Alzheimer’s disease (AD) is the predominant form of dementia constituting 60 - 80% of this condition world-wide. The cost of AD in terms of human lives and economic distress is considerable and will be estimated to exceed 100 million deaths by 2050 at a cost of $1.1 Trillion [1]. Symptomatic treatment is our only recourse presently as the mechanism(s) for the disease are unclear. Factors affecting cognition in the human brain such as neurogenesis, the formation of neurons from stem cells, may be compromised by AD. Other mechanisms, including neuronal cell death, are also being studied in efforts to find a cure for the disease. Thus, AD remains one of the major unmet medical challenges of the 21st century. Causes of AD vary from genetic determinants (approximately 2/3 of all cases) to lifestyle and environmental factors [2]. The latter include chemicals that affect hormone action and are known as endocrine disruptors (EDs). Endocrine disruptors are agents present in our water, air and soil to which we may be exposed chronically and which over time may have profound effects on our physical well-being by mimicking and disrupting hormone action [3]. EDs are grouped according to chemical type or by specific mechanisms of action. Although there is considerable evidence associating EDs with disruptive effects on wildlife species [3] and adverse developmental abnormalities in children [4], a strong connection between these chemical agents and Alzheimer’s related dementia is tenuous as work in this direction has not been given enough interest [5]. This editorial briefly outlines some of the studies regarding correlations between ED exposure and Alzheimer’s disease and posits three questions. First, what is the connection between hormone action and cognition or neurogenesis? Second, are specific EDs associated with the disruption of neurogenesis? The third question, dependent on the first two, asks if there is a connection between ED exposure and the incidence of AD or AD-associated dementia?

The endocrine system maintains the homeostasis of the body through the secretion of specific hormones by specific glands that regulate various functions. These include metabolic regulation (thyroid gland), sexual development (gonads), control of energy output from dietary sources (pancreas), response to stress (adrenal glands), and growth (anterior pituitary gland). Moreover, there is a complex interplay between endocrine and nonendocrine systems and regulation through the hypothalamus and higher brain centers. Given the number of processes controlled by the endocrine system, is there evidence that hormones affect cognition? There is in fact considerable evidence that various hormones have effects, both positive and negative, on cognition and neurogenesis [6]. Several studies indicate that the gonadotropins testosterone and estrogen have positive effects on cognition in older males and females. Clinical trials in menopausal women have shown that estrogen and progesterone administration can improve verbal memory and global cognition [7]. Testosterone supplements in older, but not younger men, were found to improve spatial cognition and working memory [8]. Moreover, it has been found that androgen supplementation in hypogonadal men results in improved memory performance [9]. Studies in male rats show that testosterone and dihydrotestosterone (DHT) treatment restored dendritic spine density that was lost when the animals were orchidectomized [10]. Synaptogenesis in female rats was found to increase at low concentrations of estradiol [11]. Trials and studies in other endocrine systems also suggest that cognition is an important element of control. One study found that thyroid hormones...
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(THs) affect acetylcholine, nerve growth factor and hippocampal function in a positive manner in rats and thyroxine (L-T4) treatment significantly enhanced learning of a special memory task [12]. Still, other work provides evidence that the endocrine system governing stress, may be correlated with dementia in the elderly [13]. This clinical study found that elevated cortisol levels are associated with dementia independent of a dominant negative gene for AD (APO-e4 allele). So, while the interactions between the endocrine system and cognition are complex, a large body of evidence indicates that the answer to the first question regarding a link between hormone action and cognition (or neurogenesis) is in the affirmative.

Endocrine disruptors include a large number of chemical types that may affect more than one endocrine system. A partial list of environmental estrogens and antiestrogens include DDT, organophosphates, fungicides, phytoestrogens (derived from plants), polycyclic aromatic hydrocarbons and heavy metals [6]. Antiandrogens are found in herbicides (atrazine and linuron) fungicides (vinlozolin and procymidone) as well as dioxins and furans (which are also estrogenic) and UV filters found in sunscreens and cosmetics [6]. Two of the most widely used EDs are Bisphenol A, an estrogenic ED (found in polycarbonate baby bottles, flame retardants and microwave ovenware), and phthalate esters, that are antiandrogenic (found in everything from hairsprays and perfume to detergents and skin moisturizers [6]. Since these compounds are present in so many products with which we come into contact, their interactions may not target just a single system. Indeed, many EDs can disrupt more than one hormone system (e.g. dioxin and polychlorinated biphenyls inhibit both Thyroid hormones and gonadotropins [14].

As to the second question (Are there studies indicating that EDs disrupt cognition or neurogenesis?), several variables must be taken into account. The mechanisms by which EDs affect endocrine systems are complex, inhibiting or enhancing one or more hormonal actions and often exhibiting nonlinear relationships between ED concentration and effect [15]. For example, the plasticizer bisphenol A, can exert strong inhibitory synaptogenic effects in female rats at concentrations lower than the US EPA reference dose [16]. In males, bisphenol A exhibits strong antiandrogenic effects [17]. It should also be noted that EDs may interact with hormones as inhibitors, enhancers or as modulators. Since both estrogens and androgens show positive effects on cognition and/or neurogenesis, it shouldn't be surprising that interruption by an environmental agent would compromise or modify their actions. Whether an ED is inhibiting or enhancing an endocrine effect, it is still disrupting the homeostasis intended by the hormone in question. In the case of gonadotropins, the ED is acting to oppose the intended function of these hormones. The answer to the second question would be a qualified yes, but more work needs to be done to provide a definitive answer.

The third question is the most difficult to answer. Can a connection be made between exposure to EDs and the increase in AD-related dementia? A rough correlation can be made between declining cognition in the elderly and a decline in gonadotropin production. Studies cited earlier indicate that androgen and estrogen administration can slow cognitive decline and that other factors may play a role as well. However, the bottom line at this point is that there is a difficulty in drawing a clear correlation between ED exposure and the incidence of AD. The main reason is due to the complexity of the systems and a lack of research in this area. Only a few comprehensive reviews have been written regarding this topic. Most work involving EDs and neuroscience pay more attention to developmental neurology in utero and in young children, clearly important areas that shouldn't be ignored. But the increasing number of aging individuals with AD-related dementia is taking a heavy toll on modern society and the time to concentrate more effort and resources on this growing problem is now. So, do I think there is a link between EDs and the rising incidence of AD? My short answer is yes. But the studies that must be pursued will be complicated by the complexities of the science, economics, and probably politics. Much more needs to be done to definitively answer this challenging question.

*Maximum acceptable oral dose of a toxic substance.

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Volume 7 Issue 11 November 2019
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