**Notes**

1. A sort of anti-philosophy philosophy. Existentialists believe human existence has no meaning but nonetheless try to find some sort of meaningful inner meaning in all the assorted meaninglessness.

2. Crippled by the seemingly senseless futility of your thesis? Visit [www.deadthesissociety.org](http://www.deadthesissociety.org)

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**REVIEW**

**The Alzheimer’s Alarm Clock**

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Alzheimer’s disease is a progressive neurological disorder characterized by memory loss and confusion, and is the most prevalent age-dependent dementia. The major risk factor of Alzheimer’s disease is age. Less than two percent of all people inflicted with Alzheimer’s disease are below the age of forty-five. This increases to approximately ten percent over the age of sixty-five, and jumps dramatically to forty-seven percent in the over eighty-five population. The familial forms of Alzheimer’s disease account for less than ten percent of all affected individuals, and the majority of these cases become affected after the age of sixty. This signifies a biological alarm clock that appears to awaken this dormant disease after the age of fifty in most individuals, and the mechanism responsible still remains unclear.

One of the most prevalent neuropathological features of Alzheimer’s disease is the deposition of amyloid in the brain, in addition to selective neuronal loss and neurofibrillary tangles. Amyloid accretions exist as either amorphous, diffuse deposits or as a dense senile plaques, which stain positive with Congo red. The principle constituent of the amyloid deposits is a peptide denoted amyloid β (Aβ), which varies from 39 to 43 amino acids in length, the most abundant forms being 40 and 42 amino acids (Aβ40 and Aβ42, respectively). The Aβ protein is normally cleaved from the proteolytic processing of the amyloid precursor protein (APP) by two enzymes, β-secretase and α-secretase (Figure 1).

β-secretase, also known as β-site APP cleaving enzyme (BACE), leads to the production of Aβ peptide after β-secretase cleavage, whereas β-secretase cleavage produces the non-toxic P3 peptide. Both Aβ40 and Aβ42 can form amyloid fibrils, but are also associated with other structural forms in the progression to the fibril state. The monomeric form of the Aβ peptide has generally been considered to not be a neurotoxic species.

It has been shown that the density of senile plaques does not increase with age, rather, patients switch from a plaque-free state to plaque-bearing. The amyloid plaques develop from initially being non-neurotoxic into mature, senile neuritic plaques. The number of these senile neuritic plaques increases after the process is first initiated, with the number approximating to the degree of cognitive impairment.

Thus the question still remains as to what major physiological change(s) occur which allow for the initiation of Alzheimer’s disease. One possibility is that a regulatory change occurs, leading to the usage of different signaling pathways, hormones and transcriptional regions. This process can be clearly defined in women as menopause, which typically occurs between the ages of forty-five and fifty. A similar change may also occur in men around the same time period. This may be the natural winding down of the human clock that inadvertently awakens the processes leading to Alzheimer’s disease. Greater understanding of the changes that occur later in life is required for prevention of age-dependent diseases such as Alzheimer’s. Prevention will not be possible until the factors that initiate the clouds of plaques in the brain are clarified; this leaves only symptomatic treatment for Alzheimer’s sufferers. However, recent findings have shed light on possible methods for treatment.

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![Figure 1: β-Secretase and α-secretase compete for the amyloid precursor protein (APP) to produce either of their respectful large extracellular fragments termed APPs. The C-terminal fragments remaining in the membrane are cleaved by γ-secretase in the transmembrane region, to release either Aβ or P3 peptides and the intracellular release of the APP intracellular domain (AICD).](image-url)
Recently, BACE knockout mice were shown to lack Aβ and appear phenotypically normal\(^6\). As well, BACE null mice which overexpress human APP have their memory and cognitive impairment rescued. Thus inhibitors targeted directly to BACE would decrease the amount of newly formed Aβ peptides and decrease the level in storage pools. This inhibitor would need to be combined with another drug that could be used to remove the Aβ peptide reserve. It has been shown that a large amount of Aβ peptide is bound and transported by albumin in human plasma\(^7\). This pool would need to be removed for the successful treatment of senile plaques by eliminating the presence of the Aβ peptide. A specific binding partner for the Aβ peptides is required in order to clear it from the body.

In summary, a prevention of Alzheimer’s disease will not be possible without a greater understanding of the physiological changes that are associated with aging. However, research is generating potential therapeutic strategies that can be used to eliminate the effects of Alzheimer’s disease. This includes a reduction in the produced Aβ peptide using a BACE inhibitor and a drug targeted directly at binding the Aβ peptides to remove them from the physiological pool. With such a potential therapy, the future of Alzheimer’s disease will be determined.

References

**REVIEW**

**Sequence and Consequence – Genomic Exploration of the Sargasso Sea**

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The Sargasso Sea, named after the type of floating algae called Sargassum that riddles its surface, is a two-million-square-mile ellipse of deep-blue water that lies in the North Atlantic. This sea’s position drifts only slightly as a result of seasonal temperature fluctuations despite being surrounded by some of the strongest currents in the world: The Florida, Gulf Stream, Canary, North Equatorial, Antilles, and Caribbean currents. These interlock to separate the Sargasso Sea from the rest of the tempestuous Atlantic, which results in a slow, clockwise rotation of the waters within. The algae that reside at the surface of the Sargasso Sea provide a deceptively lush veneer to a body of exceptionally warm and clear water traditionally described as being devoid of life at deeper levels. But even in this ocean ‘desert’ there is an intricate web of life that has adapted to existence among the Sargassum.

In 2003, controversial genomics entrepreneur Craig Venter, famed for commercializing the human genome sequence, obtained guaranteed funding of USD 9 million over three years to sequence the DNA of every microscopic organism within the waters of the Sargasso Sea\(^1\).

Venter stepped down as president of Celera in early 2002 in order to head up the Institute for Biological Energy Alternatives (IBEA), which is involved in the Sargasso Sea project. Many claimed that this move was symptomatic of the inevitable industry-wide shift in focus from gathering genome information to the development of new drugs, but Dr. Venter is hoping to put a vast body of unexplored genomic information to work in developing novel energy production technologies.

At first glance it may seem out of place that funding for this project be provided by the US Department of Energy (DOE), but this should come as no surprise considering the expansion of projects funded by the DOE into the realm of biological research. Specifically, the DOE has established a biomass program which, it explains, ‘...develops technology for conversion of biomass (plant-derived material) to valuable fuels, chemicals, materials and power, so as to reduce dependence on foreign oil and foster growth of biorefineries\(^2\). The DOE further states that ‘Biomass is one of our most important energy resources. The largest US renewable energy source every year since 2000, it also provides the only renewable alternative for liquid transportation fuel.’ – a formidable admission considering that non renewable energy sources currently drive the US economy\(^3\).

It is widely recognized that the development of energy producing technologies that utilize biomass would strengthen rural economies, decrease America’s dependence on imported oil, avoid use of highly toxic fuel additives, reduce air and water pollution, and reduce greenhouse gas emissions. Current biomass uses include ethanol and biodiesel production, along with biomass power