Good evening fellow Kats and guests.

I must own up to some apprehension as I stand before you this evening to address "The Meaning of 'Life'". One reason is pressure I feel at the end of a Kit Kat year that has produced so many memorable and "quintessential" Kit Kat essays. After each one I thought: "How can I possibly follow that?" In addition, this year we lost three esteemed and valued members: Denny Griffith, Ralph Lach, and Tadd Jeffrey, and in 2013 we lost George Meiling – reminding us how fragile life is, and how much we miss people when they are no longer with us. We are certainly pleased that Barbara Lach, Nancy Jeffrey and Suzie Meiling have joined us for tonight's meeting, and it is to the memory of Denny, Ralph, Tadd and George that I dedicate this evening's essay.

Perhaps I should begin by mentioning which aspects of "The Meaning of 'Life'" I am NOT discussing: I am not talking about "meaning" in the philosophical, metaphysical, or spiritual sense. Books, essays, movies, poems and plays throughout history have addressed that broader meaning. So I will leave that topic to some other essayist in the future.

What I AM going to address: is what does it mean to be alive? – what are the characteristics of living things that separate us from non-living things? As we sit here in this moment after dinner, our bodies are bee-hives of activity: 15 trillion cells in scores of organs – pumping blood, gathering oxygen, digesting an elegant dinner, thinking, and doing everything else it takes to exist. All the energy for this is being supplied internally – we are not plugged in or require recharging like our smart phones. We will explore how all of this has come about.

I actually chose this subject because I thought it would be easy: I thought all I would need to do is explain DNA in lay terms. When I graduated from medical school in 1967, DNA was the hot topic. I was fascinated by the field, which appeared to me to be what life was all about. After medical school, as I got further into my surgical career, I lost track of the developing story, but remained confident (as surgeons frequently do) that my understanding was reasonably current. About a year and a half ago after I settled on the topic for this essay, I thought it might be wise to do a little research to just make sure that no new discoveries have been made since 1967 in understanding of how living cells work, and what it takes to keep them alive. It turns out that concepts have dramatically evolved. Today's understanding of life is quite different, and much more nuanced, than it was in 1967.

My goal for this essay is to summarize in understandable terms what it means to be alive. Unfortunately, I cannot entirely stay away from scientific terms, so I want you to particularly listen for three terms: ATP, mitochondria and apoptosis. These three concepts are central to what it means to be alive especially for <u>higher</u> forms of life – like us. Even for a scientist like me, the take-away feeling about life is one of wonder, amazement, awe, mystery – and gratitude. We will discuss various life forms up to and including us. However, it still starts with DNA, so let us begin there.

DNA stores all the information about how to create and maintain every living thing – from the simplest bacteria to human beings. To give you an idea about how DNA operates, consider William Shakespeare's works. Last month Scott delivered a marvelous essay on that topic. All the information contained in the entirety of Shakespeare's works is really a very long string of just 26 letters, arranged in various sequences. Those sequences describe all of his characters, the drama, the humor, and the pathos. Likewise, the DNA molecule contains all the information necessary to create and maintain all forms of life and it is contained in long string of compounds arranged in various sequences. Unlike Shakespeare, the alphabet for DNA is only four different letters: A, T, C and G – the first letters of the 4 compounds – and only four – that make up DNA sequences. These compounds are attracted to each other as <u>pairs</u>: A attracts T, and C attracts G. DNA's physical form is the famous double helix. The model on the table depicts a tiny DNA segment. The four basic compounds are color-coded. The long DNA strand is, in turn, twisted and folded unto itself, so it is not a straight strand. But to give you an idea how big the DNA molecule is, consider the following. This model is 5 ¼" in diameter. If it were a human DNA strand with that diameter, straightened out and aimed east, it would end just this side of Amsterdam in the Netherlands. By the way, there is a lot of DNA around: on the entire earth, about 110 trillion pounds.

Now let us consider genes. Genes are short segments of a DNA strand that code for specific substances, such as proteins, that make cells run. Genes determine our hair color, whether we will even have hair as we mature, and virtually every aspect of who we are and how we function. Interestingly, only a small fraction of the DNA sequence actually is genes. The vast majority of DNA does not code for anything – at least that we understand right now.

Even though DNA is a crucial part of what it takes to be alive, it is not life by itself. I leave traces of my DNA every time my body contacts the outside world. That DNA is unique to me, but it is not me. It contains all the building and maintenance information for every part of me, and has guided all of my cells from the single cell that began my journey over seventy five years ago. But it is still not me. By itself, it is not alive. So what else does it take, beside DNA, to actually be alive?

To answer that question, we will begin by discussing the simplest life form: bacteria. They possess three attributes of life besides containing DNA. <u>First</u>, they are cells. <u>Second</u>, they burn fuel and creating energy. <u>Finally</u>, they can reproduce. We will examine each.

Bacteria are living beings made up of just <u>one cell</u>. They are very small – invisible to the naked eye. But just because they are small does not mean they are not mighty in other ways. Before you consider bullying a bacterium, consider the fact that in and on your body, your own cells are outnumbered ten to one by bacterial cells. The Terry Davis that stands before you delivering this essay is only 10% purebred Terry Davis cells. The other 90% are cells with some other DNA – mostly bacteria. And it gets worse. If you count all the <u>genes</u> that are inside my tuxedo, my own genes are outnumbered 360 to one by my bacterial genes. That is not just true for me; it is true for all of us.

Bacterial structure is quite simple. They have hard shells and long tails that whip around propelling them from place to place. The bacteria's DNA containing its genes is inside the cell and runs everything that is going on. Among other things, our bacteria can produce enzymes, vitamins and proteins that our own cells cannot make, and is the reason we are dependent on the bacteria that we host. We could not exist without them.

All this work takes energy. In bacteria, as in all life forms, energy is stored and distributed in a high-energy compound called Adenosine TriPhosphate, or ATP (the first term to remember). The ATP molecule can be thought of as a tiny rechargeable button battery. Thousands are available in the cell to deliver energy wherever it is needed: to maintain or repair the cell, make compounds, move, or reproduce. After delivering the energy, the depleted ATP battery gets re-charged and goes back out to do it all over again. The charge in the ATP only lasts for a few hours, so continual re-charging is necessary to keep the cell alive.

The final characteristic of life that we see in bacteria is reproduction. They reproduce by simple division. One cell becomes two, but there is no growth or development, just more and more of the same single cell that are mostly exact copies of the original. I say "mostly" because nothing is perfect. Just as a photocopy of a photocopy of a photocopy, tends to get more blurry and less accurate going forward, the same can happen with DNA. When a copying error occurs, we call it a mutation, and that can give the cell a new characteristic, such as antibiotic resistance that has led to "superbugs" like MRSA.

Life has been on earth for around four billion years. For the first two billion years, it was all bacteria. Then, two billion years ago, a real revolution occurred when a new cell type emerged, called the Eukaryocyte. It was a monumental development. It led to life forms made up of huge numbers of cells cooperating to form what we call an organism – the basis for all plant and animal life on the earth. In the old, bacterial world, the single cell is the being. In the new world of higher plants and animals, the "being" is made up of myriad cells, approximately 15 trillion cells in our bodies. The cells serve different purposes: Heart, kidney, skin and brain cells, just to name a few, all have different jobs to support our lives. This new cell type is very different from bacteria.

First consider size. In this case, size really does matter. A typical human cell is 10,000 to 100,000 times larger than a bacterium. Our huge cells don't have a rigid external cell wall – just a membrane, allowing cells to interact easily with other cells.

Other differences have to do with DNA. For starters, there is a lot more DNA in our cells: orders of magnitude more. It is packaged inside a membrane called a nucleus, which bacteria lack. The nucleus, and the nuclear DNA it contains, is the cell's boss. Also, our nuclear DNA is not simply an exact copy of the preceding generation's, but our DNA comes from two sources: half from mom, and half from dad. That is to say, sex is involved. In bacteria, one bacterium reproduces to make two new ones. In people, it takes two people to make one new one. So sexual reproduction takes a lot of energy – not to mention the energy necessary to maintain the relationships.

Another difference is the existence of mitochondria (the second term to remember). These little sausage shaped organs floating around inside cells provide energy – thousands of recharging stations for our little ATP button batteries. Some active cells contain hundreds of thousands of mitochondria. For us human beings, mitochondria alone make up about 10% of our body weight. And they are much more efficient in energy production then the few areas on the bacterial cell wall. Internalizing energy production by mitochondria is at the basis of evolution of complex life. No longer is the size of the cell limited by the amount of surface area available to generate energy.

Now, the instructions to run the mitochondria come from the the mitochondrial DNA, which is different from the nuclear DNA. Mitochondrial DNA is far simpler and there is much less of it in the mitochondria. Further, the source of mitochondrial DNA is different. Here is the reason: We all started from a single cell, the fertilized egg. That huge egg, containing about 100,000 mitochondria, was fertilized by a tiny sperm cell containing fewer than 100 mitochondria – just enough to power his tail to swim. Therefore, while half of our nuclear DNA comes from mom and half from dad, our mitochondrial DNA is 99.9% from mom only. Sorry, men, but this is just a fact of life.

As in bacteria, the currency for our energy exchange is ATP. The difference between bacteria and us is the order of magnitude. ATP energizes all our different cells to do their thing – heart muscle to squeeze, kidney cells to filter, brain cells to think - just to name a few. Since ATP only lasts for a few hours, production must be continuous. To indicate the magnitude of that process – between now and this time tomorrow night, each of our bodies will have produced – and used up – approximately 140 pounds of ATP.

Another feature that characterizes higher life is growth and development. Bacteria just divide and make more bacteria. That is their whole life. They don't substantially change their form. At the other end of the spectrum look how each of us has grown and changed from the moment of our conception to where we are tonight. For starters, we start out small, and end up big – we grow. Further, our original cell has not only multiplied, but groups of cells in our developing bodies have taken totally different pathways to become different organs playing different roles. As we sit here tonight each of us is an individual organism made up of genetically identical cells which are specialized to perform diverse tasks for the good of the whole. I long ago stopped growing, but I continue to develop. That was painfully obvious to me as I recently looked through pictures of me at various stages of my life, beginning as a child. Throughout all these years, I have been various versions of Terry Davis: the same individual being, yet very different with time.

How does that happen? How can I be the same person, albeit a shorter and more shop worn version than earlier in my life, when this body does not contain a single atom that is the same as a few days ago, let alone 75 years ago. Everything, including my own DNA, has turned over countless times. What IS the same, and why I am still me, and you are still you, is the unique sequence of those four letters in each of our DNAs – A, T, C and G. It is that information which still runs my current cells, just as it did my original cell. To go back to the Shakespeare metaphor, I could go home tonight and print out a copy of Hamlet in its original version and I would have that play, just as it was first produced over four hundred years ago – complete with the characters, drama, and all the tragedy. The reason is that the information is all contained in that same sequence of 26 letters. It is still the same play, even though it is now printed out on my computer screen, a very different form than the original medium; and it is now 411 years later.

What about plants? Plants and algae make up much more mass of life on earth than do animals. Indeed, life as we know it could not exist without plants because they can convert the energy of the sun into a usable form for us animals. Their cells look much like ours, with one main difference: chloroplasts. These are little organs in plant cells that look like mitochondria, but they can harness the energy in sunlight to synthesize sugar from water and carbon dioxide, and to produce oxygen in the process, all of which is necessary for animals like us to survive.

The largest living organisms on earth are plants and fungi. One fungus in Washington State is calculated to weigh 825,000 pounds. As big as that sounds, it is dwarfed by Aspen. What we normally consider an Aspen “tree” is not an individual tree, as is an oak tree. An Aspen grove is all one single organism, one unique DNA creating a single huge underground root, from which individual shoots spring upward to form what we see as trees. One such clone – a single DNA based organism – in Utah consists of 47,000 tree trunks covering 106 acres, and calculated to weigh 13 million pounds – one plant. Its name is Pando, or the trembling giant. And it is 80,000 years old, pre-dating all recorded human history since the late Pleistocene period, surviving fires and other environmental challenges. I will defer to Jim Ginter, based on his Kit Kat essay in January, to estimate how far Pando predates the arrival of humans in the region.

An additional characteristic of life, both at the cell level, as well as the organism as a whole, is death. Like taxes, death is a natural consequence of life, but what may be surprising is how important cell death is to the life of the overall organism. Indeed, it is absolutely necessary for cells to die in order for the organism itself to develop and grow as well as to simply maintain itself. As an example, consider the embryonic formation of our hands. Our fingers are not formed by sprouting out of our palm. Rather, in the embryo, our hand starts out as a web, and programmed cell death of the tissue in between the fingers allows them to emerge as separate digits. Also, in the brain we start out with many more brain cells then we end up with. Neurons disappear during embryonic development – in some areas, more than 80% of the original nerve cells disappear before birth! The remaining cells are wired with great precision. So some aspects of our formation are more like sculpture, where the final form is created by <u>taking away</u> material from the initial block. That "taking away" is done by programmed cell death and it is called apoptosis (the last term to remember). It is actually very benign and is triggered by any one of a number of events, including eliminating sick cells from the general population. Cells that die this way simply dissolve, all their ingredients slipping into the general soup to be used by other cells. It is atraumatic, and happens without leaving a trace.

Apoptosis can also be triggered by death genes. These genes program cells to die after a certain number of divisions. That number is specific to different cell types, determining their turnover rate. Some cells – in our blood stream – turn over daily. Cells in our small intestine turn over every 2-4 days. Fat cells turn over only once every 8 years – you actually gain or lose <u>fat</u> weight by individual fat cells getting bigger or smaller, not by changing the number of those cells. Some cells types never turn over – such as central nervous system, eye lense, and eggs in the female – girls are born with all the future eggs they will ever have. The total amount of cell turnover is quite impressive. By this time tomorrow evening, 10 billion cells in my body will have died by apoptosis, and been replaced by fresh undamaged cells. What a wonderful, selfless thing it is for an individual cell to do for the good of the overall body. So this is another aspect of the meaning of "life". And where do you think the death genes live? In the nuclear DNA?

Actually, they are in the mitochondrial DNA, from our mom, not our dad – another reason the mitochondria are so important to what it means to be alive.

A final characteristic of higher life that comes from its marvelous complexity is referred to as "convergent evolution" – the tendency of various different life forms to come up with similar solutions to similar challenges. For example, the ability to fly is a good trick to enable an organism to get around. Despite the obvious engineering challenges, flight evolved independently at least four different times in four different life forms – all evolving wings, regardless of their different ancestries. Insects, birds, and even mammals such as bats all fly using wings. Likewise the now extinct reptile, the pterodactyl, did the same. Although we humans can't fly ourselves, over generations we used our brain to invent airplanes with wings to allow us to fly. Beyond airplanes, we did Mother Nature one better by inventing rockets that can fly in the total absence of air – all living flying creatures and airplanes require air to fly in.

Another good idea is sight – allowing an organism to visually understand its environment. Eyes have evolved independently as many as forty times, including the camera eye of mammals and the compound eyes of insects. Once again, humans, using our brains, have extended the <u>ability to see</u> dramatically by inventing the microscope to view incredibly small things and the telescope to view things farther away than we can see with the naked eye.

A third good idea is intelligence – the ability to think, to come up with new ideas, create solutions to problems, allowing organisms to occupy various niches in the universe. It turns out we are not alone in our ability to think and communicate. Insects, such as the ant colony you see on the table before me, are not acting by reflex. Each ant has its own job. They are going down a specific tunnel to bring up a specific amount of material to the top, and going down again. They are gathering at the top to talk to each other by touching antennae. They come together in groups (planning committees?) before they go down to connect two tunnels requiring cooperation. All of this is coordinated by an almost microscopic brain. Now I am not suggesting that they are self-aware, or understand <u>where</u> they are tonight, and <u>why</u> they are here, but they are communicating, working together to impact and change their environment.

What about the highest level of intelligence: consciousness and self-awareness? Are we the only forms of life with these two characteristics? Consider the story of "Inky" – the Octopus

– who, until recently, lived at the National Aquarium of New Zealand. His ingenuity and daring have made him a folk hero. One day, late in the evening, when the aquarium was virtually deserted, this basketball sized mollusk squeezed through a narrow gap at the top of his tank and flopped down to the floor. Sensing freedom, he slithered to a 164' long pipe which led into the sea, and is now "at large somewhere in Hawke's Bay". According to marine biologists at the aquarium, they are not surprised. Octopi, they say, are remarkably intelligent. They monitor their environments closely and learn quickly to solve problems. They have been seen opening jars to get food and using makeshift tools. They also recognize human faces and form positive and negative judgements of people.

We human beings are not the soul possessors of intelligence and self-consciousness. Data suggests that these characteristics are actually widespread among animals from dolphins to elephants to gorillas. It is a matter of degree. At the moment, we seem to be atop the intelligence heap. At least, that is our opinion. However, if we eliminate ourselves by shear hubris or ruining our environment, who is to say that given a few tens of millions of years, some other organism might not evolve a similar degree of intelligence and occupy similar niche?

What then is the meaning of "life"? What does it mean to be alive- particularly for us? DNA; cells; mitochondria; energy production; reproduction; growth and development; apoptosis; intelligence. You could make a case that, beside DNA, the mitochondria are the most important element of all, with their highly efficient and mobile energy delivery system and programming of cell life spans which makes everything else happen.

What does "life" mean to me? For 35 years, as a pediatric heart surgeon, almost daily I had the honor of entering into the body of an infant or child to fix their heart. When I would open the chest and see the heart beating, it was always amazing to me how small it is – especially compared to the 1250 pound heart lung machine at my feet that will be necessary to take over its functions for the short time it will be down for repair. In congenital heart surgery it is always about fixing a part of the heart that has not formed properly - because some gene on some chromosome programing heart development did not quite copy properly. As a result a wall didn't form completely, leaving a hole; or a valve was misshapen, or a part of the heart was too small, or too large, or upside down, or even backwards. The ability of our entire team to be able, most of the time, to make that heart work was a great joy. However, over time I came to understand that the important fact of life is not that a single genetic miss-copy can occasionally cause trouble, but rather – better than 99% of the time – the heart, just like my own heart, is formed perfectly. That is the real mystery. Now I will admit that through my membership in the "Bacon-of-the-Month Club" and other dietary indiscretions, I may have necessitated some maintenance work on my perfectly formed heart by clogging up its coronaries – but that is another story.

So for me, life is a magnificent symphony of many different instruments coming together to create a beautiful piece of music. Each instrument, by itself, understandable, but the whole symphony is much greater than sum of its individual parts. What I know and understand is but a small piece of the puzzle. By far, most of it is mystery to me, and I am just fine with that. The more I understand about the complexity of life itself, the more I appreciate how precious it is.

Hopefully, when I awake tomorrow, I will be grateful for everything that happened overnight to allow me to greet the new day. And to the memory of Denny, Ralph, Tadd and George – hats off to lives well lived, energy well spent, and great legacies left behind.

Thank you.