

2012

Aging is the primary risk factor for the majority of neurodegenerative diseases, including Alzheimer's disease (AD) and Parkinson's disease (PD). There are almost 40 million people aged 65+ in the United States. Statistics predict that if you reach age 65 you can expect to live almost 20 more years. The average age of onset of PD is 60 years. If you are 85 years of age, you have an almost 50% risk of developing AD. The population of persons 85+ is projected to increase from 4.2 million in the year 2000 to 6.6 million in the year 2020. This suggests that these neurodegenerative diseases will reach a prevalence of epidemic proportions.

The current dogma holds that cellular mechanisms that are associated with aging and those that are related to neuron degeneration in PD and AD *are unrelated*. However, more recent evidence suggests that normal aging and the degeneration of specific neuron populations in AD or PD may be linked by the same cellular mechanisms. This remains a topic of debate. For your comprehensive exam, choose either AD or PD and use this disease to address the following questions:

- 1) Discuss what is known about one primary molecular mechanism that creates the pathology that occurs in one of these age-related neurodegenerative conditions. Discuss age-related changes in brain physiology that may promote, enhance, and/or allow the appearance of the disease specific pathology to be exaggerated in middle age and beyond.
- 2) For this section, assume that neurodegenerative disease exists along a continuum with natural aging. The implication of this is that if individuals survive long enough, it is inevitable that they will eventually develop AD or PD. Keep in mind that AD and PD are each viewed as genetically heterogeneous and complex disorders caused or influenced by multiple factors (e.g., specific genes, susceptibility alleles, environmental exposures, gene-environment interactions). Thus the development of "cause-directed therapies" is a goal of future research in these fields. Indeed, one model suggests that elements of lifestyle and genetics that promote healthy aging will decrease the incidence of these diseases in the general population. In this regard, discuss the following issues:
 - A.) how elements of lifestyle, genetics, or an intervention might impact the incidence of AD or PD.
 - B.) whether current data suggests a *single* target to cure AD or PD or if a multi-pronged approach is necessary.
 - C.) In the realm of "personalized medicine," how one could tailor a specific therapy or lifestyle for two patients with different "forms"* of AD or PD .

NSP Comp Question 2011

Deep brain stimulation (DBS) is presently in use, or under development, to treat an ever expanding array of neurobiological disorders, including Parkinson's disease, epilepsy, essential tremor, Tourette's, obsessive-compulsive disorder, depression, Huntington's disease and dystonia.

For this comprehensive exam question:

- 1) Discuss the application of DBS to one of the above disorders. Include within this discussion: (*4 pages*)
 - a. A summary of the neurobiological basis of the disorder, specifically detailing the neural circuitry involved.
 - b. The mechanism by which DBS alleviates (or if in development, is likely to alleviate) the symptoms of the disorder. Include mechanistic details at a cellular and systems level, for example, does DBS excite or inhibit neuronal firing, or both? What circuitry is involved, if any? What is the evidence from preclinical and/or clinical studies to support the purported mechanism?
 - c. Identify and discuss key unanswered questions regarding the mechanism of DBS action for alleviating the disorder that should be addressed to better understand how this therapy works.
- 2) Summarize and describe the new technology of optogenetics. Include mechanistic details at a cellular level. (*2 pages*)
- 3) Compare and contrast DBS and optogenetic stimulation using what you have learned and discussed in sections 1 and 2. What are the major differences between optogenetics and DBS? What are the advantages and disadvantages of each methodology? Speculate on the likelihood that optogenetics could someday be successfully applied as a therapeutic strategy, providing reasons for why or why not? (*3 pages*)
- 4) Design an experiment using optogenetics to address an unanswered question you identified for DBS in item 1. (*2 pages*)