

# REVIEW

## Latest advances in antiaging medicine

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**Abstract.** Rapid progress is being made in our ability to modify the aging process. Rather than serving as a period of debility and decreasing health, for many people, the later years of life are becoming a period of continued productivity, independence and good health. Progress is also being made in increasing average lifespan. The leading causes of death (cardiovascular disease, cancer, lung disease, diabetes) are the end result of decades-long processes. With current knowledge, it is possible to delay the onset of these diseases. This can be assisted by lifestyle choices incorporating healthful diet, exercise, stress management, and nutritional supplementation. Emerging genomics technology will allow individuals to establish personalized programs, while early detection of heart disease and cancer will contribute to longevity. Biotechnological therapies involving stem cells, recombinant DNA, proteomics, therapeutic cloning and gene-based therapies are expected to play major roles in promoting successful aging. We are at the threshold of artificial intelligence (AI) and nanotechnology (NT). AI will allow for a merging of our biological thinking with advanced forms of non-biological intelligence to vastly expand our ability to think, create and experience. NT will ultimately allow us to build devices able to build molecules much like our current cellular machinery does, one atom at a time. It is the goal of today's antiaging medicine to forestall disease and aging long enough for people to utilize the powerful biotechnology and nanotechnology therapies that will be developed over the decades ahead. These future therapies have the potential to greatly extend longevity. (Keio J Med 54 (2): 85–94, June 2005)

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People are very interested in learning what they can do to live longer as well as to remain healthy during their later years. Numerous books have written about this topic, and, in fact, I have contributed to the growing number of titles by writing two books specifically addressing this topic, *The Baby Boomers' Guide to Living Forever* (Hubristic Press, 2000) and *Fantastic Voyage: Live Long Enough to Live Forever* (Rodale Press, October 2004), which I coauthored with Ray Kurzweil.

### Changing Views of Aging

Views about aging are changing rapidly. The old view of aging was that much of one's latter years were basically spent in a state of disability. Conventional wisdom was that seniors of advanced age (the "oldest of the old") would spend their final years unable to

contribute to society, with several of these years often requiring skilled care such as a nursing home. The new view of aging is that people will remain physically and mentally healthy until very old age. This is what people today are looking for in their later years: to remain vibrant and in very good health, as contributing members of society. This paradigm shift is possible for many people today with present-day strategies, so this is a realistic goal for many people.

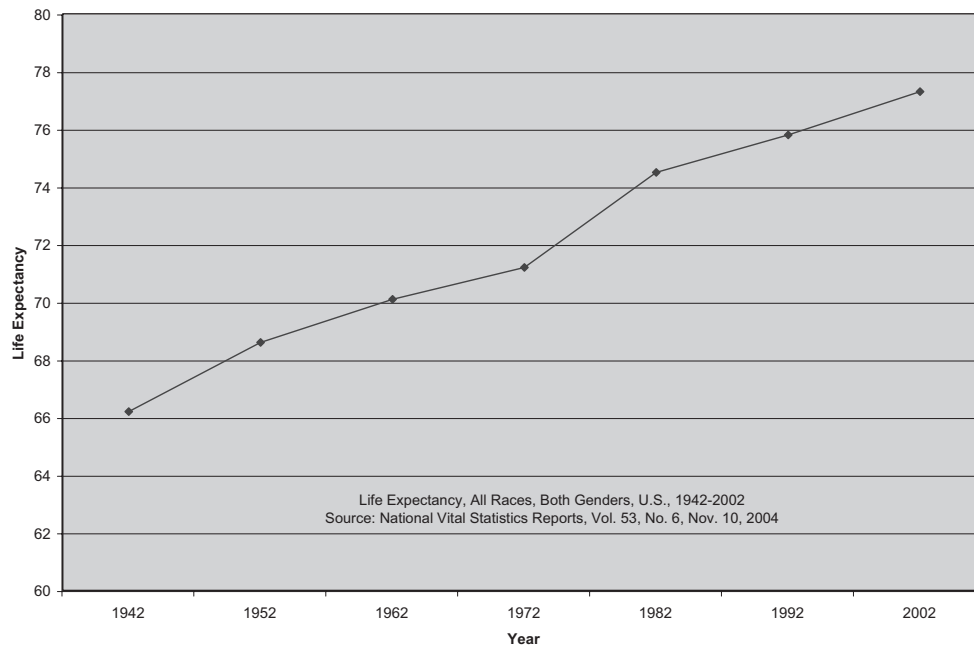
We have the technology and medical knowledge to enable a significant portion of the population to live to more than 100 years of age already. Several factors are intersecting to create a scenario where this will become increasingly common in the years ahead.

It is even possible that within the next few decades, life spans of 100 years may appear quite short. Today, human life expectancy has been steadily increasing by about 2.2 months per year.<sup>1</sup> This progress has been

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**Fig. 1** Life expectancy U.S. 1942–2002.

steady for at least the past 60 years (see Figure 1). Due to the acceleration in the rate of technological change, within 10–15 years, some authors feel that life expectancy will continue to increase and at an increasing rate in the years ahead.<sup>2</sup> Others researchers put the maximum life expectancy for the human population at 85–90 years, although individuals within the population may live longer.<sup>3</sup>

### Evolution Is Not on Our Side

The problem is that, historically, from a biological point of view, evolution was not on our side to live so long. We need to recall that biological evolution took place in an era of scarcity. In primordial times, there were a limited number of calories to go around for our ancient predecessors. Since older individuals in the community were simply competing for the limited food and other resources available, it was not in the best interest for the survival of the tribe or community to allow its elderly to remain alive too long. There was a survival advantage to a community whose members remained alive and healthy (just) long enough to reproduce and raise their children; but then it would be best if “aging genes” were to express themselves and cause adults to age rapidly, essentially to shrivel up and blow away. A community whose individuals didn’t survive much beyond the time their offspring were self-sufficient would possess a natural selection advantage over a community where the members lived into ripe-old age (and decrepitude). In the first community, it is more likely that the younger members would have a

greater chance of surviving because of less competition for scarce calories and these would be genes increasing survival advantage. It is important to realize that our DNA really hasn’t changed very much in the past 100,000 years or so. These “aging genes” remains key letters in the genetic alphabet soup in which we still swim today. But, in modern times, the conditions that selected for these genes in millennia past no longer apply. Today we live in an era of abundance. Granted, many people still live under conditions where there isn’t enough food to go around, and a significant portion of human kind still lives precariously close to starvation, but this reflects political and social issues more than lack of technological capability. If allowed, technology could easily solve the problem of inadequate food for all peoples of the world.<sup>4</sup> So, technology has allowed us to override this remnant of our biological heritage, and, there is no longer a survival advantage to short-lived humans.

### The Grandmother Hypothesis

Keeping the elderly around longer is also good for business: the business of the human race. Seniors represent a repository of wisdom. It is a shame and tragedy for people to die at just the time they are at the apogee of their accumulated knowledge. It seems ironic to allow people to accumulate knowledge over the course of a lifetime and then cut them down at their pinnacle and allow this wisdom be lost to the cemetery plot or “go up in smoke” on the funeral pyre. It is in the best interest of a modern, technological society to keep the elderly alive and vibrant and to make use of their vast collec-

tive knowledge base. This is the so-called “grandmother hypothesis” in which “older individuals specifically retain the ability to preserve their knowledge base that allows them to focus on transmitting to children knowledge accumulated over generations.”<sup>5</sup> This is modern evolution at its finest, and by utilizing the intellectual resources of our seniors more effectively, we will be able to evolve even more quickly. But we must keep our bodies (and minds) in our senior years in good condition to accomplish this.

In most cases, people can achieve this goal of remaining healthy until very late in life. The knowledge to do so exists today. Chronic disease does not happen overnight. While the overt clinical manifestation of a disease may appear suddenly, most of the disease processes that constitute the leading causes of death, such as cancer, heart disease, kidney failure, etc. are almost always decades in the making. We now have the ability to assess where we are personally in the progression of these processes and, with this knowledge, take sensible and effective and preventive action to halt and reverse the lethal march towards disease, disability and death. Effective testing is the key; uncovering incubating disease processes and curing them before symptoms appear and it is too late.

The leading cause of death in the United States is coronary heart disease. Yet, 50 per cent of men and 64 per cent of women discover they have heart disease by suffering a fatal heart attack. This means that half of men and almost two-thirds of women with heart disease receive no warning symptoms such as chest pain people before succumbing to a fatal myocardial infarction.<sup>6</sup> By aggressively utilizing non-invasive diagnostic testing available today, many people could take effective, preventive action before suffering a myocardial infarction.

The second leading cause of death is cancer, but, all too often, cancer is not detected until after it has metastasized and then is very difficult to treat. The same applies to strokes, the third leading cause of death. Strokes typically come on without warning, all too often resulting in permanent damage.

But, it does not need to be this way. By aggressively applying the medical knowledge we have today, people can assess where they are in the progression of disease and take effective action to halt and reverse the disease process before irreversible damage occurs.

### **The Aging Process: No One’s Friend**

We need to begin by taking aging for what it is. Aging is no one’s friend. Aging is our enemy. A fundamental principle of antiaging medicine is, in fact, that aging can be regarded as a disease, an enemy. And, as with any enemy, we must fight it with all the tools and weapons at our disposal: with multiple independent

methodologies. We don’t go to war with one soldier or one weapon. If we want to win, we attack our enemy with everything we have. Since aging is our enemy, we should use everything we have to fight it.

But, on the road to longevity, we have other enemies as well. We need to acknowledge that we are our own worst enemies. We sabotage our health by making poor lifestyle choices. We know we shouldn’t eat doughnuts or potato chips, but we do. We know we should exercise regularly and control the stress in our lives, but we don’t. We ignore our genetics. We know that lung cancer runs in our family, but we smoke anyway. We know alcohol-related liver disease and cirrhosis runs in our family, but we still drink alcohol.

In addition, the disease processes themselves are our enemy. Cardiovascular disease, cancer, pneumonia, and Alzheimer’s disease are nobody’s friend. In addition, there is a vocal body of opposition to longevity research. For instance, some researchers feel any efforts to extend human longevity beyond its current 80 or so years are actually immoral.<sup>7</sup> This was epitomized by an enormously insensitive statement made by former governor of Colorado, Richard Lamm, who stated in 1984 that the elderly “have a duty to die.”<sup>8</sup> Some two decades later, Mr. Lamm is now approaching his 70<sup>th</sup> birthday. One wonders if he still feels the same way (and if he thinks it applies to him).

### **The Three Bridges to Longevity**

One way to look at our path to longevity is to regard it as a journey over three sequential bridges. Bridge One is based on therapies that exist today. Bridge One therapies consist of the best of present-day medicine, including biotechnology breakthroughs that are occurring every day. Bridge One will take us to Bridge Two, which consists of the full blossoming of the biotechnology revolution. Then Bridge Two will take us to Bridge Three, the nanotechnology/artificial intelligence revolution, which will lead to life spans that are currently incomprehensible, but which will soon be commonplace, measuring in the hundreds of years.

There are several Bridge One technologies that people can do themselves without the aid of medical professionals. These include things like proper diet, caloric restriction, adequate exercise, stress management, aggressive nutritional supplementation, detoxification and proper care of your brain.

There are also things that can be done with the help of medical professionals. For example, you can have your genomics tested; you can have tests done to determine specifics of your metabolism such as methylation, inflammation and glycation defects. You can undergo testing to detect heart disease early and then take measures before it has a chance to strike. You

can detect and prevent cancer before it has a chance to spread. You can avail yourself of bio identical hormone replacement therapies.

### **Bridge One – What People Can Do Themselves**

#### *Diet*

There are 4 sources of calories: carbohydrates, proteins, fats and alcohol. People can make good and bad choices for each of these types of calories. Carbohydrates, for example, are not inherently bad; rather there are good and bad carbohydrates. Similarly, proteins, fats and alcohol are not inherently bad, but there are good and bad choices within each of these categories.

Whole grains like brown rice, legumes such as lentils and beans, and above-ground green vegetables are examples of good carbohydrates. They have a low glycemic index, meaning they do not turn into sugar quickly in the body. There are “bad” carbohydrates, however. Bad carbohydrates are ones which tend to turn into sugar quickly, causing excessive weight. Refined sugar, refined flour products, breads, root vegetables that grow underground, such as potatoes and beets, have a high glycemic index and are not optimal sources of energy.<sup>9</sup> Consumption of these should be limited.

Proteins are available in good and bad varieties. Fish and seafood, vegetable-based protein sources such as tofu and other soy products are good proteins. Less beneficial proteins are fatty red meats, which are high in saturated fat, and egg yoke, high in inflammatory arachidonic acid.

There are good and bad fats. Fish and fish oils are good as are avocado and olive oils; raw, unsalted nuts and seeds contain beneficial fats. Bad fats include deep-fried foods, processed vegetable oils like corn oil, and “trans” fats such as are found in margarine.<sup>10,11</sup>

People are often surprised to learn that alcohol is also available in good and bad varieties. Red wine has benefit, as it is rich in phytonutrients such as resveratrol, an anticancer agent.<sup>12–14</sup> Beer is an example of a somewhat bad alcohol, since beer is rich in amylose, which has a high glycemic index. Although this is the conventional wisdom, this is controversial.<sup>15</sup>

#### *Caloric restriction*

Caloric restriction has been proven to extend lifespan of laboratory animals.<sup>16,17</sup> Lifespan is how long the longest living individual in a species can live. Currently, the maximum human lifespan seems to be about 120 years. No human being has ever been scientifically documented as living more than 124 years. But, like Olympic records, we expect this soon to be broken and rebroken again and again as Bridge Two and Three therapies come into their own.

For now, however, caloric restriction is the only thing proven to help lifespan. For example, fruit flies have a lifespan measured in days or weeks; laboratory rodents have a lifespan of two or three years. In animal experiments involving caloric restriction, researchers were able to extend the healthy lifespan of laboratory animals and insects drastically. Increases in lifespan of 50–100 percent or more were seen. We know that consuming excess calories reduce life expectancy; conversely, restricting calories can extend lifespan, at least in laboratory animals.<sup>18</sup>

In yeast experiments done by David Sinclair, caloric restriction was shown to activate the SIRT1 gene that expresses SirT1 deacetylase that stabilizes DNA, extending lifespan. The authors postulate that caloric restriction “could extend life-span by inducing SIRT1 expression and promoting the long-term survival of irreplaceable cells”.<sup>19</sup> Polyphenols are a dietary substance that also activates this gene and may extend lifespan by 70 percent in yeast. A potent polyphenol known as resveratrol is found in red wine.

Rodent experiments have been done by Richard Weindrach at the University of Wisconsin, and he has done gene profiling to find out which genes are turned on and which genes are turned off during the aging process. It seems only a handful of genes are involved. By caloric restriction, he was able to show 30–50% increase in lifespan in rodents, fish, spiders and other animals. We know that in youth certain genes are active and certain genes are not, and in aging, these often change. We know that caloric restriction can move those genetic switches in older animals to more closely resemble the gene expression of a younger animal.<sup>20</sup>

For humans we have the results of real life experiments, not laboratory data. For example, on the Japanese island of Okinawa, a common phrase is “hara hachi bu,” which means “belly 80 percent full.” This concept means you should try to eat approximately 80 percent of what you would need to feel full. You try to leave the table a little hungry. The caloric intake of the average adult Okinawan is 1800 calories per day compared to Americans who eat 2500 calories or more each day. This seems clearly related to their lifestyle choices and not genetics, because as Okinawans move away from their homes on Okinawa and adopt different lifestyles, they live shorter lifespans like their neighbors. So there is nothing genetic about their long lifespans. They live longer because of their lifestyle choices, particularly caloric restriction.<sup>21,22</sup>

#### *Other lifestyle choices*

Japan is a land of other healthy lifestyle choices – at least as far as diet is concerned. Even though many Japanese smoke and live high stress lifestyles, the

number of Japanese over 100 years of age has doubled in the past five years. This is a new phenomenon felt to be due to improved health-care coupled with their underlying healthy diet. In 1998 there were 10,000 Japanese over 100 years of age. In 2003, five years later, the number had doubled over 20,000. Women, by the way, constitute 85 percent of this centenarian population in Japan.

It is interesting to compare this to the United States, a land characterized by bad lifestyle choices, certainly as regards diet. A leading cause of death in the United States is, in fact, poor lifestyle choices. Half of the deaths in the U.S. are the result of easily modifiable lifestyle choices. The number one cause of death in the U.S. is tobacco, which causes 18.1 percent of deaths. The second is bad diet and lack of exercise, which causes 16.6 percent of deaths.<sup>23</sup>

Another healthy lifestyle choice that people can make is regular aerobic exercise. Proper aerobic exercise consists of getting your heart rate up to 60–80 percent of your maximum predicted heart rate (which is equal to 220 less your age) and keeping it there for a sustained period of time. Some type of aerobic exercise should be done continuously for 30 minutes at least every other day. In addition to aerobic exercise, weight training and stretching are valuable.

In addition we can take nutritional supplements. Modern farming methods unfortunately have led to significant decreases in the vitamin and mineral content of our food.<sup>24</sup> Also, almost no one eats enough fruits and vegetables to get adequate nutrition without taking supplementation. Chemical reactions in the body occur because of enzymes and many enzymes in the body need vitamins and minerals as cofactors in order to function properly. By taking nutritional supplements, you can ensure that the raw minerals are always available to ensure that your youth-sustaining enzymes function optimally at all times. By taking supplements we can help neutralize the now outdated genetic time bombs programmed within our genes designed to take us out of competition for scarce calories as we age. We can help accomplish some of the same goals by caloric restriction, namely turning genes of youth on and genes of aging off at least for a while.<sup>25</sup> In effect, by aggressive supplementation and other lifestyle choices we're trying to "reprogram our biochemistry."

### **Bridge One – What People Can Do With Physician Assistance**

#### *Genomics testing*

One thing doctors can do is to help people test their genes. Genomics testing tells you what genes you have. The Human Genome Project was recently completed

and all 35,000 human genes have been identified. But, the key to genomics is the realization that genes just represent *tendencies* in most cases. Most people do not have a "breast cancer gene" or an "Alzheimer's gene." You may have a gene that increases your *risk* of breast cancer or Alzheimer's disease, particularly if you make the wrong lifestyle choices. But you can often change this outcome by making *proper* lifestyle choices. But you won't know what specific lifestyle choices to make unless you know what specific genes you have, and this is where genomics can provide critical information.

Here are some practical examples of what genomics testing can tell you. The cytochrome P 450 (CYP 450) genes code for proteins that help the body detoxify toxins in the liver. One cytochrome P 450 gene is known as C17. Women who have a mutated C17 gene can have an increased risk of breast cancer or osteoporosis.<sup>26,27</sup> If a woman performs genomics testing and finds she has mutated C17, she should avoid taking estrogen, since she would be at higher risk of developing breast cancer by doing so. Another CYP 450 gene is 1A1. Some mutations of this gene may render people much more susceptible to lung cancer. Individuals who have mutated CYP 1A1 should be especially careful not to smoke because they are at much higher risk of developing lung cancer. A mutated CYP 450 2E1 gene increases susceptibility to alcohol-related liver disease and cirrhosis.<sup>28</sup> People with this mutation should be very careful with regard to alcohol consumption. So these are examples of how genomics testing can help you make specific lifestyle choices.

#### *Early detection of cardiovascular disease and cancer*

Cardiovascular disease is the leading cause of death in many developed countries. Medical professionals can help their patients avoid heart disease with early detection. The usual blood tests that are used to determine risk of heart disease (cholesterol subfractions, triglycerides, etc.) are not adequate. Highly sensitive-CRP, homocysteine and lipoprotein (a) levels need to be checked as well. In addition, the "acceptable limits" given by many reference laboratories are also often inappropriate. As one example, the reference laboratory I use in my medical practice considers levels of homocysteine less than 15 as acceptable; yet risk of heart disease increases with levels greater than 7.0. Cholesterol levels under 200 are considered acceptable, but levels between 130–160 may be optimal. Specific cardiovascular-related genomics tests are available as well and can provide useful patient-specific information.

Recently, non-invasive test for delineation of atherosclerosis have become available. Ultrafast CT scans can quantitate the amount of calcified plaque in the coronary arteries. Virtual angiograms and MRIs are

becoming available in several metropolitan areas, obviating the need for invasive angiography.

Cancer is the second leading cause of death. Medical professionals can help with early detection and prevention of cancer. They can also suggest supplements like vitamin C, selenium, curcumin, fish oil, and folic acid. A diet rich in soy products and green tea is cancer-protective as well. It is important to make lifestyle choices including regular aerobic exercise and strict avoidance of smoking and exposure to passive cigarette smoke as well. These are proven methods of reducing cancer risk. Physicians can help detect cancer in the very earliest stages even before a detectable lesion is present by utilizing the DR-70 test which is undergoing FDA testing as a possible screening test for colorectal cancer.<sup>29</sup> This blood test only requires a few cancer cells to be present in the body for detection. This can help detect cancer in a very early stage before it has had a chance to metastasize.

#### *Hormone replacement*

High hormone levels are a hallmark of youth, while declining hormone levels are characteristic of advancing age. At around 30 years of age an individual's hormones begin to decrease, which then begins to accelerate the aging process. By restoring hormone levels to more youthful levels, people can often experience the benefits of higher hormone levels similar to what they had when they were younger. Antiaging hormones include estrogen, progesterone, testosterone, thyroid, melatonin and human growth hormone (hGH). The cornerstone of hormone replacement therapy, however, is to only replace hormones whose levels are low and for which there is a demonstrable deficiency. The indiscriminate prescribing of anabolic steroid hormones, such as human growth hormone for bodybuilders who merely wish to enhance the appearance of their physique, yet have adequate levels of hGH, is an inappropriate use of hormone replacement therapy and is not recommended.

Optimally one should use bio identical hormones, hormones which are chemically identical in their structure to those found naturally in the human body. For example when prescribing estrogen replacement for women, we want to use estradiol, estrone and estradiol, which are the same estrogens found naturally in the body. Similarly, we prefer to use bio identical progesterone, not a progestin like medroxyprogesterone (which is not progesterone at all, but a synthetic drug, which possesses progesterone-like activity). We use testosterone itself (not medroxytestosterone), which can improve muscle mass and sex drive in both men and women. Melatonin is useful in promoting deep sleep and also fights some cancers<sup>30</sup> and, in certain cases of

documented growth hormone deficiency, we have found the use of human growth injections of value.

### **Bridge Two (The Biotechnology Revolution)**

Bridge Two consists largely of the biotechnology revolution, which has already begun and which will find its full expression over the course of the next 15 years. Among the most important items of Bridge Two will include stem cell therapy, therapeutic cloning, recombinant gene technology or "pharming" (genetically modifying bacteria, plants and farm animals to produce desired proteins) and developing a deeper understanding of the human genome with the ultimate goal of creating designer proteins ("proteomics"). All of these therapies are very exciting and will change medicine as we know it, so that is completely unrecognizable from the medicine of today. By optimizing care of our present biological bodies and eliminating the expression of undesirable genes, the life expectancy for most people should easily exceed 100 years.<sup>31</sup>

#### *Stem cell therapies*

Stem cells occur naturally in the human body and have the ability to differentiate themselves into many different cell types; for example, a stem cell found in a hair follicle can be coaxed to turn into a heart muscle cell or a nerve cell depending on the chemical environment in which it finds itself. Recently, there has been considerable political and ethical debate about the use of a specific type of stem cell that is found early in fetal development – the embryonic stem cell. Embryonic stem cells are characterized by an extreme degree of "plasticity," namely, the ability to change or differentiate into any type of tissue. Since the production of embryonic stem cells involves the destruction of human embryos, this has created a moral dilemma for many political and religious leaders, particularly in the United States.

Fetal stem cells are found in two main varieties: totipotent and pluripotent stem cells. Totipotent stem cells are found in the embryo immediately after fertilization. Because some people feel that as soon as the embryo starts to divide it constitutes a human being, it is sacrosanct and must not be destroyed. A little further along the line of cell division come the pluripotent stem cells. These cells are not as plastic as the totipotent stem cells and cannot form every cell type, at least not with today's technologies, so they are not as valuable to scientists as the embryonic stem cells. However, even the totipotent stem cells can be encouraged to differentiate into many different cell types under the influence of specific growth factors. In the near future, it is not unrealistic to envision a scenario in which a patient

suffers, say, a myocardial infarction and receives a transplant of cloned heart muscle cells generated from his own stem cells to replace the region of infarcted myocardium. Patients with spinal cord injuries or a history of cerebrovascular accident may soon be able to receive stem cell implants to regenerate damaged tissues and restore function.

A small number of stem cells persist into adult life. Most adult tissues have a few stem cells, but they are rare. Their function remains incompletely understood, but we may soon be able to transform these adult stem cells into any cell type in the body. As we perfect this technology the debate over embryonic stem cells will end, and we will be able to harness the full potential of this therapy. A group in South Korea recently was able to create a pure clone of embryonic stem cells, obviating the need for actual embryos. Woo Suk Hwang and Shin Yong Moon of Seoul National University have successfully cloned a line of human pluripotent stem cells. This research paves the way for production of human-replacement tissues and organs from a cloned stem cell line.<sup>32</sup>

### *Pharming*

Another very powerful technique is known as “pharming.” It involves recombinant technology. This refers to modifying or inserting desired genes into animals, plants and bacteria. Then these so-called “pharm” animals or plants create the desired proteins. An interesting variant of this therapy involves genetically modifying bananas or tomatoes to create a vaccine against hepatitis B. In order to get vaccinated, the patient would simply eat the banana or tomato. It is estimated that these plant derived vaccines could be produced for less than 2 cents per dose, a 99 per cent saving from conventional vaccines. So, in effect, there would be bananas and tomatoes growing in the field producing hepatitis vaccine. When we give patients human insulin, it is a bioengineered product that is made by recombinant bacteria; similarly, human growth hormone for injection is fabricated in the laboratory by recombinant bacteria. There now exist “pharms” comprised entirely of different “pharm” animals, in which the milk of the goats is used to create silk threads stronger than those created by spiders,<sup>33</sup> and, in the fields are grown plants that are particularly high in protein such as tobacco and corn, which have had their genetic structure modified to create other desirable proteins.

### *Proteomics*

Proteomics, in many ways, is an even more exciting field of development. Proteomics involves systemati-

cally creating desired proteins in the laboratory de novo. This may be the most important medical technological development to occur within the next two decades. In a typical scenario, doctors will determine what protein a patient needs to recover from a given illness and then the proteomics engineers in the laboratory will fabricate the needed protein molecules. The full expression of this therapy still lies 10–15 years away, but when this therapy is mature, it will offer incredibly powerful therapies. Proteomics will also be utilized for diagnostic tests, and medical diagnoses will be able to be made much more quickly.

A major problem with proteomics relates to the three-dimensional configuration of proteins. While the chemical structure of a protein molecule can be written as a linear chain of amino acids, determining in advance the sequence of amino acids that will be needed to create a desired three-dimensional protein molecule with folding and cross-linking of the amino acids is an incredibly difficult task. Determining what chain of amino acids is required to create a desired three-dimensional structure remains a problem that exceeds the computational capacities of even the world’s fastest computers. There are some new supercomputers designed to work on the protein folding problem. IBM has just introduced the Blue Gene/L, a supercomputer that operates at a speed out of 360 trillion operations per second and one of its main goals is solving the protein folding problem. It is anticipated within the next 10 years some early proteomics therapies will be available and significantly affect our abilities to diagnose and treat many diseases.

### *Cloning*

There are two types of cloning: reproductive cloning and therapeutic cloning. In reproductive cloning, you recreate an entirely genetically identical organism. Reproductive cloning has already been used in animals, but due to the thorny moral issues involved, has not been used in humans. “Dolly the sheep” was the first cloned animal, and there have been many additional animal species that had been cloned. Genetics Savings & Clone, Inc., for example, is a private company that is in business of cloning beloved pets for their owners.

This is to be differentiated from therapeutic cloning in which you create individual tissues, not entire organisms. Therapeutic cloning uses germ cell lines before they are implanted and causes them to differentiate and develop into specific tissues or organs. Currently, researchers are growing simpler organs such as corneas and urinary bladders, and soon should be able to grow skin, blood vessels and other complex tissues and organs by cloning them from germ cells.

### *Gene therapies*

Gene therapies are also very powerful aspects of the Bridge Two biochemical revolution. Some of the current therapies available include RNA interference (RNAi), and antisense RNA, which are available now, but are in a very primitive stage of development. RNA interference therapy involves taking short double-stranded segments of RNA and inserting them into the cytoplasm of the cell. These match and lock onto portions of the native messenger RNA (mRNA) that is transcribed from mutated genes. This causes the native RNA segment to be cut apart and destroyed, silencing expression of the undesirable gene. Antisense RNA also blocks the mRNA created by the defective genes so they are unable to make undesired proteins. Antisense therapy uses mirror-image sequences of RNA (antisense RNA), which stick to the abnormal protein-encoding RNA, preventing it from being expressed.<sup>34</sup>

It is hoped that these therapies which affect gene expression indirectly, by interfering with the mRNA coded for by the defective genes, will eventually lead to “somatic gene therapy,” which is the holy grail of gene therapy. In somatic gene therapy the goal is to insert a desired gene directly into the patient’s genome and delete or turn off undesired or defective genes. Somatic gene therapy is most important gene therapy of all, but is probably 25 years away. But when this therapy is mature, it will be possible take any type of adult or somatic cell in the body and turn it into any other cell type because all somatic cells contain all the genes needed to create every cell type. We will, for example, be able to turn hair follicle or fat cells into heart muscle cells simply by manipulating their genes.

Gains are already being made in this arena by using adult stem cells. Adult liver stem cells have been transformed into pancreatic cells<sup>35</sup> and adult muscle stem cells have been transformed into heart muscle cells, neural tissue, and blood vessels.<sup>36</sup>

Yet, as exciting as these Bridge Two therapies will be, they will pale in comparison to the Bridge Three therapies to which they will lead, the full flowering of which will occur 25 to 30 years from now.

### **Bridge Three (The Nanotechnology/AI Revolution)**

The hallmarks of Bridge Three include development of artificial intelligence (AI) and molecular nanotechnology (MNT). Artificial Intelligence refers to nonbiological (computer) intelligence, while nanotechnology is a term coined by Dr. K. Eric Drexler at MIT in 1978 and which he elaborated in his seminal book, “Engines of Creation.”<sup>37</sup> MNT refers to machines that operate on the scale of nanometers ( $10^{-9}$  m) and which will be able to create molecules one atom at a

time much like our cellular machinery does today. As AI and MNT technologies combine with and are incorporated into our biological bodies, serious increases in human lifespan well beyond 120 years will be not only possible, but highly probable.<sup>38</sup>

### *Artificial intelligence*

Artificial Intelligence refers to forms of non-biological intelligence that will soon rival the capacity of the human brain and then rapidly exceed human intelligence by a billion-fold or more within the next few decades. Limited forms of artificial intelligence exist today such as pattern recognition software programs which allow computers to “understand” human language (and which I am using right now to type this article). Other AI programs write poetry and create original works of art. But the type of advanced AI that we will see unfold during Bridge Three will center on the “reverse engineering” of the human brain, a task which experts in the field estimate will be completed within 20 years. Reverse engineering (understand the inner workings) of the brain will not only provide key insights into how the brain performs its many functions, but will lead to a radical increase in human intelligence resulting from the merging of our current biological brain power with nonbiological (computer) intelligence. As we ultimately merge our biological thinking with artificial intelligence, we will vastly expand both the scope and speed of the thinking experience.

This development will provide key insights into how the human brain performs its pattern recognition and cognitive functions. These insights in turn will greatly accelerate the development of artificial intelligence in nonbiological systems such as nanobots, a key to the biological application of nanotechnology. Microscopic, but intelligent nanobots will course through our blood stream, bodily organs, and brain, downloading software either from the Internet or from our own personal “Wi-Fi” network that will enable us to overcome virtually any obstacle to keeping us healthy. This will ultimately lead to dramatic increases in human longevity.

### *Nanotechnology*

Nanotechnology refers to engineering done on the scale of nanometers and will enable scientists to manipulate atoms, moving them from place to place, one at a time. The textbooks for the practical medical application of nanotechnology are already being written, and Robert Freitas, M.D. has already completed 2 of the 4 volumes of his “Nanomedicine” series of books.

According to Dr. Freitas, “The comprehensive knowledge of human molecular structure so painstakingly acquired during the 20th and early 21st centuries



will be used in the 21st century to design medically-active microscopic machines. These machines, rather than being tasked primarily with voyages of pure discovery, will instead most often be sent on missions of cellular inspection, repair, and reconstruction.” He goes on to say “If the idea of placing millions of autonomous nanorobots inside one’s body might seem odd, even alarming, the fact is that the body already teems with a vast number of mobile nanodevices.”<sup>39</sup>

#### *Nanobiotic red blood cells – respirocytes*

Programmable red blood cells are an example of nanotechnological devices on Freitas’ drawing board. Like most of our biological systems, red blood cells perform their function of oxygenating the body very inefficiently. So, Freitas has redesigned them for optimal performance.

With an ounce or two of Freitas’ “respirocytes” (nanobiotic red blood cells) circulating along with your normal blood, you could go hours without oxygen. You would be able to go “scuba diving” without scuba gear. An ounce or two of respirocytes in your blood stream could provide several hours worth of oxygen. An untrained teenager with respirocyte-enhanced blood would be easily able to outrun a highly trained, but unenhanced Olympic athlete. Astronauts could explore other planets without oxygen tanks. In a less frivolous application, in the event of a cardiac arrest, an injection of respirocytes administered by emergency medical personnel would allow the patient’s brain and other vital organs to be perfused with oxygen for several hours while they awaited definitive repair of the underlying process that led to the cardiac arrest. Analyses have shown that these respirocytes could be hundreds or thousands of times more efficient than our own biological blood.

In a television documentary entitled “Beyond Human”, which was originally broadcast nationwide in the U.S. on 15 May 2001, respirocytes were shown being injected into the bloodstream of a smoke inhalation victim who was suffering from carbon monoxide poisoning. The video depicted the respirocytes passing through the arteries on their way to the capillary bed, where they then released their store of oxygen in the patient’s tissues to help keep the victim alive while awaiting definitive care.

#### *Nanobiotic white blood cells – microbivores*

Nanotechnology will also create programmable white blood cells. These nanobiotic white blood cells (“microbivores”) will patrol the bloodstream, seeking out and destroying undesirable bacteria, viruses and other pathogens.

These nanobots will download software from the Internet for particular problems, and could be programmed to recognize and destroy cancer cells before they would have a chance to grow and spread.<sup>40</sup>

Won’t it be nice to have some programmable white blood cells in your blood stream to defend against the possibility of biological warfare attack? It would be a simple matter to realize the organism that had been released and your microbivores would immediately download the appropriate program from the Internet to destroy that pathogen. So programmable microbivores will be the ultimate defense against biological weapons of mass distraction or biological warfare agents, as well as against any influenza pandemic or other potential pathogen.

### **Conclusion**

According to Harvey Mackey, 61 percent of famous people didn’t achieve their most noble achievements until after 60 years of age. So, there is a great deal of advantage to remaining in good health until your later decades of life. In the 19<sup>th</sup> century, Victor Hugo said “Forty is the old age of youth, fifty the youth of old age.” At the beginning of the 21<sup>st</sup> century, we can now safely say that 50 or 60 is only the beginning of the second half of life. On December 31, 2004, there were 41 documented “supercentenarians, individuals over 110 years of age.”<sup>41</sup> By the middle of this century, many longevity researchers believe these numbers will increase dramatically.

We have discussed some of the Bridge One strategies we can use to keep our bodies in good health until the Biotechnology (Bridge Two) and Nanotechnology/AI (Bridge Three) revolutions find full expression. There is no doubt that the 21<sup>st</sup> century will be worth living to experience. By following the Bridge One strategies that exist today, many people alive today will have the opportunity to see it in its entirety.

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