Alzheimer disease (AD) is an age-related neurodegenerative disease characterized biochemically by an abnormal buildup of amyloid β (Aβ) protein.1

BACKGROUND ON AD
The divalent cations zinc (Zn++) and copper (Cu++) have both been associated with the development of AD. Brain homeostasis of Zn and Cu is severely disrupted in AD.2 An alteration in brain Zn homeostasis, resulting in either above or below normal levels, has been implicated in the pathogenesis of senile dementia characteristic of AD. Excess Zn and Cu at high concentrations seems to promote the neurotoxic effects of Aβ.3,4 High levels of Zn may generate brain neurotoxicity and neurodegeneration by interfering with the normal functioning of ligand-gated ion channels.5 Excess Cu contributes to the toxic effects of Zn relating to the aggregation of Aβ and formation of the amyloid plaques prevalent in AD.6,8

AD AND AMD
There are similarities between the operative pathological mechanisms in AD and several types of retinal degenerative disease, including age-related macular degeneration (AMD).9 It has even been suggested that retinal changes in AMD may function as a biological marker for AD diagnosis and progression.9 In addition, there are data supporting an association between AMD and cognitive impairment.10

AREDS
Prior to the AREDS (Age-Related Eye Diseases Study) investigations, the effects of Zn supplementation on the development and progression of AMD were inconclusive, with some studies showing at least some beneficial effects,11,12 while other studies showed no association.13-16

The original AREDS investigation (AREDS Report No. 8)17 demonstrated that high levels of Zn supplementation (80 mg per day—as much as 10 times the recommended dietary allowance, plus 2 mg of Cu) together with high levels of vitamins C, E, and beta-carotene, reduced the risk of progression to advanced AMD by 25% and the risk of moderate vision loss by 19%. The AREDS2 trial lowered the daily dose of Zn for one subgroup of subjects to 25 mg per day. There was no statistically significant effect on progression to advanced AMD between the higher dose Zn used in the original AREDS formulation compared to the lower dose Zn used in AREDS2.18 Yet, the National Eye Institute continues to recommend the high (80 mg) daily dose of Zn.

GENETIC FACTORS
There are currently a total of 19 genomic loci that have been identified as being potential risk factors in
the development of AMD. The first and probably most important of these in terms of risk was identified by four independent investigations in 2005 and involves a single nucleotide polymorphism in complement factor H (CFH). CFH is a negative modulator of the alternate complement pathway. This discovery linked the pathogenesis of AMD to the complement cascade and its concomitant inflammation.

A more recent article (2008) demonstrated that high levels of Zn (and copper) cause CFH to aggregate, thereby inhibiting its ability to downregulate the complement cascade. This finding has, in turn, led to a new hypothesis concerning the effect of Zn on AMD—that it has opposing roles; specifically that Zn may be protective at later stages of disease, whereas it may trigger development of AMD in the disease’s early stages. So, a combination of the previously mentioned single nucleotide polymorphism in CFH and the presence of high levels of Zn may inactivate a key component of the alternate complement pathway to such an extent that the inflammatory process is not properly controlled, thereby significantly increasing the risk of developing AMD.

Another gene implicated in AMD is APOE, which codes for apolipoprotein E, a major component of a specific type of lipoprotein called very-low-density lipoproteins. Very-low-density lipoproteins remove excess cholesterol from the blood and carry it to the liver for processing.

 Mutants of both CFH and APOE are also involved in the development of AD. The same CFH polymorphism, Y402H, that is a major risk factor for AMD is also associated with AD. In addition, both APOE and Zn are involved in Aβ aggregation and deposition. Add to all this the recent study which demonstrated that for AMD patients with one or two CFH risk alleles and no ARMS2 risk alleles, supplementation with Zn was associated with increased progression to advanced AMD.

CONCLUSION

With an elderly population of patients already at risk for both AD and AMD based solely on age, and with all the aforementioned overlap in biochemical mechanisms and genetic factors between the two conditions, it is scientifically reasonable and justifiable for the NEI to discourage genetic testing for AMD and to continue to recommend a daily supplement containing a high dose of Zn?

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