

## **James L. Holly, M.D.**

### **Part II: You Can Get There But You have to Walk!**

#### **ApoE and Alzheimer's Disease**

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**Your Life Your Health**

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As my column last week suggested, most of us would echo the plaintiff cry of actress Susan Hayward in the 1959 movie entitled, "I want to live." But many of us would add an "if" to that declaration. There are many "ifs" we think of, but one which might be common to all of us is, "if I am in my right mind." Certainly, the desire to live for family would include that "if." As we said last week, "you can get there but you'll have to walk." That does not refer so much to locomotion but to motion itself. But, I am getting ahead of our story, more about that later. It was coincidental that simultaneously with the publication of last week's article that a laboratory test on me was returned to our clinic. The test was an Apolipoprotein E Genotype, but you ask, "What is that, what does it mean and why would I want to know?"

#### **My father was a great man but**

In 2005, my father died. My grief at his death was palpable but within that grief was a lingering question about the cause of his condition. Several years before his death, he began to experience memory loss and it progressed until it was severe. This was the experience of his brother and sisters, also. To my knowledge, no one in my mother's family has had any form of dementia. My mother is 92 years old and still sharp as a tack. When my father died, I wanted an autopsy on his brain to see if he had the typical changes associated with Alzheimer's but the pathologist in his small town was not available and it would have meant delaying his funeral for almost a week. We will never have that information.

#### ***Genealogy***

I have known for years that there is a test for the risk of Alzheimer's and have from time to time thought about doing it but didn't until now. I suspected that the results would show that I inherited from my father a risk for Alzheimer's and inherited no risk from my mother. That is exactly the results of the test. Let me explain.

I have always been amused when people who are into genealogy are very proud that a famous person is in their family history. For instance, if you research your "gene pool" – your genealogy and thus the people from which your DNA came – and you discover that George Washington was one of your ancestors, here is what you would have. If you regress from your father, of whom you have one, back through approximately ten generations, you would come to George.

Now remember, you only get half of your gene pool from your father's side of the family. The other half comes from your mother. So, in the tenth generation back, you would have

had 1,024 great, great, great, great, great, great, great, great, great, great grandfathers. And, you would also have the same number of grandmothers. Thus, you would have received .00049% of your gene pool from our nation's Founding Father.

### **ApoE and Alzheimer's**

In the case of the gene which places one at increased risk of Alzheimer's, you will get one gene, which is called an "allele" from your mother and one from your father. The ApoE gene is found in the form of three possible alleles: e2, e3 and e4. The current state of our knowledge is:

- Apo e2 seems to provide a protection against the development of Alzheimer's disease
- Apo e3 seems to be neutral neither increasing the risk nor providing protection.
- Apo e4 seems to increase the risk of developing Alzheimer's considerably

Remember, however, you have two ApoE alleles: one from your father and one from your mother. The possible combinations are:

- Apo e2/e2 this is the best you can have and seems to provide a significant protection
- Apo e2/e3 this tends to take the characteristic of the weaker allele and is similar in risk to the next pairing.
- Apo e3/e3 this is neutral, neither providing protection nor increasing the risk
- Apo e3/e4 this pairing shows a significant increased risk of developing Alzheimer's disease
- Apo e4/e4 this pairing appears to dramatically increase the risk of developing Alzheimer's disease
- Apo e2/e4 this is a very rare combination but a recent study in JAMA suggested that the risk would be similar to the e3/e4 although the onset might be delayed due to the e3 allele.

I suspected that I had gotten an e4 from my father and either an e2 or e3 from my mother. Although, that it is not possible to know that absolutely, my results did show an e3/e4 pairing. When I received this result, I realized that this was the first negative health information I have ever received about myself. At my age, that in itself is remarkable. My response was gratitude for the health that I have enjoyed and a resolution to do what I can, based on good science, to avoid the development of Alzheimer's.

### **What is the Science of ApoE?**

First, few genetic studies are absolutely predictive of future health problems. There are a few conditions where, if you have this allele or that pairing, you will definitely get a particular disease, but these are rare at the present state of our knowledge. Most genetic studies (see next week's Your Life Your Health on DNA analysis) only show risks or probabilities. One clever geneticist said, "Genetics loads the gun, but life style and habits

pull the trigger.” That is to say, while I may have a higher risk for Alzheimer’s than the general population, the choices I make in life will aggravate or mitigate that risk, i.e., increase or decrease it. Many people with high risk will never develop dementia and many people with low risk, or even no risk, will.

The reference laboratory which performed my test made the following comment on the results sheet:

“An ApoE 4 allele is found in 46-64% of the patients presenting with possible or probable Alzheimer’s disease. In usual and reasonable diagnostic settings the present of an ApoE 4 allele indicated with greater than 97% positive predictive value that Alzheimer’s disease is the cause of or contributor to the patient’s dementia. This compares with a diagnostic accuracy of 85% experienced late in the disease’s progression at leading Alzheimer’s research centers without the use of ApoE analyses.

“The absence of an Apo 4 allele, however, does not rule out the diagnosis of Alzheimer’s disease... Please note that there is no evidence that the ApoE genotype can be used to predict whether an asymptomatic individual will develop Alzheimer’s not present with dementia. For this reason, our policy is not to test asymptomatic individuals.”

This is an extremely balanced statement and represents exactly what I think at this present time.

### **What Can Be Done About the Risk of Developing Alzheimer’s Disease?**

- Cognitive training -- A variety of studies have shown that persons at risk for Alzheimers can reduce their chance of contracting the disease by undergoing cognitive training to sharpen cognitive skills. In fact, cognitive training has been shown to reduce cognitive decline in the early stages of Alzheimers Disease. It's been shown that persons involved in occupations where they continuously challenge themselves mentally also have a lower risk of developing the disease. It seems to be true what they say about "use it or lose it". Keep your brain well exercised by pursuing creative and challenging activities. Formal, cognitive training consists of a variety of exercises designed to help improve functioning in areas such as sustaining attention, thinking before acting, visual and auditory processing, listening, reading. Keeping your mind active is cognitive training.
- Keep your heart healthy -- Studies have shown the same factors that increase your risk for heart disease also increase your risk for Alzheimers Disease. The focus here should be on reducing blood lipid levels, controlling hypertension, and keeping diabetes under control. By doing these things, you're also practicing Alzheimers-Disease prevention.
- Stay at a healthy weight -- Obesity and overeating in general has been shown to be a risk factor for the development of Alzheimers Disease. Get your weight under control if you want to preserve your brain function later.

- Limit your alcohol intake -- Alcohol in high doses can cause damage to brain cells. Limit your alcohol intake to 1 drink per day, preferably red wine, which has lots of heart healthy antioxidants.
- Start moving! -- Not only does regular, aerobic exercise decrease the risk of developing Alzheimers Disease, it also slows cognitive decline in those who already have it. A brisk walk for 30-45 minutes three times a week should help to keep your brain cells healthy and act as good Alzheimers Disease prevention.
- Stop smoking -- Not only is smoking unhealthy for your heart and lung, it increases your risk of developing Alzheimers Disease. Smokers have up to a five times faster rate of decline in mental function as they age when compared to nonsmokers. There appears to be little doubt that smoking has unhealthy effects on brain tissue.
- Diet -- Studies have shown consumption of a Mediterranean style diet with lots of omega 3 fatty acids from sources such as fish may reduce our risk of developing Alzheimers Disease. Spare the red meat and go heavy on the fish and vegetables and you may end up preserving your brain function.
- Avoid head injury -- Studies show that patients who have had previous mild head trauma may be more at risk of developing Alzheimers Disease. What can you do to prevent head injury? Wear a helmet when you ride a bike or motorcycle, always wear a seat belt when driving, and avoid walking on slippery surfaces in wet or icy weather.
- Increase your social circle -- Studies have shown that an active social network is excellent Alzheimers Disease prevention. When you actively interact with others on a social basis, you're stimulating your brain cells to function at peak capacity and, possibly, forming new brain cell connections. Get out and interact with others by doing volunteer work, joining clubs, and attending social functions. It's a great way to keep your brain sharp!
- Can certain drugs reduce your risk of Alzheimers Disease? -- Some medications that show promise in Alzheimers Disease prevention include statin drugs which are used to treat elevated cholesterol levels as well as non steroidal anti-inflammatory drugs such as Ibuprofen. Studies are still ongoing with these drugs, so it's too early to recommend these to the general public.

The ApoE test costs \$400 – \$800. The day may come when we have an inoculation against the amyloidal build-up in the brain associated with and probably the cause of Alzheimer 's disease. The day will come when we will have a retro-virus “gene fix” for the e4 allele. Even then, you will be responsible for your life-style choices.

As a clinician, I was “interested” in knowing my results, but as a counselor to my patients, I would say, “If you have or had parents who have a form of dementia, you are at a higher risk of having the same. You can either get depressed and despondent over that or you can “get moving.” Remember the story about the elderly lady who said, “All my life, I have worried and worried and worried. Most of the things I worried about never happened. That just goes to show you, ‘Worrying really works!’”

Stop worrying and do something about it: lose weight, exercise, stop smoking. Read, talk, visit, write letters, solve puzzles, play chess, or bridge. Keep your mind active. On Thursday, October 1<sup>st</sup>, when this article appears in the paper, I'll be on the track for my 103rd day in a row to walk 5.5 miles. In 17 days, I will be 1/3<sup>rd</sup> of the way to doing so for one year. Want to join me? Give me a call.