CYTOPLAN

THE HEALTH INFORMATION SERIES

Prevention & Reversal of Cognitive Decline

CYTOPLAN
EDUCATION

Nutritional Supplements for Professionals

Prevention and Reversal of Cognitive Decline

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PREVENTION AND REVERSAL OF COGNITIVE DECLINE

"From the moment we first saw publication of Professor Bredesen's research paper[1] 'Reversal of Cognitive Decline; a novel therapeutic programme' in October 2014, and realised the programme involved almost exclusively diet and lifestyle intervention, it was something that excited us greatly.

It was particularly exciting to see his work demonstrate that a disease such as Alzheimer's – which is presently viewed as one which cannot be treated, prevented or reversed and is inciting such widespread fear among the population – is indeed not omnipotent and in fact is far more dynamic than popular medical opinion leads us to believe."

Amanda Williams, Managing Director, Cytoplan Ltd

In November 2016, new figures from the Office for National Statistics showed that dementia is now the leading cause of death in England and Wales, replacing ischaemic heart disease. It is the leading cause for women and overall, heart disease remains the leading cause for men[2]. Thirty million people are affected globally (likely to be 160 million by 2050)[3].

It can no longer be considered a disease-process that occurs only in old age. For example, extensive neuroinflammation, oxidative stress,

and hallmarks of Alzheimer's disease pathology have been seen in the brains of Mexico City children and young adults with chronic year-long exposures to high levels of ozone and particulate matter[4].

Alzheimer's disease has 'touched' most of us through friends and family who suffer, or have died, from the disease. There isn't a week that passes where Alzheimer's or dementia is not in the news – a new drug offers hope, a new drug has failed, a well loved celebrity has the disease, a therapy has shown promise. Nevertheless, drugs have failed to make any real, lasting difference, other than perhaps some short-term symptom improvement.

Genetic and biochemical research has revealed an extensive network of molecular interactions involved in the pathogenesis of Alzheimer's disease. Hence a network approach, rather than a single target drug approach, is likely to be more appropriate. Using a network approach, Professor Bredesen, who has spent his life in Alzheimer's research, has developed **The Bredesen Protocol™** with which he has, so far, reversed symptoms of Alzheimer's in more than 90% of the 140 patients he has worked with[5].

His initial study published in 2014[1] discussed the first 10 patients treated with a novel, therapeutic approach, now called The Bredesen Protocol™.

"Of the first ten patients tested, nine showed subjective or objective improvement. These included people with memory loss associated with Alzheimer's disease and/or varying degrees of cognitive impairment. All six patients who had given up or severely limited work, returned to work or were able to work without difficulty."

WHAT IS THE BREDESEN PROTOCOL™?

The Bredesen Protocol™ targets the multiple underlying causes of Alzheimer's disease, with a goal to improve cognitive function. The protocol takes into account an individual's genetic, metabolic, hormonal, and behavioural make-up to produce a personalised therapeutic programme that is based on the underlying pathogenesis of Alzheimer's disease, and which involves multiple modalities in the treatment protocol.

A combination of - diet changes, supplements, detoxification, brain stimulation, exercise, stress reduction and sleep optimisation - can positively affect brain chemistry. Proprietary software forms a key part of the patient diagnostics, treatment programme and ongoing management.

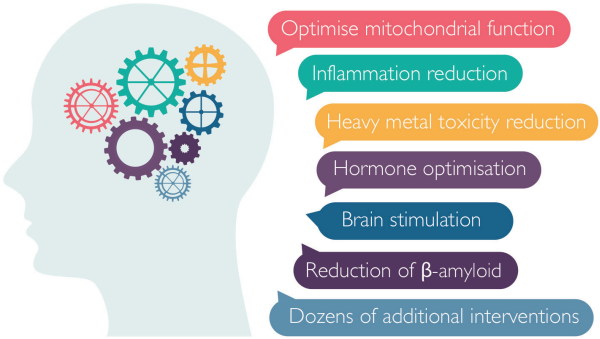
Professor Bredesen likens Alzheimer's pathology to a 'roof with many holes'. There are dozens of biological mechanisms that need to be optimised in order to return a person to health. Monotherapy (single agent drug therapy) plugs just one of these holes, however, one needs to plug a good number of the holes to have any chance of improving the condition. This latter approach utilised in the Bredesen Protocol™ equates to a multiple therapeutic approach, identifying and addressing the areas of imbalance.

HOW ALZHEIMER'S DISEASE AFFECTS THE BRAIN

The brain of a person with Alzheimer's disease usually has an abundance of plaques and tangles and/or atrophy of the hippocampus, an area of the brain important for short term memory. Plaques are deposits of a protein called beta-amyloid that builds up in spaces between nerve cells. Tangles are twisted fibres of another protein called tau that builds up inside the cells. The plaques and tangles block cell communication and disrupt cellular processes.

The Bredesen Protocol™ simultaneously addresses: insoluble and soluble beta-amyloid, tau and tau tangles, metabolic issues, inflammation, toxicity, insufficiency of trophic factors and nutrient deficiencies, hormone imbalance, gut health and lifestyle factors that contribute to the pathology such as poor sleep; stress; lack of exercise; poor diet high in sugar.

The same programme can be used by healthy individuals wanting to prevent Alzheimer's disease and it is a programme that will optimise every area of health.



SUBTYPES OF ALZHEIMER'S DISEASE

Professor Bredesen has identified **5 subtypes of Alzheimer's Disease**[5], each with a similar pathology but different aetiology.

1) Inflammatory / infectious (hot)

These people have biomarkers of systemic inflammation including increased CRP, globulin:albumin ratio, IL-6, NFkappaB. They are often insulin resistant. Inflammation drives metabolic dysfunction and may be sterile or associated with infectious agents such as spirochetes, viruses (eg HSV-1) or fungi.

1.5) Glycotoxic (sweet)

People in this subtype present with features of both type I inflammatory Alzheimer's disease and type 2 atrophic. This subtype may be characterised by people with insulin resistance / type 2 diabetes.

2) Atrophic (cold Alzheimer's)

Low trophic support (low insulin production – insulin is a trophic factor for new neuronal and synapse formation), low hormones, low vitamin D, high homocysteine, low TNF-alpha, IL-6, other metabolic abnormalities are present (burn out).

3) Toxic

Distinctly different – this tends to affect younger people (45-65 years of age), often non-amnesic but instead presents with dyscalculia or aphasia or disordered executive function. Often zinc deficient, often toxic. Mould/mycotoxin sensitivity or metals such as mercury are often contributory, as is systemic inflammatory response syndrome (SIRS). Cortical atrophy may occur.

4) Vascular

This subtype is characterised by impaired / reduced blood flow and damage to the vascular system within the brain. Underlying cardiovascular disease / diabetes is implicated in this subtype.

5) Traumatic

Traumatic brain injury is a risk factor for Alzheimer's disease. Pathogenic mechanisms that may occur after injury to the brain involve proteins known to contribute to the hallmarks of Alzheimer's.

KEY ELEMENTS ADDRESSED AS PART OF THE BREDESEN PROTOCOL™

Nutrition is at the heart of the programme *which also addresses gut health, toxins, stress, sleep, exercise and brain training to deal with metabolic imbalances and inflammation*

A functional medicine approach, including extensive tests, determines the precise intervention, including supplements for the patient

NUTRITION

A **low glycaemic load** diet in order to prevent the development of hypoglycaemia and/or insulin resistance (and conversely to increase insulin sensitivity) is central to the programme; a Mediterranean, Paleo or ketogenic diet depending on the patient. Hypoglycemia and insulin resistance in the brain have a number of effects – for example, brain cells can become starved of fuel because glucose cannot effectively enter cells and insulin resistance (with hyperglycemia) results in the production of Advanced Glycation End Products (AGEs) which cause damage to lipids and proteins within cell membranes; trigger beta-amyloid production, tau hyperphosphorylation, microglia activation and oxidative stress/inflammation[6].

Essential fatty acids

The brain is 60% fat, so adequate healthy dietary fats are important, including omega-3 fatty acids – both EPA and DHA. DHA is the predominant omega-3 found in the brain and is important for neurotransmission and neurogenesis, synaptic plasticity and neuroinflammation. Blood levels of DHA have been inversely correlated with mild cognitive impairment and dementia[7].

Antioxidants

With lipids comprising the main structural components of the brain along with the brain's high metabolic rate (resulting in high production of free radicals), the brain is particularly susceptible to oxidative stress; this is coupled with the fact the brain's natural antioxidant capacity declines with age. Oxidative stress and inflammation are key factors that can contribute to cognitive decline[8].

Vitamin A

Concentrations of vitamin A have been reported as lower in cerebrospinal fluid and plasma of Alzheimer's patients[9]. In vitro studies have demonstrated vitamin A inhibits the formation and extension of beta-amyloid fibrils[10]. Vitamin A's role in maintenance of mucous membranes is also important as this helps maintain integrity of the gut lining which is important for reducing inflammation. Inflammatory mediators, as a result of leaky gut, have the potential to cross the blood-brain barrier and activate immune cells in the brain. Neuroinflammation is a risk factor for the development of Alzheimer's (and other neurodegenerative diseases)[10].

B vitamins

Are needed for energy production, methylation and homocysteine reduction.

- Energy production: The brain consumes up to 20% of the body's energy (ie ATP); one third of which is used for cell maintenance and repair[11]
- Methylation reactions are needed for the production and metabolism of brain neurotransmitters important for memory and mood
- High homocysteine is a risk factor for dementia (and cardiovascular disease)[12]

Vitamin C

Vitamin C has a number of roles in the brain relevant to the prevention of cognitive decline. Vitamin C i) is an antioxidant, can inhibit LDL oxidation and increase the resistance of LDL to oxidation; ii) is a cofactor for a number of dioxygenase enzymes involved in the synthesis of carnitine and neurotransmitters including dopamine, norepinephrine and serotonin; iii) plays a role in the function of endothelial nitric oxide synthase (eNOS) by recycling the eNOS cofactor, tetrahydrobiopterin, which is relevant for arterial elasticity and blood pressure regulation; iv) is released from astrocytes as glutamate is taken up which may moderate the oxidative stress induced by glutamate and protect against overstimulation and cell death; v) vitamin C helps conjugate and remove water soluble toxins[13]; and vi) it also helps mobilise mercury and other metals from intracellular stores and is used in heavy metal detoxification programmes[14].

Vitamin D

Vitamin D receptors are widely expressed in the brain and evidence has linked serum vitamin D deficiency to cognitive impairment and dementia. In vitro studies show that vitamin D can stimulate the clearance of amyloid plaques by inducing macrophage phagocytosis. Vitamin D also reduces amyloid-induced cytotoxicity, apoptosis (cell death), and inflammatory responses in neurons[15].

Vitamin E

Patients with Alzheimer's and mild cognitive impairment have been found to have lower levels of total tocopherols, total tocotrienols, total vitamin E and increased vitamin E damage[16]. Some epidemiological studies have suggested that high intake of vitamin E through food is inversely associated with the incidence of Alzheimer's disease. Randomised controlled studies have shown that treatment with vitamin E could delay functional decline in patients with mild to moderate Alzheimer's disease[17].

Magnesium

Magnesium is an enzyme cofactor for more than 300 enzymes. In the brain it acts as a modulator of synaptic plasticity[18]. Plasticity refers to the ability of tissue to strengthen and weaken and change shape according to need and the signals/nourishment it receives. Magnesium's roles in energy (ie ATP) synthesis and insulin signalling are also important in the brain.

Zinc

Zinc deficiency has been shown to affect neurogenesis and increase neuronal apoptosis (cell death) which can lead to learning and memory deficits. Both low and high concentrations of zinc are associated with increased oxidative stress[19]. Zinc deficiency is seen in particular in the 'toxic' sub-type of Alzheimer's[5].

SUPPLEMENTS

In addition to essential vitamin and mineral micronutrients, there are many other supplemental nutrients and herbals that are being researched and used to support brain health including **curcumin, gotu kola, ashwagandha, bacopa, resveratrol, glutathione and others. See pages 19-22 for a brief summary of supplements available in our cognitive health range.**

GUT HEALTH

There is a link via several mechanisms between gut health and brain health. One mechanism is through the gut barrier function. Compromised gut barrier function, or 'leaky gut', may underpin the chronic low grade inflammation observed in many disorders[20]. The gut microbiota can modulate brain development, function and behaviour by immune, hormonal and neural pathways. Endotoxins (eg LPS) that derive from certain gut bacteria are often found in the plaque lesions characteristic of Alzheimer's[21]. Animal studies have shown that increased LPS is linked to cognitive dysfunction and elevated levels of inflammatory cytokines and beta-amyloid in the hippocampus[22]. Certain species of gut bacteria can increase Brain Derived Neurotrophic Factor and the brain neurotransmitter GABA (a calming 'brain chemical')[23,24].

STRESS

Persistently high levels of the stress hormone cortisol can cause death of brain cells[25]. Stress also affects brain function through other mechanisms including by i) raising blood sugar which over time can lead to insulin resistance; ii) affecting gut barrier function and contributing to the development of leaky gut iii) disturbing quality / quantity of sleep and iv) depleting micronutrients that are used up in the stress response.

SLEEP

Is when cell maintenance and repair occurs and when, for example, beta-amyloid plaque, one of the proteins responsible for blocking cell communication etc in Alzheimer's, is cleared from the brain. Melatonin, the hormone released prior to and during sleep, upregulates antioxidant enzymes and helps break down beta-amyloid plaques, inhibits tau tangles from forming and helps promote Brain Derived Neurotrophic Factor (BDNF), which promotes growth and regeneration of new nerve cells[26]. Poor sleep can also result in insulin resistance[27].

EXERCISE

Increases blood flow to the brain and thus the delivery of oxygen and nutrients[28]. Moderate exercise upregulates anti-inflammatory pathways. Research has shown that physical activity reduces plaque formation and hippocampal atrophy in the elderly and helps maintain cognitive function. The mechanism for this is less well understood but exercise increases the release of BDNF[29]. Exercise increases insulin sensitivity.[30]

BRAIN TRAINING

Challenging and stretching the brain allows new connections to be created and maintained. It maintains brain plasticity – this refers to the brain's lifelong capacity for learning, physical and functional change. The adult brain continuously adapts to relevant sensory stimuli so activities which challenge all the senses will help maintain positive plasticity and processing speed[31].

THE BRAIN HEALTH PROGRAMME

A nutrition and lifestyle programme to **optimise your wellbeing, memory and mood**

CYTOPLAN'S BRAIN HEALTH PROGRAMME

What is The Brain Health Programme and how can it help?

The Brain Health Programme is a coaching programme delivered by Nutritional Therapists to small groups of the public through a series of six interactive workshops covering topics including nutrition, optimising gut health, stress reduction, improving sleep, exercise and brain training. The workshops include talks, activities and discussion to educate individuals on how they can make, and sustain, lifelong food and lifestyle choices to protect the health of their brain.

Who is The Brain Health Programme for?

In short, it has been developed for anyone wishing to learn how to protect their mental health and wellbeing and prevent cognitive decline. Individuals who experience brain fog, poor memory, anxiety, low mood, stress, a reduction in their ability to concentrate or who are concerned about their risk of cognitive decline, perhaps because they have a family member that has been diagnosed with dementia, may want to sign up to this programme.

Interested in becoming involved?

- **Are you a qualified Nutritional Therapist registered with the CNHC?**
- **Do you have an interest in brain health?**
- **Would you like to run workshops in your local area?**

To find out more about the programme and how you can become involved, visit our website **www.thebrainhealthprogramme.co.uk** or contact Kate by emailing **info@thebrainhealthprogramme.co.uk** or calling **01684 310099**.

You can also follow us on Facebook and Twitter to keep up to date with The Brain Health Programme news and events.

The most important thing to come out of Professor Bredesen's research is that Alzheimer's disease is not an omnipotent neurological disorder over which we have no control, but a metabolic disease which, at least in the early stages, is wholly within our control. The approach is also relevant for prevention.

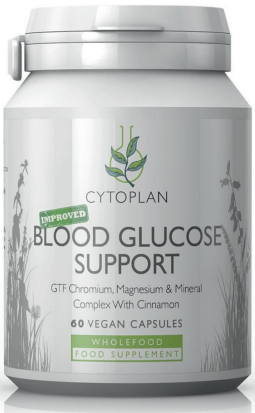
With this knowledge we can all be self-empowered for our health, not only for Alzheimer's disease, but for many other chronic diseases too.

SUPPLEMENTS TO SUPPORT COGNITIVE HEALTH

COQ10 MULTI

All encompassing wholefood multivitamin and mineral containing all nutrients you would expect to see in a good multi. It includes active forms eg pyridoxal-5-phosphate, methylfolate, methylcobalamin (B12), adenosylcobalamin (B12) and ubiquinol (CoQ10). Nutrients are included at effective levels eg B12 200 mcg, vitamin D3 40 mcg, vitamin C 200 mg, zinc 15 mg etc; per 2 capsule dose.

OTHER VITAMIN AND MINERAL FORMULAE



VITAMINS

Methylcobalamin & Adenosylcobalamin

Hydroxocobalamin

Other vitamin products in cognitive health range: Pantothenic Acid, Cell-Active Phospholec, Vitamin A, Vitamin C + Bioflavonoids, K2/D3

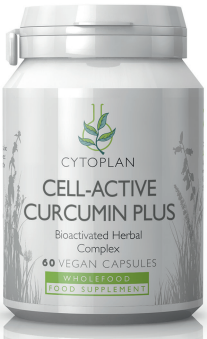
MINERALS

ESSENTIAL FATS

DHA (40%),
EPA (15%)
High in phospholipids

DHA (33%),
EPA (16%)
From an algal source

ANTI-INFLAMMATORY



Liposomal
curcumin, ginger

Flavonoids and
carotenoids

Liposomal
glutathione,
N-acetyl L-carnitine,
alpha lipoic acid,
Gingko biloba,
rosemary leaf,
resveratrol.

OTHER HERBALS AND PLANT BIOACTIVES

Other products in cognitive health range: Guggulu Plus, Kapikcacchu Plus, L-Theanine.

OUR FULL RANGE CAN BE FOUND IN OUR CATALOGUE

ABOUT PROFESSOR DALE BREDESEN

A Visiting Professor of Neurology and Director of Neurodegenerative Disease Research at UCLA, Professor Bredesen trained with Nobel laureate Prof. Stanley Prusiner, and has published over 200 papers focused on the mechanisms and treatment of neurodegenerative disease.

Professor Bredesen has spent over 30 years researching the treatment and prevention of Alzheimer's disease and is an acknowledged leader in the field of Alzheimer's research, utilising programmatics rather than outmoded monotherapeutics.

ABOUT CYTOPLAN

Cytoplan is a nutritional supplement company that has specialised in food based nutrients for the healthcare professional market since 1990. Cytoplan is wholly owned by a charitable foundation (The AIM Foundation) that is helping fund UK pre-trial research using a multi-modal diet and lifestyle approach.

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REFERENCES

1. Bredesen D (2014) - Reversal of cognitive decline: A novel therapeutic program. 2014. Aging, 6, 9, 707-17

2. Alzheimer's Society – https://www.alzheimers.org.uk/news/article/132/alzheimers_society_responds_to_ons_statistic_showing_that_dementia_and_alzheimers_disease_are_the_leading_cause_of_death_for_the_first_time

3. Prince MA et al (2014) - World Alzheimer Report 2014 United Kingdom: Alzheimer's Disease International.

4. Calderón-Garcidueñas, Liliana et al (2016) - Markers associated with Alzheimer's and Parkinson's diseases are present in Mexico City children chronically exposed to concentrations of fine particulate matter PM2.5 above the current EPA USA standards. Journal of Alzheimer's Disease, vol. 54, no. 2, pp. 597-613, 2016

5. Bredesen D (2016) - Why Nutrition is the Key to Alzheimer's. Cytoplan Education Event, 8 September 2016, London. Seminar slides

6. De la Monte and Tong M (2014) – Brain metabolic dysfunction at the core of Alzheimer's disease. Biochem Pharmacol, 88, 4, 548-559

7. Kosicek M and Hecimovic S (2013) – Phospholipids and Alzheimer's disease: Alterations, mechanisms and potential biomarkers. International Journal of Molecular Sciences, 14, 1310, 1322

REFERENCES

continued

8. Massaad C A et al (2011) – Reactive oxygen species in the regulation of synaptic plasticity and memory. Antioxid Redox Signal, 14(10): 2013–2054.

9. Ono K & Yamada M (2012) – Vitamin A and Alzheimer's disease. Geriatrics & Gerontology International, 12, 2, 180-8

10. Cunningham C & Hennessy E (2015) – Co-morbidity and systemic inflammation as drivers of cognitive decline: new experimental models adopting a broader paradigm in dementia research. Alzheimer's Research & Therapy, 7, 1, p.33

11. Du F et al (2008) - Tightly coupled brain activity and cerebral ATP metabolic rate. PNAS, 105, 17, 6409–6414

12. Troesch B et al (2016) – Potential links between impaired one carbon metabolism due to polymorphisms, inadequate B-vitamin status and the development of Alzheimer's disease. Nutrients, 10, 8(12), p E803

13. Harrison F E et al (2014) – Ascorbic acid and the brain: rationale for the use against cognitive decline. Nutrients, 6, 4, 1752-1781

14. Dawson E B et al (1999) – The effect of ascorbic acid supplementation on blood lead levels of smokers. J Am Coll Nutr, 18, 2, 166-70

15. Banerjee A et al (2015) – Vitamin D and Alzheimer's Disease: Neurocognition to therapeutics. International Journal of Alzheimer's Disease, pp 1-11

REFERENCES

continued

16. Mangialasche F et al (2012) – Tocopherols and tocotrienols plasma levels are associated with cognitive impairment. Neurobiol Aging, 33, 10, 2282

17. Shinohara M and Yamada M (2015) – Vitamin E and Alzheimer's Disease. Brain Nerve, 57, 12, 1509-13

18. Slutsky I et al (2010) – Enhancement of learning and memory by elevating brain magnesium. Neuron, 65, 165-177

19. Szewckzyk B (2013) – Zinc homeostasis and neurodegenerative disorders. Front Aging Neurosci, 5, 33

20. Kelly et al (2015) – Breaking down the barriers: the gut microbiome, intestinal permeability and stress relatded psychiatric disorders. Front Cell Neurosci, 14, 9, 392

21. Zhao Y et al (2015) – Microbial sources of amyloid and relevance to amyloidogenesis and Alzheimer's disease (AD). J Alzheimer's Dis Parkinsonism, 5, 1, 177

22. Zhu B et al (2014) – Chronic lipopolysaccharide exposure induces cognitive dysfunction without affecting BDNF expression in the rat hippocampus. Exp Ther Med, 7, 3, 750-754

23. Hill J M et al (2014) – The gastrointestinal tract microbiome and potential link to Alzheimer's disease. Front Neurol, 4, 5, 43

24. Bhattacharjee S & Lukiw W J (2013) – Alzheimer's disease and the microbiome. Front Cell Neurosci, 17, 7, 153

REFERENCES

continued

25. Dong H & Csernansky J G (2009) – Effects of Stress and Stress Hormones on Amyloid-β Protein and Plaque Deposition. J Alzheimers Dis, 18, 2, 459-469

26. Meng X et al (2017) – Dietary sources and bioactivities of melatonin. Nutrients, 7, 9, (4), E367

27. Koren D et al (2016) – Role of sleep quality in the metabolic syndrome, Diabetes Metab Syndr Obes. 25, 9, 281-310

28. Kharrazian D (2013) – Why Isnt my Brain Working? Elephant Press

29. Seong-Soo B (2016) – Role of exercise on the brain, 12, 5, 380-385. Exerc Rehabil

30. Way K L et al (2016) – The effect of regular exercise on insulin sensitivity in type 2 diabetes mellitus: a systematic review and meta-analysis. Diabetes Metab J, 40, 4, 253-71

31. Bin Yin Li et al (2017) – The role of cognitive activity in cognition protection: from bedside to bench, Transl Neurodegener, 6, 7

NOTES

Cytoplan celebrates 28 years in the field of food-based supplementation and from the moment of conception to the present day we have promoted the philosophy that nutrients are best delivered to the body "in the same form as food".

The philosophy and message of Cytoplan was founded on the simple logic that our bodies are designed to eat food and utilise its components for the maintenance of life. The ultimate goal of Cytoplan is to 'improve the health of the nation' by supplying supplements in a bio-effective form for optimal absorption and utilisation.

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THIS LEAFLET IS FOR HEALTH PROFESSIONALS

Science Based Supplements