Mullis

"Autumn is really the best of the seasons; and I'm not sure that old age isn't the best part of life. But of course, like autumn, it doesn't last."

C.S. Lewis

Mullis

Chapter 4 Mid-Life

The photograph below is a very funny and extreme way of looking at mid-life. Now that really is a crisis. The song as good as I once was really sets the tone for this stage of life. It talks about how his body says he caint do things that he used to but his pride will not let him accept it. The movies for this chapter are pretty funny and also depict some extreme mid life crises.

Chapter Intro

This chapter is about the strange stage known as mid-life. There are many dangers that can overtake you if you are not prepared. Therefore I have taken it upon myself to help you through this stage by warning you in advance of the dangers, and showing you how to cleanly navigate through the obstacles. If you listen closely and do as I say, your transition will be as smooth as butter; which reminds me, you're going to have to start being more modest with the butter intake, but we will get into that later. So here we go.

I just want to start off by saying I understand that this is all happening very fast but if we do not act now it will be too late. You have to understand that mid-life is strange in many different ways. One of the biggest is that you find that people, without your consent, begin to consider you as OLD. It is like you just wake up one day and you are suddenly put in the category of "old person". I know that it is confusing because just yesterday you were no different than the thirty year old in your office but you have are going to have to accept your 'oldness' as a fact. Now I know what thoughts are going through your head right now. You are thinking that you can possibly overcome these thoughts by changing the way you dress something but trust me, you cannot. You must persevere through these thoughts, because if you do not, you are going to get stuck in a crisis situation. You will lose all rational thought and begin acting in very strange ways. You might even spend all your savings on a sports car or motor cycle. It won't change anything though; you will just be an old guy that dresses weird and drive a car worth more than

his house. You don't want that. Well guess what, we just successfully avoided the first trap. See, what did I tell you? Just stick with me and you will be just fine.

Now that the first obstacle is out of the way we can slow down a little bit, I know you must be tired after all that work. Luckily for you, old people are allowed to take naps, I understand that you have viewed naps as a waste of time in the past but trust me, you are going to begin to warm up to the idea. Zzzzzzzzzzzzzzzzzzzzzzzzzzzzzzzzzzzzzzzzzzzzzzzzzzzzzz

Zzzzzzzzzzzzzz…… hey there sleepy head, you feel great now do you not. Of course you do, I can tell that you are slowly beginning to realize the inevitable. See, this whole getting old thing is not all that bad. Since you are well rested we should move on to the next obstacle. This next thing you are going to encounter is something that will stay with you for awhile. The good news is that it can actually be beneficial to you. Those thoughts you have been having about your life and those questions you have been asking yourself are not a result of the pizza you ate; we need to talk about that later by the way so don't let me forget. No, those thoughts and questions were also a result of you getting old. When people begin to see an end in sight, they begin to think about how they have spent the time that they have already lived. I'm going to take a wild guess and say that you asked yourself a question like, "How are people going to remember me when I am gone?" And or "what have I accomplished?" When handled right, these questions will drive you to become a better you. You have to be careful about these thoughts though, because if you lived a really sucky life and were a jerk to people, you may be susceptible to depression, anxiety, and or suicidal thoughts. You don't have to worry about that though; you seem like a pretty nice guy.

Well it is getting about lunch time so I figure it is a good time to go over your diet. Yeah, I know, on top of everything else that is going on you have to watch what you eat. You are going to have to learn the discipline of not getting loose with the salt shaker. Unless you want die you are going to have to take it easy on the sodium. You see when you get old you begin to here this word "cholesterol" in your dreams. You are also going to have to cut down on the fried food and on the butter. I know it sucks but if you want to spend your retirement from a bed then you go right ahead and eat some more hot wings. But that's enough about all this depressing talk, let us move on to the final hurdle.

This final obstacle is actually going to be the most fun. We are going to make a list of the things that you want to do and places you want to go. This may seem unnecessary but trust me, if you don't decide what you want to do you will piss-away the window of time where you are healthy enough to travel. You need to list places that you have always wanted to go and then make plans on how to get there. These can be the best years of your life if you take advantage of the time you have and don't let the fact that you are getting old get in the way. Take this time and enjoy your family and friends and your husband or wife. Live life to the fullest.

As we progress through life, we build a massive mental library of memories. All the things that were important to us - a special present at Christmas, our first kiss, our wedding day, or the birth of a child - we store safely away inside our minds. So it comes as no surprise that diseases such as Alzheimer's, which invariably strip us of our most cherished memories before eventually consuming our lives, scares us so much. The search for a cure is on and has been raging for some time. "Shutting Down Alzheimer's" offers up some examples of the type of work that's being done in hopes of finding a cure for Alzheimer's.

Shutting Down Alzheimer's

The human brain is a remarkably complex organic computer, taking in a wide variety of sensory experiences, processing and storing this information, and recalling and integrating selected bits at the right moments. The destruction caused by Alzheimer's disease has been likened to the erasure of a hard drive, beginning with the most recent files and working backward. An initial sign of the disease is often the failure to recall events of the past few days--a phone conversation with a friend, a repairman's visit to the house-while recollections from long ago remain intact. As the illness progresses, however, the old as well as the new memories gradually disappear until even loved ones are no longer recognized. The fear of Alzheimer's stems not so much from anticipated physical pain and suffering but rather from the inexorable loss of a lifetime of memories that make up a person's very identity.

Unfortunately, the computer analogy breaks down: one cannot simply reboot the human brain and reload the files and programs. The problem is that Alzheimer's does not only erase information; it destroys the very hardware of the brain, which is composed of more than 100 billion nerve cells (neurons), with 100 trillion connections among them. Most current medications for Alzheimer's take advantage of the fact that many of the neurons lost to the disease release a type of chemical communicator (or neurotransmitter) called acetylcholine. Because these medicines block an enzyme responsible for the normal decomposition of acetylcholine, they increase the levels of this otherwise depleted neurotransmitter. The result is stimulation of neurons and clearer thinking, but these drugs typically become ineffective within six months to a year because they cannot stop the relentless devastation of neurons. Another medication, called memantine, appears to slow the cognitive decline in patients with moderate to severe Alzheimer's by blocking excessive activity of a different neurotransmitter (glutamate), but investigators have not yet determined whether the drug's effects last more than a year.

More than a decade ago few people were optimistic about the prospects for defeating Alzheimer's. Scientists knew so little about the biology of the disease, and its origins and course were thought to be hopelessly complex. Recently, however, researchers have made tremendous progress toward understanding the molecular events that appear to trigger the illness, and they are now exploring a variety of strategies for slowing or halting these destructive processes. Perhaps one of these treatments, or a combination of them, could impede the degeneration of neurons enough to stop Alzheimer's disease in its tracks. Several candidate therapies are undergoing clinical trials and have yielded some

promising preliminary results. More and more researchers are feeling hope--a word not usually associated with Alzheimer's.

The Amyloid Hypothesis

THE TWO KEY FEATURES of the disease, first noted by German neurologist Alois Alzheimer 100 years ago, are plaques and tangles of proteins in the cerebral cortex and limbic system, which are responsible for higher brain functions. The plaques are deposits found outside the neurons and are composed primarily of a small protein called amyloid-beta, or A-beta. The tangles are located inside neurons and their branching projections (axons and dendrites) and are made of filaments of a protein called tau. The observation of these anomalies started a debate that lasted throughout most of the 20th century: Are the plaques and tangles responsible for the degeneration of brain neurons, or are they merely markers of where neuronal death has already occurred? In the past decade, the weight of evidence has shifted toward the amyloid-cascade hypothesis, which posits that both A-beta and tau are intimately involved in causing Alzheimer's disease, with A-beta providing the initial insult.

A-beta is a short peptide, or protein fragment, first isolated and characterized in 1984 by George G. Glenner and Cai'ne W. Wong, then at the University of California, San Diego. This peptide is derived from a larger protein called the amyloid-beta precursor protein, or APP. Molecules of APP stick through the cellular membrane, with one part of the protein inside the cell and another part outside. Two protein-cutting enzymes, or proteases--beta-secretase and gamma-secretase--carve out A-beta from APP, a process that

occurs normally in virtually all cells in the body. The reason why cells make A-beta is unclear, but current evidence suggests that the process is part of a signaling pathway.

A portion of the A-beta region of APP is inside the membrane itself, between its outer and inner layers. Because membranes are composed of water-repelling lipids, the regions of proteins that pass through membranes typically contain water-repelling amino acids. When A beta is cut out of APP by beta- and gamma-secretase and released into the aqueous environment outside the membrane, the water-repelling regions of different A-beta molecules cling to one another, forming small soluble assemblies. In the early 1990s Peter T. Lansbury, Jr., now at Harvard Medical School, showed that at high enough concentrations, A-beta molecules in a test tube can assemble into fiber-like structures similar to those found in the plaques of Alzheimer's disease. The soluble assemblies as well as the fibers of A-beta are toxic to neurons cultured in petri dishes, and the former can interfere with processes critical to learning and memory in mice.

These findings supported the amyloid-cascade hypothesis, but the strongest evidence came from studies of families at especially high risk of getting Alzheimer's. Members of these families carry rare genetic mutations that predestine them for the disease at a relatively young age, typically before 60. In 1991 John A. Hardy, now at the National Institute on Aging, and his colleagues discovered the first such mutations in the gene that encodes APP, specifically affecting the areas of the protein in and around the A-beta region. Soon afterward, Dennis J. Selkoe of Harvard and Steven Younkin of the Mayo Clinic in Jacksonville, Fla., independently found that these mutations increase the formation of either A-beta in general or a particular type of A-beta that is highly prone to forming

deposits. Moreover, people with Down syndrome, who carry three copies of chromosome 21 instead of the normal two copies, have a much higher incidence of Alzheimer's in middle age. Because chromosome 21 contains the APP gene, people with Down syndrome produce higher levels of A-beta from birth, and amyloid deposits can be found in their brains as early as age 12.

Researchers soon discovered other connections between Alzheimer's disease and the genes that regulate the production of A-beta. In 1995 Peter St. George-Hyslop and his colleagues at the University of Toronto identified mutations in two related genes dubbed presenilin 1 and 2 that cause very early and aggressive forms of Alzheimer's, typically appearing when the carrier is in his or her 30s or 40s. Further studies showed that these mutations increase the proportion of A-beta that is prone to clumping. We now know that the proteins encoded by the presenilin genes are part of the gamma-secretase enzyme.

Thus, of the three genes known to cause Alzheimer's early in life, one encodes the precursor to A-beta and the other two specify components of a protease enzyme that helps to manufacture the harmful peptide. Furthermore, scientists have found that people carrying a certain variation in the gene encoding apolipoprotein E--a protein that helps to bring together the A-beta peptides in assemblies and filaments--have a substantially elevated risk of developing Alzheimer's later in life. A variety of genetic factors most likely play a role in the onset of the disease, with each contributing in a small way, and mouse studies indicate that environmental factors may also affect the disease risk (exercise, for example, may lower it).