AVOIDING FATES OF RONALD REAGAN OR MICHAEL J FOX.

READERS SUMMARY:
1. Why the presence of genes means nothing to disease risk.
2. What do people over 100 years old teach us about genetics?
3. What six pieces of evidence found in 2011 tell us about AD or PD etiology?
4. How will industry try to solve the mystery?
5. What you can do right now to obliterate your current risk of AD and PD?

If you did not know that Ronald Reagan suffered and died from end stage Alzheimer's, you do now. Micheal J. Fox is afflicted with Parkinson's disease and trying to solve its etiology as a fundraiser. Recently in 2011, several announcements were made that several genetic mutations seem to predispose us to Alzheimer's disease (AD) and Parkinson's Disease (PD). I tend to glance over these findings often because based upon my current understanding, genetic mutations are not where science seems to be headed these days. Genetic determinism has been the dogma for the last 50 years, but the most recent data suggest that we can reprogram our genes by turning on and off their function if we know how. This makes sense considering that most biologic systems don't rely on the presence or absence of genes in disease states. In fact, in Mount Sinai's supercentenarian group they found that the longest lived people all tend to have the "bad genes" in their cells we all worry about. The interesting part is that they are not "turned on" and appear to be of no consequence to those people.

The old dogma led us to believe that the mere presence of these genes spelled doom. If you don't think genetic determinism is alive and well in 2011, talk to any woman who tests positive for the BRCA 1 gene for breast cancer. Many of these women are electing for mastectomies in the face of no

immediate cancer presence just because of the scare due to the BRCA 1 gene being present. I don't advocate that kind of thinking. WHY? The Mount Sinai supercentenary group makes a great example for us to learn from. Think of an analogy of genes and their epigenetic signals to a "stick of dynamite" and "lit match". A stick of dynamite is not dangerous to us unless it is around a lit match. It appears the same is true for genes. The mere presence means little as long as the on switch is not present at the same time. This is where genetic testing is now headed.

The recent AD announcements gained lots of attention but the thing that caught my eye about the genes found in AD patients were all tied to lipid metabolism and inflammation generation. The AD jigsaw puzzle is a long way from complete, but pieces are emerging that suggest inflammation is the root cause of this condition. So Dr. Kruse, what exactly are those pieces of evidence? What six things have we learned about the brain and neurodegenerative disorders as of 2011?

1. The genesis cause of AD et al is caused by the presence of insoluble plaques made up of a protein called Amyloid beta (A-beta) inside neurons.

These proteins block signal transmission and molecule transfers that occur in the brain normally. This process continues for sometime and then another protein becomes more common called Tau protein. When both occur together they begin to interact and form the insoluble protein called a neurofibrillary tangle that is classically associated with many neurodegenerative diseases. (AD, Parkinson's, and Mad Cow disease are a few)

2. The second bit of evidence is found on the APO E gene present on chromosome 19. If it is present, many researchers and clinicians believe your risk of getting AD rises. In fact, having two copies of the many we have of this gene, raises your risk of developing AD 20-fold before the age of 75! So

APO E presence sounds bad does it not?

Guess what APO E gene function is for? It is to remove the build up of the A-beta and Tau proteins before they induce nerve damage and eventual cell suicide. The solubility factor is important because it is determined by how the protein folds after it is made. If it folds incorrectly it become less soluble. This is why we can see these tangles under a microscope. So this means that the presence of APO E gene is a great thing and not a bad thing that many have been led to believe the last 15 years. More proof that genetic determinism is not as important as the epigenomic effects upon those genes.

3. The third bit of evidence comes from Dr Chris Dobson's lab in Cambridge University.

He cleverly made 17 small genetic adjustments to the A-beta protein in the lab to make it either more or less soluble. After doing this he then transferred these genetically altered proteins into the DNA of fruit flies and clearly proved that the less soluble the protein transferred the shorter lived were the flies. Their life spans clearly correlated with the percent solubility of the protein transferred to the mutant flies. So after his experiment neuroscientists began to ask why do misfolded proteins show up in elderly brains to begin with?

4. It appears that all neurons have an internal quality control mechanism that not only detects misfolded proteins, but one that also self corrects this process from happening.

Research was published in March of 2011 from Brown University that both parts of this mechanism, the detector and refolder, are functional but overwhelmed in diseased brains with neurodegenerative changes. They can not keep up with the workload of all the A- beta protein being made.

5. Then the 5th bit of evidence came in April of 2011 from Dr.

Jeffrey Kelly.

Dr Kelly is at the Scripps Research Institute, and found that a chemical formed when cholesterol reacts with ozone attaches to A-beta and makes misfolding hundreds of times more likely. Take a guess where Dr. Kelly found the ozone came from? It comes from inflammation generated within the neurons from cellular metabolism. This linked the etiology of protein misfolding directly to carbohydrate and omega six fuels in our diet and their eventual metabolism over years. Both of these pathways are known to cause the development of inflammation in human biochemistry. It also links diabetes risk to AD fairly tightly. This news is not surprising to my readers at all if you follow the Quilt's Levees.

6. The last bit of evidence comes from the recent studies on studies on stress and the development of all neurodegenerative diseases. That is the hormone cortisol. This links another levee to the "brick in the wall."

This is a clearly a hormone most of my blog readers have become quite familiar with. Remember that cortisol rises in end-stage leptin resistance to cause the generation of even more inflammatory cytokines. Remember that cortisol is made from the cholesterol backbone, pregnenolone. 2011 work done at the University of California at Irvine has pointed to the elevation of cortisol as the main generator of the inflammation in diseased neurons. This further fuels protein misfolding and overwhelms the detector and refolding mechanisms in the brain.

SUMMARY:
It appears that the brains cholesterol stores are used up to make the cortisol that fuels the inflammation that drives this pathologic process. This inflammation becomes the currency that overwhelms the internal quality assurance system of neurons to make sure proper protein folding occurs. When the system is overwhelmed the end result is the formation of

neurofibrillary tangles from insoluble proteins. These insoluble proteins then block the transport of vital ingredients into the brain cells to offset the assault. One of those ingredients appears to be cholesterol itself. It appears that normal lipid metabolism repair mechanisms become so unbalanced that it induces the nerve cells to undergo apoptosis! This ties another levee to the AD and Parkinson's disease story.

Many physicians and researchers are hoping that we can find a place in this chain of events that can be attacked or blocked by a medication to prevent the inflammation, production of ozone reactions, slow the conversion of cholesterol to cortisol, and encourage the refolding apparatus that evolution provided us to make a dent in this disease. Maybe then we can improve protein solubility and even boost the plaque removal mechanism that we were born with? I have a better idea. Why don't we stop providing that the fuels that are known to provide the " lit match" to the dynamite?

Maybe we should advocate a low carb paleolithic diet that decreases carbohydrates that upregulate IGF 1 and 2 and lower omega six free fatty acids? We know that will help slow the progression of the disease since we now know what drives it. Some how I bet they'd rather make a drug they could make money on then teach people what really might help now? After all, no food company makes money unless they are selling the SAD do they. The choice is clearly yours to ponder.

CITES:

1. http://yourlife.usatoday.com/health/story/2011/08/Researchers-say-theyve-found-common-cause-of-of-ALS/50089982/1