It's hard to choose your parents.

Presented to the Athenaeum Society by Bill Watson

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Mr. President, Mr. Secretary, Mr. Radford, and fellow members of the Athenaeum Society. It is a pleasure to address you this evening.

The NCAA record for the highest points per game average in college basketball is 44.2 points per game. The record was set between 1968 and 1970. Now mind you, that was before the three point shot had been introduced. The record holder is Peter Press Maravich. His nickname was Pistol Pete. He averaged an astounding 44.2 points per game while only scoring two points for each basket he made. It has been estimated that if he had played during the time of the three-point shot, he may have averaged 57 points per game. Pistol Pete Maravich played at LSU while his father Press Maravich was the coach. After an outstanding college career, Pistol Pete went on to play in the NBA for ten years. He was drafted third overall in 1970 by the Atlanta Hawks where he played from 1970-1974 until being traded to the New Orleans Jazz (74-79). He played for the Jazz from 1974 through 1979. He accompanied the Jazz when they moved from New Orleans to Utah for the 1979-1980 season. He was traded during the season and finished the season with the Boston Celtics (79-80). He retired from the Celtics after a leg injury in 1980. I like many others watched Pistol Pete play ball and marveled at his shooting ability. Years later I would again come in contact with Pistol Pete.

About fifteen years ago, I was attending a medical conference and one of the topics was spine conditions. The speaker was detailing the various spinal conditions that can plague us and that can be sources of chronic disabling pain and deformity. One back x-ray was particularly memorable. It was an x-ray of a young man with a spinal condition known as ankylosing spondylitis (AS). This particular x-ray was very striking with its forward curvature and the amount of calcium deposits fusing the spine in place. During my twenty one years as a family physician, I took care of several patients with AS. These individuals walk with a distinctive gait at a relatively young age. Their backs develop a progressive distinctive forward curvature as their disease progresses. (Demonstrate.)

The back x-ray that was shown at the conference was the x-ray of Pistol Pete Maravich. Pistol Pete had an inherited condition of the back, ankylosing spondylitis. Yet despite this diagnosis you would not have known of his disease on the basketball court.

Ankylosing spondylitis is a condition that has an inherited tendency. By an inherited tendency, we mean it has a genetic predisposition, but there may be more to it than that, the disease may also be impacted by environmental or other factors as well. AS usually shows up between the ages of 15 and 30 and has a 2:1 male preponderance. The disease is marked by spinal inflammation, calcification leading to immobility and fusion over time. Those individuals who are positive for a blood marker known as human leukocyte antigen B*27 (HLA-B27) have the highest likelihood of developing the disorder. HLA-B27 is a surface antigen encoded by the B locus in the major histocompatibility complex located on chromosome six. The relationship between HLA-B27 and many diseases has not yet been fully elucidated. Though it is associated with a wide range of pathology, it does not appear to be the sole mediator in development of disease. For example, while nearly all people with AS are HLA-B27 positive, only a fraction of people with HLA-B27 ever develop AS.

The inherited tendency or genetic connection of AS provoked my interest in the subject of this paper. I am interested in the connection between our genetic makeup and our health. An example of what we have known for a long time has finally been acknowledged in pharmaceutical commercials for cholesterol lowering drugs. Cholesterol doesn't just come from what we eat, more importantly it also comes from our Aunt Mildred and Uncle Frank as the commercials announce. Our bodies are genetically programmed in the way we produce and metabolize cholesterol and this has the largest impact on our blood cholesterol level.

Much of what impacts our health is the result of our genetic makeup. We can see changes in blood work at an early age that sheds light on a person's genetic patterns and makeup. This genetic heritage or makeup affects our chances of developing heart disease, hypertension, diabetes, cancer, and other conditions as our lives progress. As a family physician this information would frequently come to light when I was reviewing the results of a physical exam with one of my patients. Someone feeling well would come for the recommended comprehensive exam and during the discussion of findings this genetic

information would come to light. The impact of this knowledge left me shaking my head when informing patients of the genetic tendencies that they had inherited. To cut some of the tension at such a point I might say, "It is so hard to choose our parents." That comment would put the information in perspective. Our genetic makeup is determined for us. We didn't ask for it and we had no control over receiving it. We can however, have a significant impact on how our genetic makeup expresses itself over the course of our lives. With the advantage of certain knowledge we can adopt a lifestyle designed with an eye to limiting the genetic impact at least in terms of certain metabolic diseases. Perhaps more significantly for the future are the therapies and treatments that are rapidly being developed which specifically seek to impact the expression of genetic disorders.

We inherit our genetic profile equally from our parents, half from our mother and half from our father. That genetic code is carried on our chromosomes inside the nucleus of each cell in our body. The initial work on genetics was done by an Augustinian Monk, Gregor Mendel. Mendel working in 1865 found that individual traits were determined by discrete "factors" later known as genes inherited from parents.
Each person has a defining set of chromosomes that contains all genetic information.

In the 1950's, research into the structure of our genetic material became the hot topic that it remains today. Watson and Crick in 1953 proposed the first accurate model of the structure of deoxyribonucleic acid or (DNA), the famed double helix, in an article in the journal, *Nature*. Their work utilized the X-ray diffraction images of DNA made by Rosalind Franklin that revealed that bases were paired. In 1962, after Franklin's death, the Nobel Prize in Medicine or Physiology was awarded to James Watson, Francis Crick, and Maurice Wilkins for their pioneering work on the structure of our genetic material.*

Our chromosomes are located in the nucleus of each cell and chromosomes are composed of DNA which is arranged or oriented in the classic double helix structure. DNA contains the instructions that encode for proteins and ribonucleic acid or RNA as well as for other cell components. Chemically, DNA is a long polymer of simple units called nucleotides, with a backbone made of sugars and phosphate atoms joined by ester bonds. Attached to each sugar is one of four types of molecules called bases. It is the sequence of these four bases along the backbone that encodes information. This information is read using the genetic code, which specifies the sequence of the amino acids

within proteins. The code is read by copying stretches of DNA into the related nucleic acid RNA, in a process called transcription. Most of these RNA molecules are used to synthesize proteins, but others are used directly in intracellular structures such as ribosomes. DNA is the storage form of genetic material, while RNA is the actual material produced that is sent out to work.

RNA plays several important roles in the processes that translate genetic information from DNA into protein products. RNA acts as a messenger between DNA and the protein synthesis complexes known as ribosomes, forms vital portions of ribosomes, and acts as an essential carrier molecule for amino acids to be used in protein synthesis.

RNA is very similar to DNA, but differs in a few important structural details: RNA nucleotides contain ribose sugars while DNA contains deoxyribose and RNA uses predominantly uracil instead of thymine present in DNA. RNA is transcribed from DNA by enzymes called RNA polymerases and further processed by other enzymes. RNA serves as the template for translation of genes into proteins, transferring amino acids to the ribosome to form proteins, and also translating the transcript into proteins.

In only a little over a half century our knowledge of genetics has exploded. The knowledge of chromosomes and their specific genes and their function has been elucidated as well as the processes surrounding gene replication and expression. Most exciting is the actual elucidation of the specific complete genetic code of the human person.

Characterizing the complete genetic code has been the task of the human genome project. The human genome project (HGP) began in 1990 after exploratory work in the 1980's. The goal was to understand the genetic makeup of the human species by identifying all the genes in the human genome and mapping how individual genes are sequenced. In May 2006, the final chromosome sequence was published in the journal, *Nature.* The goals of the original HGP were not only to determine more than 3 billion base pairs in the human genome with a minimal error rate, but also to identify all the genes in this vast amount of data. This part of the project is still ongoing, although a preliminary count indicates about 30,000 genes in the human genome, which is fewer than earlier predictions by many scientists. It is hoped that this complete genetic map will provide new avenues for medicine and biotechnology.

So let's go back to the beginning, to conception. The comedian, Jeff Foxworthy, was asked after the birth of his first child if he had any pictures of the child's delivery. He replied, "delivery, ugh, no thanks, but I have some great shots of the conception." So I brought a DVD to show with some images of conception, but alas the decision not to purchase a computer projector and concern for my day job prevent me from showing them.

But yes, life begins with conception; we'll just have to quiet our imaginations and memories in order to focus on the science involved, rather than the intimate activity that brings an egg in contact with a spermatozoon. The human organism develops from the point of fertilization of the female egg by a spermatozoon. The fertilized ovum then begins a process of cell cleavage. When the cell cleavage has resulted in 50-150 cells at about day 4 or 5, the embryo is known as a blastocyst. The embryo at this stage travels down the fallopian tube and implants in the uterine lining. The cells in the blastocyst are all pluripotent. That is they are primitive and as yet undifferentiated. With further division and development, they are capable of developing into any of the specialized cells in our body. These cells are known as embryonic stem cells. With further divisions the process of organogenesis begins and the cells differentiate from stem cells to one of three germ layers. With further division, growth, and development these cells become transformed into one of 200 dedicated specialized cells in the body.

Much research centers on the biology of embryonic stem cells. Working with embryonic stem cell lines has revealed a great deal about the processes by which stem cells undergo transformation into specific cell lines. If a specific cell line is diseased or not functioning properly, the idea of introducing stem cells that can encode for normal cell function in the specific body area has led to excitement in scientific circles. In the future, medical researchers anticipate being able to use technologies derived from stem cell research to treat a wider variety of diseases including cancer, Parkinson's disease, spinal cord injuries, and muscle damage, amongst a number of other impairments and conditions. However, there still exists a great deal of social and scientific uncertainty surrounding stem cell research.

Much of this uncertainty is the byproduct of stem cell research having been caught up in a national debate about the moral implications of the sources of stem cell lines. Stem cell research has become a cause that has both religious and political connections. Further

exploration of stem cell research might take us in the words of a previous Athenaeum president who shall remain unnamed but whose initials are G.B., "dangerously close to the two forbidden topics of politics and religion." Not knowing exactly what happens to speakers who "come too close" we will stop at this point and leave to other distinguished groups the task of further informing public discourse on stem cell research.

At the same time that work was being done on stem cells and mapping gene sequences, ideas and experiments have been developed that look at intervention. With knowledge about specific genetic conditions work has been undertaken to address how these abnormalities or variations might be "corrected." How might genes be altered, replaced or their expression modified? Treatments that seek to alter a gene are known as gene therapy. Gene therapy is the insertion of genes into a person's cells and tissues to treat a hereditary disease in which a defective mutant allele is replaced with a functional one.

Scientists took the logical step of trying to introduce genes straight into human cells, focusing on diseases caused by single-gene defects, such as cystic fibrosis, hemophilia, muscular dystrophy, and sickle cell anemia. However, this has been much harder than modifying simple bacteria, primarily because of the problems involved in carrying large sections of DNA and delivering it to the correct site on the comparatively large human genome.

In most gene therapy studies, a "normal" gene is inserted into the genome to replace an "abnormal," disease-causing gene. A carrier called a vector must be used to deliver the therapeutic gene to the patient's target cells. Currently, the most common type of vector are viruses that have been genetically altered to carry normal human DNA. Viruses have evolved a way of encapsulating and delivering their genes to human cells in a pathogenic manner. Scientists have tried to harness this ability by manipulating the viral genome to remove disease-causing genes and insert therapeutic ones.

Target cells such as the patient's liver or lung cells are infected with the vector. The vector then unloads its genetic material containing the therapeutic human gene into the target cell. This therapeutic normal genetic material can now generate a functional protein product thus restoring the target cell to a normal state. That is the theory at least and a great deal of research is underway in this area. This work is still in its infancy.

(Study in 2007 of gene therapy for retinal blindness. In early 2007, Moorfields Eye Hospital and University college London's Institute of Opthalmology announced the world's first gene therapy trial for inherited retinal disease. The first operation was carried out on a 23 year-old man, in early 2007, but it is currently too early for results.)

While work on gene therapies continues, basic science research into the mechanisms surrounding DNA and RNA encoding and gene expression has led to other discoveries. Perhaps no discovery has matched the excitement generated by the work in the field of RNA interference. This is designated by RNAi.

RNAi is an RNA-dependent gene silencing process that is mediated by the RNA-induced silencing complex (RISC) and is initiated by short double-stranded RNA (dsRNA) molecules in the cytoplasm, where they interact with the catalytic RISC component argonaute. Two pathways for exogenous and endogenous dsRNA converge at the RISC complex, which mediates gene silencing effects.

In a 1998 paper in *Nature,* Andrew Fire and Craig Mello reported a potent gene silencing effect after injecting double stranded RNA into the nematode worm, C. elegans. In investigating the regulation of muscle protein production, they observed that neither mRNA nor antisense RNA injections had an effect on protein production, but double-stranded RNA successfully silenced the targeted gene. As a result of this work, they coined the term RNAi. Fire and Mello's discovery was particularly notable because it represented the first identification of the causative agent of a previously inexplicable phenomenon. Fire and Mello were awarded the Nobel Prize in Medicine or Physiology in 2006 for their work. Fire and Mello have demonstrated that RNAi is a way to shut down defective genes. It is also an active mechanism to regulate genes. RNAi has been shown to be important in the immune response to viruses and other foreign genetic material. Components of the RNA interference pathway are also used in the organization and structure of genomes. RNA interference components are also very important in the regulation of prenatal development. Thus RNAi holds a great deal of promise therapeutically as yet another way to influence gene expression. RNAi are very short molecules and thus are more easily manipulated. It is hoped that this will allow for the rapid development of RNAi based treatments.

So here we have in a period of only a decade knowledge from basic science research that is now being looked at for use in many possible clinical disease situations. In the future the impact of RNA interference may allow us to treat many diseases outside the realm of present genetic intervention strategies. It may be possible to identify specific RNAi which can impact specific areas in the genetic structure and influence the development of disease.

Although it is difficult to introduce long dsRNA strands into mammalian cells due to the interferon response, the use of short interfering RNA (siRNA) mimics has been more successful. The nematode C. elegans was the first organism in which the down regulating of gene expression was demonstrated in 1993. RNAi has also been shown effective in the reversal of induced liver failure in mouse models. In humans, the first applications to reach clinical trials were in the treatment of macular degeneration and respiratory syncytial virus.

Other proposed clinical uses center on antiviral therapies, including the inhibition of viral gene expression in cancerous cells, knockdown of host receptors and co-receptors for HIV, the silencing of hepatitis A and hepatitis B genes, silencing of influenza gene expression, and inhibition of measles viral replication. Potential treatments for neurodegenerative diseases have also been proposed, with particular attention being paid to the polyglutamine diseases such as Huntington's disease. RNA interference is also often seen as a promising way to treat cancer by silencing genes differentially up-regulated in tumor cells or genes involved in cell division. A key area of research in the use of RNAi for clinical applications is the development of a safe delivery method, which to date has involved mainly viral vector systems similar to those suggested for gene therapy.

I think you get the idea that the future is bright in the field of human genetics. As science understands the processes regulating gene expression, new avenues of possible treatment emerge. Clinical trials are underway in several disease conditions utilizing RNA interference strategies.

Perhaps in the future the expression of diseases of the HLA-B27 histocompatibility group may be amenable to RNA interference technology. If this is the case, RNA inhibition might inhibit the area on chromosome six that expresses the histocompatibility antigens. With such material you could limit or halt the development of certain HLA-B27

related conditions, like ankylosing spondylitis. If so, then people may not suffer the disfiguring and limiting deformity of AS.

But what happened to Pistol Pete Maravich (June 22, 1947-January 5, 1988)? Seven years after his retirement from the NBA, in May 1987, he was inducted into the Basketball Hall of Fame. Strangely, the next year he would die on a basketball court at an early age. Pete Maravich died at the age of 40. He was warming up to play a basketball game when he collapsed and died. The autopsy showed a congenital defect. He had only one coronary artery supplying blood to his heart muscle rather than the usual two. Pete Maravich did not have a left coronary artery. The left coronary artery is the major or dominant coronary artery for most of us. Pete had only a right coronary artery which was very enlarged supplying blood to the entire heart muscle. While the enlarged artery had supplied his heart muscle for 40 years, it failed on January 5, 1988. So Pistol Pete's genetic makeup had a profound influence on his life. The same is true of each of us as well. Pistol Pete had ankylosing spondylitis, a disease that while expressed in him, did not seem to impact his career or his scoring ability. As I have commented perhaps further genetic research may be able one day to impact or limit the expression of AS and other HLA-B27 associated conditions.

But alas his other congenital condition, his single coronary artery is determined very early in fetal development as stem cells become specialized into the cells of the circulatory system and the architecture of the heart is laid down. That process is far from understood and will be a much tougher one to crack.

So will it always be so hard to choose our parents, and the genetic heritage they bequeath us? Yes, it will always be impossible to choose one's parents. But with continued research and advances in medicine it may be possible to alter specific genetic predispositions with gene therapies and thereby improve the quality of life for many people.