INVITED ARTICLE FROM THE 2020 TEXAS ACADEMY OF SCIENCE TEXAS DISTINGUISHED SCIENTIST

BIOLOGY OF ALZHEIMER'S DISEASE

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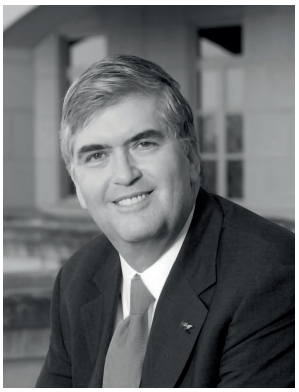

George Perry is Professor of Biology and Chemistry, Semmes Foundation Distinguished University Chair in Neurobiology, and former Dean of Sciences at The University of Texas at San Antonio. Perry has studied Alzheimer's disease since 1982 and was the first to discover that oxidative stress is a key feature of this and related neurodegenerative diseases. His studies identified oxidative damage, its source from metabolic/ mitochondria failure and catalysis by iron and copper. This work led to a novel interpretation of the role of amyloid—that instead of causing Alzheimer's disease, it is a protective antioxidant response, and the reason all the amyloid-based therapies have failed.

Perry is distinguished as one of the top Alzheimer's disease researchers with over 1,000 publications, one of the top 100 most-cited scientists in neuroscience and behavior and one of the top 25 scientists in free radical research. He was named the 2020 Texas Distinguished Scientist at the annual meeting of the Texas Academy of Science.

It is a great honor to receive the Distinguished Texas Scientist Award from the Texas Academy of Science (TAS) in consideration of the accomplishments of prior awardees, and even more, the success of over a century of TAS promoting science in Texas. I thank the Academy for this honor and the opportunity to present an overview of my studies on Alzheimer's disease seen from the perspective of a life in science. Science, evidence-based understanding of the world, is responsible for most human progress, technical and conceptual, extending even before the age of enlightenment. It is critical to remember that science cannot answer all human questions; when it can, its answers are *always* tentative to new data.

As far as I can remember, understanding the natural world consumed my interests. Encouraged by my father and having the most pristine habitat in Central Coastal California as a home (Figure 1), I

https://doi.org/10.32011/txjsci_72_1_TDS.

Figure 1. Photo, gift of Norman Perry.

studied the marine and land life of the region, eventually leading to my formal education in marine biology at the University of California Santa Barbara, Scripps Institution of Oceanography, Woods Hole and Hopkins Marine Station. This training impressed upon me the range of diversity, adaptation, and evolution of the natural world.

When I later entered biomedical research at Baylor College of Medicine and a career at Case Western Reserve University and the University of Texas at San Antonio, the contrast between two evidence-based sciences—biology and medicine—became apparent. Biology is the broader concept of adaptation and survival. Change to the environment is the primary constant of life and without it, extinction. A corollary is that the adaptations of thriving species are essential adaptations: we now know the appendix/tonsils and microbiome are not relics of evolution but appreciated as adaptations. Medicine, as applied biology, must understand the mechanisms underlying our biological success are adaptability and redundant homeostasis. While the most common diseases of a century ago were of mutation, injury, or infection, the chronic age-related diseases of

man are those where defect (mutation) or external agents play but minor roles, instead they are those of the failure of physiology.

With this background, I came to Alzheimer's disease (AD) in 1982 as a condition needing a solution. The late 1970s-early 1980s were the beginning of the modern era of AD research where biochemical, molecular, and genetic approaches were first applied to a disease known since 1906, and only in the early 1970s appreciated as a common condition, with now nearly 6 million cases in the US. These "modern" approaches were guided by the logic of removing the bad to restore the good, an approach that served patient treatment well when the disorder was a pathogen or defect, and is responsible for the doubling life expectancy seen in the past century, primarily through increased hygiene, vaccines, and antibiotics. With this approach in mind my primary focus was to find what is wrong in AD so we can remove or correct it.

The obvious targets were the lesions first described by Alois Alzheimer in 1906: senile plaques (SP) and neurofibrillary tangles (NFT) (Figure 2). Electron microscopy and antibody approaches yielded to biochemical analysis that revealed the SP were made of fibrillary protein, amyloid β, and the NFT of tau protein. What was missed by these analyses, specifically of NFT, was the strict biochemical rigor of an accounting of components due to their insolubility, leading to either antibody identification of components or analysis of similar but not identical fibers from brain (Perry et al. 1985). I found this pattern of developing postulates without definitive identification often repeated in AD research. In the quest to benefit patients now, the goal of medicine, the quest for rigor called for by biology was often lost. The goals of science and medicine are not always parallel, due to need for expediency in patient treatment.

My efforts to resolve the components of SP and NFT led to examining the cellular precursor leading to these abnormalities. Amyloid β of SP and vascular deposits were demonstrated as independent but similar processes involving cell death, extracellular matrix proteins, and NFT. The latter acted as nucleation sites for Aβ

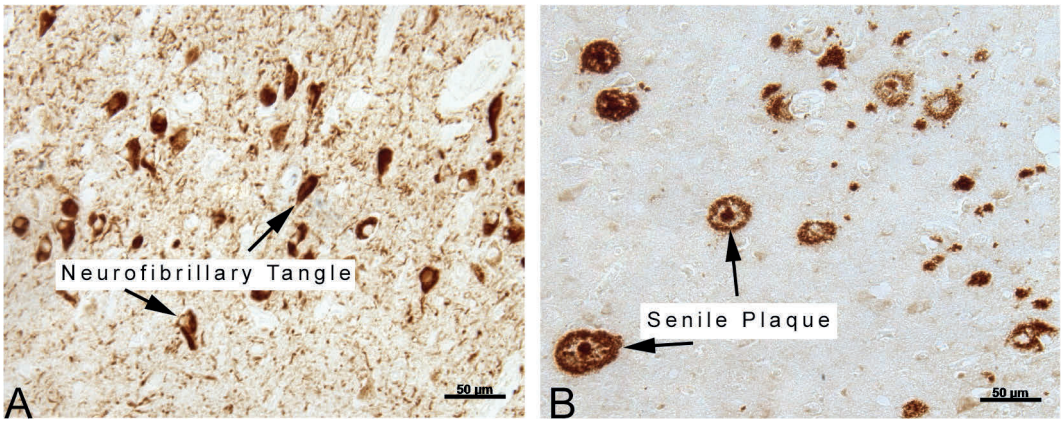

Figure 2. Tissue sections from case of Alzheimer's disease stained by antibodies specific to tau (A) and Amyloid ß (B).

deposition through high affinity binding sites on tau, suggesting SP and NFT are synergistic (Perry 1993; Smith et al. 1995).

Genetics revealed Aβ's precursor as a large transmembrane protein where mutations were linked to AD risk. Further genes linked Aβ processing to AD, leading to the amyloid cascade hypothesis, a linear logic that Aβ caused AD through neurotoxicity. *In vitro* cell culture, further genetic studies, transgenic mice studies, all seemed to support Aβ as causative.

The general thrust of the field was to align all research to the Aβ cascade for the past 30 years (Hardy & Higgins 1992). I too began with this hypothesis. The first discrepancy was the narrow range of Aβ toxicity *in vitro*, where it could have a trophic or toxic effect, depending on conditions, and isolated SP were never toxic. Second, I found Aβ is marked by a reduction in oxidative stress (Nunomura et al. 2000).

My PhD thesis focused on oxidative stress at fertilization in marine organisms (Perry & Epel 1985). I applied the principles of oxidative stress to understand AD, initially finding neuron specific increases in damage to proteins, lipids, sugars, and nucleic acids. The increase was greatest in the transition of normal to AD, mild cognitive impairment, and decreased thereafter. The decrease was inversely correlated with

Aβ levels in the same anatomic region and held true for sporadic and genetic AD and Down syndrome (where AD changes occur at an early age) (Figure 3) (Nunomura et al. 2000).

These biological observations led to reversing the amyloid cascade hypothesis (Smith et al. 2000) to the amyloid protective hypothesis. Fundamentally, the amyloid cascade hypothesis was a proposal that humans produce a detrimental response to the aging process that causes damage to the brain. Biology would never maintain Aβ as a common response to injury and aging without adaptive value. Aβ is deposited in numerous animals with well developed brains: dogs, bears, and others, and the sequence is highly conserved among species, attesting to its adaptive value. The genetics supporting a role of Aβ in AD is just that, correlational data, not causality. Causality could not be proven by transgenic mice, where removal of the created abnormality as expected restores normality.

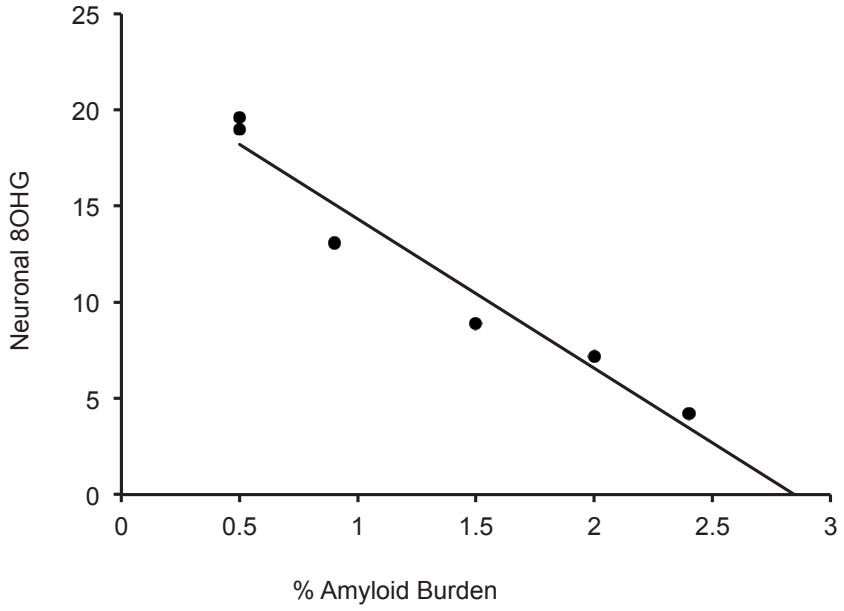

Figure 3. There is an inverse relationship (r =- 0.97, $p < 0.001$) between the levels of neuronal 80HG (oxidized RNA) and Aß deposition. Modified from Nunomura et al. (2000).

AD is human biology, and causality for Aβ could have been demonstrated by removing Aβ and reversing or arresting the progress of AD: it does neither. In numerous clinical trials Aβ has been removed from the brain with no benefit. Without benefit, Aβ is dead as a causative agent, but rather is one of correlation. The logics of medicine dictated a linear interpretation of correlative data that could lead to treatment. The same pattern of causality is developing for tau proteins; modification of tau is not providing clinical benefit. The focus of Aβ and tau removal as therapeutic is based on the abnormality of SP and NFT, rather than as their reflection of both as responses to brain injury, analogous to the repair seen in inflammation.

Finding that Aβ reduces oxidative damage relies on Aβ's binding of copper that blocks copper catalyzed lipid peroxidation (Hayashi et al. 2007). Aβ has a strong copper binding site that is critical to Aβ fibril formation and bundling of the fibers in SP. Within the Aβ deposits of SP are magnetite (Fe^{+2}/Fe^{+3}), suggesting that copper chemistry is precipitating, removing and protecting the brain from iron redox chemistry (Plascencia-Villa et al. 2016). At the core, iron and copper are essential elements of cells as they catalyze biological oxidations, aerobic respiration, and other reactions that are essential to metabolism. The primary organelle containing copper and iron is the mitochondria. Transport, fusion/fission and turnover of mitochondria are greatly altered in AD, leading to the accumulation of mitochondria debris in autophagic vesicles and lysomes demonstrated by mitochondria DNA accumulation in these degradation pathways (Hirai et al. 2001). It is not surprising that the same organelles as well as their terminal feature, lipofuscin, accumulate iron and copper in AD. Aβ also accumulates in the same organelles, suggesting it is critical for safe iron and copper recycling. There can be no benefit by removing critical biology. Similar clinical results are expected for tau, as it is also associated with reduced oxidative stress due to concurrent induction of the powerful antioxidant heme oxygenase 1 on tau fibers.

Biological selection avoids system failure: disease. Disease reveals and follows the rules of biology in requiring elements to be adaptable; irreversible disease is not. Understanding the benefits of medicine

versus biology in developing clinical care in therapy is imperative. The major diseases facing our society are those, like AD, that are the result of homeostatic failure. Effective therapeutics must address restarting failed systems.

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