 3 days allows autophagy to take place – this has also been shown to remove Aβ fragments from the brain.
- *BUT do not fast patients to remove toxins if already diagnosed with a neurodegenerative disease! Fast for prevention only, e.g. if have the Apo E4 allele.*

Other measures for detoxing the brain

- Ketosis (fasting or ketogenic diet), as brain mitochondria prefer ketones as a fuel. Mild ketosis has been found to induce production of BDNF.
- Adequate methylation is vital for the brain. Testing.
- Ensure adequate DHEA levels. DHEA enhances neuroplasticity and protects the brain from inflammation and free radical damage. Testing.
- Optimise the microbiome, as this resets brain gene expression.

Useful foods/supplements for the brain

- Green tea extract (EGCG): chelates iron as effectively as desferrioxamine.
- Magnesium aids brain fibrinolytic degradation.
- Curcumin protects against pesticide-induced oxidative damage.
- Parkinson's: fish intake protective against multiple toxins [also smoking and alcohol consumption]; ω3 intake protective against pesticides.
- Resveratrol protects against formaldehyde-induced hyperphosphorylation of tau protein.

Liposomal detoxification agents

- Liposomes are able to cross the BBB: liposomal anti-cancer agents have been used effectively to treat cancer of glioma cells.
- A useful website is www.quicksilverscientific.com which make a liposomal products, including EDTA for removing metals from the brain.
- Safety?

So, back to the original questions

- How common are these toxins?
- Which category of toxins is the most dangerous for the brain?
- Are the mechanisms of effect for each the same?
- Does the body adapt to toxins?
- How can we avoid them?
- How can we test for them?
- How can we get rid of them from the brain? *

AD as type 3 diabetes

Importance of insulin to the brain

- In the brain, oxygen, insulin and a fuel (glucose or ketones) are vital for normal signalling function, metabolic activity and energy production.
- There are a high concentration of insulin receptors on neurons, allowing insulin to control a range of neuronal functions, including neurotransmitter release at the synapses and activation of signalling pathways associated with learning and long-term memory.
- Insulin signalling is one of the most important signals for neuronal survival.
- Insulin-sensitive glucose transporters are localised to regions in the brain responsible for memory.

AD is a metabolic disease: what is the evidence?

- AD is associated with progressive brain insulin resistance, even in the absence of T2D, obesity or peripheral insulin resistance.
- This means that the brain can become insulin resistant, even if the body is not.
- Many studies have shown that insulin resistance, metabolic syndrome, pre-diabetes and T2D are risk factors for AD. Approximately 50% of people with T2D go on to develop AD.
- A common finding in AD is deterioration of the brain's ability to use and metabolize glucose and impaired insulin signalling. This appears to precede cognitive impairment and reduction in brain volume and predicts progressive cognitive impairment.

Insulin resistance in AD (1)

- Post mortem or PET/MRI studies show that in AD patients there may be severe insulin resistance, with insulin expression being inversely proportional to AD progression.
- As in the body, brain insulin resistance is associated with reduced insulin receptor binding and decreased insulin responsiveness, setting up a positive feedback loop here, as well as in the body.
- This results in lack of glucose (the usual substrate for energy production). This has been described as ‘brain glucose starvation’.

Insulin resistance in AD (2)

- Furthermore, the continually high levels of insulin in the circulation have to be degraded by IDE (insulin degrading enzyme). But IDE also degrades Aβ. IDE is a rate-limiting enzyme, so if it is diverted to degrade insulin, it is not degrading amyloid.
- And the advanced glycation end products (AGEs) seen with elevated blood glucose can impact the brain by triggering inflammation, causing ROS formation, inducing autoantibodies and altering proteins which damage blood vessels, reducing the oxygen and nutrients reaching the brain. They may also damage the BBB.
- Insulin treatment, however, reduces amyloid plaques. It also normalises the production and functioning of dopamine and ameliorates motor impairments in rat PD models.

Association of toxins with insulin resistance

- Environmental toxins are increasingly being seen as a cause of insulin resistance in the body through blocking of insulin receptors by molecular mimicry.
- Rats administered intracerebral streptozotocin to induce diabetes, developed brain insulin resistance, insulin deficiency, cognitive impairment and AD-like neurodegeneration.
- Streptozotocin is a nitrosamine-related compound, found in processed and preserved foods. We saw before that nitrosamine intake was associated with later neurodegeneration. *

Bredesen's Hypothesis No 1:

- Bredesen found 3 distinct types of AD *(Bredesen, 2015)*:
  - Type 1: driven by systemic inflammation. Develops in the 60s.
  - Type 2: driven by insulin resistance, high homocysteine and reduced trophic support from oestradiol, progesterone, testosterone, insulin and vitamin D. Develops in the 70s.
  - Type 3: driven by dementogens: toxins, microbes and stress.
- Types 1 and 2 are strongly influenced by the ApoE4 allele but type 3 occurs more often in those who are ApoE4 negative and have at least one ApoE3 allele.

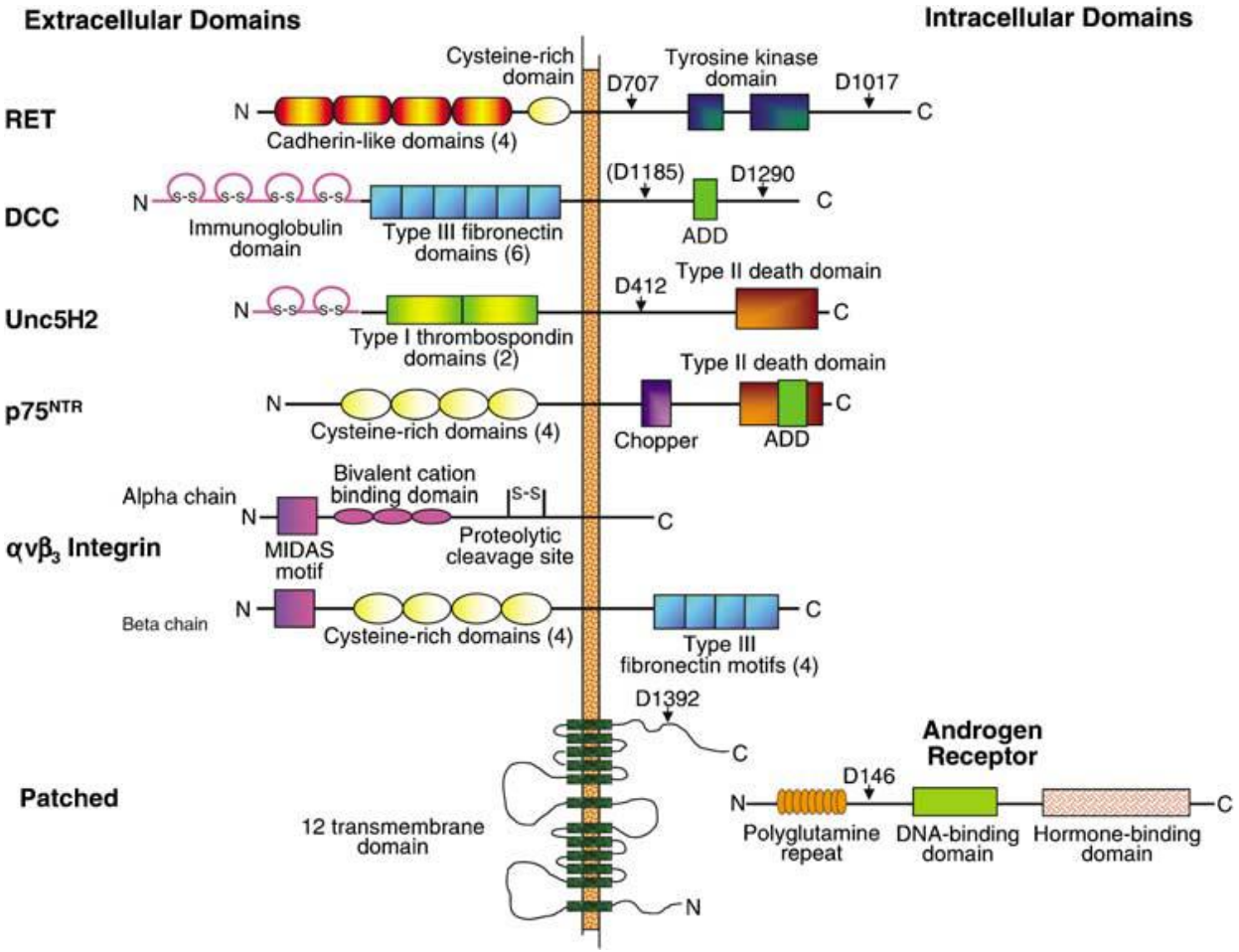
Bredeson's type 3 AD :

- Type 3 AD tends not to present with cognitive impairment (although it will develop later) but will show executive function problems, depression and stress hypersensitivity. Patients may have been diagnosed with some other form of dementia but the diagnosis will be changed to AD later.
- No family history. Can develop any time from the 40s onwards. Meno/andropause?
- Low serum zinc and zinc/copper ratio.
- Low triglycerides and low ratio of triglycerides to total cholesterol.
- Hormonal abnormalities, particularly related to stress, and HPA axis dysfunctional. Low DHEA and morning cortisol.

Hypothesis No 2: AD is driven by a new type of receptor on neurons (Mehlen, 2011)

- A normal receptor will lie dormant, waiting for a ligand to bind to it, when it will be activated and carry out its normal function, such as cell signalling.
- But in 1993, Bredesen and his team discovered an opposite form of receptor, known as a 'dependence receptor', because these receptors send an apoptosis signal when a ligand does not bind to them but will remain dormant when bound to a ligand.
- Their existence is thought to be as a safeguard against tumour progression.
- As at 2011, 17 dependence receptors had been identified. There may be more.

Examples of dependence receptors



How do dependence receptors relate to AD?

- One of the key dependence receptors is none other than amyloid precursor protein (APP).
- APP is looking for a ligand. In the brain, these ligands are called neurotrophic factors, or neurotrophins: helper peptides, that allow neurons to develop and maintain synapses.
- Neurotrophin binding to APP can be prevented by Aβ peptide, so this competes with neurotrophins to bind to APP, i.e. it is an ‘anti-trophin’.
- If neurotrophins have failed to bind to APP, APP initiates a caspase signal, which results in the synaptic loss, neurite retraction and neuronal death that characterises AD.

Examples of neurotrophins or states that act as neurotrophins

- Brain-derived neurotrophic factor (BDNF), which supports neuronal survival and promotes growth and differentiation of new neurons and synapses. BDNF is critical for long-term memory.
- Optimised levels of oestrogen, progesterone, thyroid hormone, DHEA, vitamin D and insulin (another reason why insulin resistance induces AD)
- Optimised nutrient intake
- SIRT1 (but the gene is shut down by ApoE4).
- Exercise
- A good night's sleep
- Absence of toxins, pathogenic microbes and stress
- Absence of inflammation
- Absence of high homocysteine *

The amyloid cascade hypothesis: fact or fiction?

- The amyloid cascade hypothesis states that neurodegeneration is mainly caused by Aβ accumulation in plaques.
- Many drugs have been designed to remove or prevent the action of Aβ. They are mostly antibodies which bind to Aβ and remove it from the brain or block the enzyme which produces Aβ. In these tasks, they were highly successful.
- However, not only did they fail to even stabilise AD, in some cases they significantly increased disease progression.
- More than 200 such drugs have now been assessed by the US FDA. None were found to be effective in even slowing AD progression.
- Donezepil (Aricept) and Memantine, drugs which can help patients a little, do not act on Aβ. Aricept is a cholinesterase inhibitor (which retains acetylcholine in the brain for longer), while Memantine reduces the excitotoxicity of glutamate. Neither drug can even slow progression of the disease, let alone reverse it!

Maybe amyloid is not neurotoxic?

- Aβ is present in the brain and CSF of normal healthy individuals in monomer form and….
- Post mortem studies have found brains riddled with amyloid plaques, but in people who had died in their nineties and had retained an excellent memory up until death.
- So it seems that Aβ is not necessarily neurotoxic.

Hypothesis 3: the true role of amyloid β

- Bredesen proposes that APP produces amyloid as a protective response whenever a threat is detected in the brain.
- These threats could take several forms:
  - Inflammation (from toxins, infection, diet, lifestyle)
  - Oxidative stress (from toxins, infection, diet, lifestyle)
  - Shortage of nutrients (poor diet, nutrient-poor foods)
  - Insulin resistance (high sugar and carb intake, toxins)
- APP balances the threats and availability of neurotrophins to determine whether there is adequate support for neurons and synapses.
- Because a neuron or synapse that cannot be adequately maintained is better dead, the decision is made that they must be sacrificed so that scarce resources (neurotrophic factors) can focus on those that have a chance of survival.
- APP therefore triggers caspases to downsize the number of neurons and synapses to a level at which they can be adequately supported by the scarce neurotrophins.

Mechanism of neuron/synapse sacrifice

- APP does this by grabbing a piece of Aβ peptide, which triggers APP to produce more amyloid which triggers the caspases to kill neurons.
- This makes Aβ prionic, similar to the prions in mad cow disease: amyloid begets amyloid without the need for any genetic material.
- This progressive destruction (sacrifice) of neurons and synapses is typical of AD development.
- So APP appears to function as a molecular switch, mediating the survival or destruction of neurons and synapses.
- Happily, not all the neurotrophic factors have to be in place before APP decides it is worth keeping neurons alive. But it is a critical balancing act.

So where is the evidence for this hypothesis?

- In vitro studies show that Aβ 1-42 in monomer form protects developing and mature neurons against excitotoxic death under conditions of trophic deprivation (Giuffrida, 2009).
- Aβ 1-42 carries out its protective role via insulin receptor signalling – another reason why insulin resistance could induce pathology.
- In mice with induced MS, treatment with Aβ peptides reduced motor paralysis and brain inflammation. Importantly, the protection conferred by Aβ treatment did not require its delivery to the brain; instead, treated lymphocytes were injected in the body. (Grant, 2012)
- A 1997 study concluded that 'Aβ fragments…attenuate the toxicity of Al'.
- Human Aβ has already been successfully trialled in transgenic mice to inhibit the growth of tumours transplanted into the brain and there are suggestions that Aβ might be developed as a natural antibiotic.
- Other benefits:

OPEN ACCESS Freely available online

PLOS ONE

Amyloid-β and APP Deficiencies Cause Severe Cerebrovascular Defects: Important Work for an Old Villain

Salvadore Luna[1,2], D. Joshua Cameron[1,3], Douglas W. Ethell[1,2,4*]

Aβ plays an important role in regulating capillary bed density within the brain…. APP-deficient zebrafish had fewer cerebrovascular branches and shorter vessels in the hindbrain…this phenotype was rescued by treatment with human Aβ peptide.

i.e. Aβ increases and lengthens blood capillaries in the brain, improving blood and oxygen flow.

Microbes in the brain

Post mortem studies of AD patients' brains have found:

- oral bacteria,
- viruses (particularly herpes),
- fungi,
- mycotoxins from moulds,
- spirochetes, such as Borrelia (the Lyme disease pathogen) and the parasites Toxoplasma gondii, Babesia and Bartonella.

Published in final edited form as:
Sci Transl Med. 2016 May 25; 8(340): 340ra72. doi:10.1126/scitranslmed.aaf1059.

Amyloid-β Peptide Protects Against Microbial Infection In Mouse and Worm Models of Alzheimer's Disease

Deepak Kumar Vijaya Kumar[1,†], Se Hoon Choi[1,†], Kevin J. Washicosky[1,†], William A. Eimer[1], Stephanie Tucker[1], Jessica Ghofrani[1], Aaron Lefkowitz[1], Gawain McColl[2], Lee E. Goldstein[3], Rudolph E. Tanzi[*,1], and Robert D. Moir[*,1]

Abstract: We present in vivo data showing that **Aβ expression protects against fungal and bacterial infections in mouse, nematode, and cell culture models of AD**.

Aβ works by disrupting microbial membranes, while the 'Aβ fibrils capture, agglutinate and finally entrap microbes in a network of β-amyloid.'

Finally, the microbes are marked (opsonised) for phagocytosis.

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PLoS one

The Alzheimer's Disease-Associated Amyloid β-Protein Is an Antimicrobial Peptide

Stephanie J. Soscia[1,2], James E. Kirby[3], Kevin J. Washicosky[1], Stephanie M. Tucker[1], Martin Ingelsson[4], Bradley Hyman[1,5], Mark A. Burton[6,7], Lee E. Goldstein[6,7], Scott Duong[3], Rudolph E. Tanzi[1,5]*, Robert D. Moir[1,5]

Aβ exerts antimicrobial activity against eight common and clinically relevant microorganisms; this effect was abolished with anti-Aβ antibodies

Cell danger response?

- Does the presence of inflammation, toxins and microbes and an absence of neurotrophic factors initiate the cell danger response for neurons?
- Bredesen never mentions it by name, but….

JLB Review

Danger-associated molecular patterns in Alzheimer's disease

Carmen Venegas and Michael T. Heneka*,†,1*

…we highlight the role of danger-associated molecular patterns (DAMPs), including Aβ……in the innate-immune activation during the course of Alzheimer disease. *

If the evidence is there, why aren't environmental toxins recognised as a cause of neurogedenerative disease?

Environmental medicine: problems with human studies

- RCTs – ethics – causality – gold standard
- Control group – animals – PC and translation
- Symptoms not uniform
- Diseases not specific to toxins
- Body burden
- No association, industry lobbying?
- Direct vs indirect effect?

The adaptive response

- All these problems are compounded by the fact that small doses of many toxins may be therapeutic.
- They are thought to operate via the ‘adaptive response’ (hormesis or preconditioning): a small stressor which makes the body stronger to withstand a larger stressor.
- This confuses the results of epidemiological studies, where a small dose is beneficial and a larger dose is harmful, the net effect may be zero!
- In addition we have the problem of endocrine disruptors, where low doses tend to have a stronger effect than high doses!

Other problems in getting environmental toxins recognised as disease agents

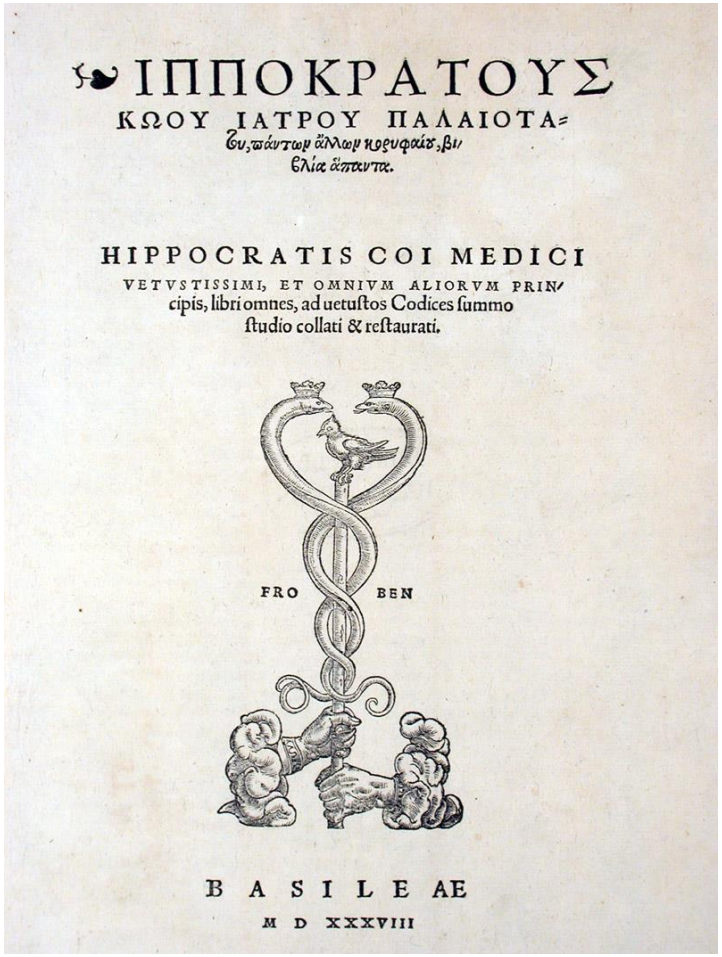
- There is a disconnect between science and orthodox medicine as in nutritional medicine - orthodox medicine will not adopt nutritional remedies despite clear evidence of benefit.
- Many of the companies that make toxic chemicals also manufacture the pharmaceuticals that are prescribed to treat the damage.
- No-one has yet found a mechanism to assign a monetary value to life, health or quality of life.
- However, there is a monetary value to the cost of disease, as we saw for external air pollution.
- And the general public believe that every substance in current use and on the market has been tested for toxicity, is safe and ‘approved’ for use. Nothing could be further from the truth.

No-one is investigating the indirect effect of toxins

Individual susceptibility is dependent on

- (Genetic predisposition),
- Antioxidant status,
- Methylation status,
- Detoxification status
- Microbiome status
- Mitochondrial status
- Extent of emotional and physical stress.

The first acknowledgement of susceptibility?



Hippocrates (On Ancient Medicine) allegedly stated:

'Since some people who eat cheese do well on it, while others do not, the difference must lie in a constituent of the body which is hostile to cheese and is roused and stirred to action under its influence'.