

FANTASTIC VOYAGE

LIVE LONG ENOUGH
TO LIVE FOREVER

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2004



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THE BRIDGES TO COME

"Life expectancy will be in the region of 5,000 years . . . by the year 2100."

—Aubrey de Grey

Biological systems are remarkable in their cleverness. In the 15th century, Leonardo da Vinci wrote, "Human ingenuity may make various inventions, but it will never devise any inventions more beautiful, nor more simple, nor more to the purpose than nature does; because in her inventions nothing is wanting and nothing is superfluous." We share da Vinci's sense of awe at the designs of biology, but we do not agree with him on our inability to improve on nature. Da Vinci was not aware of nanotechnology, and it turns out that nature, for all its apparent creativity, is dramatically suboptimal. For example, the neuronal connections in our brains compute at only 200 transactions per second, which is millions of times slower than today's electronic circuits.

Despite the elegant way our red blood cells carry oxygen in our bloodstream and deliver it to our tissues, it is still a slow and cumbersome system, and robotic replacements (respirocytes) already on the drawing board will be thousands of times more efficient than red blood cells. The reality is that biology will never be able to match what we will be capable of engineering once we fully understand biology's principles of operation.

Another major component of the coming revolution is molecular nanotechnology, which will ultimately enable us to redesign and rebuild, molecule by molecule, our bodies and brains.¹ The timing of these two revolutions—biotechnology and nanotechnology—is overlapping, but the biotechnology revolution is leading the full realization of nanotechnology by a decade or two. That's why we describe these as the second and third bridges, respectively, to radical life extension. Most of the material in this book is Bridge One material—ways to take maximum advantage of the most advanced diagnostic testing and preventive strategies currently available so you can get to Bridges Two and Three.

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A BRIDGE TO A BRIDGE TO A BRIDGE

This book describes three bridges.

1. The First Bridge—**Ray & Terry's Longevity Program**—consists of present-day therapies and guidance that will enable you to remain healthy long enough to take full advantage of the construction of the Second Bridge.
2. The Second Bridge is the **biotechnology revolution**. As we learn the genetic and protein codes of our biology, we are gaining the means of turning off disease and aging while we turn on our full human potential. This Second Bridge, in turn, will lead to the Third Bridge.
3. The Third Bridge is the **nanotechnology-AI (artificial intelligence) revolution**. This revolution will enable us to rebuild our bodies and brains at the molecular level.²

These emerging transformations in technology will usher in powerful new tools to expand your health and human powers. Eventually, the knowledge represented in this book will be automated within you. Today, however, you have to apply that knowledge yourself. We will talk about each of these three bridges as they relate to the topics under discussion. In each chapter, we will begin with Bridge One strategies that you can apply starting today. Where relevant, we will include a tantalizing look at what Bridges Two and Three have to offer in the near future.

BRIDGE TWO:

THE BIOTECHNOLOGY REVOLUTION

As we learn how information is transformed in biological processes, many strategies are emerging for overcoming disease and aging processes. We'll review some of the more promising approaches here, and then discuss further examples in the chapters ahead. One powerful approach is to start with biology's information backbone: the genome. With gene technologies, we're now on the verge of being able to control how genes express themselves. Ultimately, we will actually be able to change the genes themselves.

We are already deploying gene technologies in other species. Using a method called recombinant technology, which is being used commercially to provide many new pharmaceutical drugs, the genes of organisms ranging from bacteria to farmyard animals are being modified to produce the proteins we need to combat human diseases.

Another important line of attack is to regrow our cells, tissues, and even whole organs, and introduce them into our bodies without surgery. One major benefit of this therapeutic cloning technique is that we will be able to create these new tissues and organs from versions of our cells that have also been made younger—the emerging field of rejuvenation medicine.

As we are learning about the information processes underlying biology, we are devising ways of mastering them to overcome disease and aging and extend human potential. Drug discovery was once a matter of finding substances that produced some beneficial effect without excessive side effects. This process was similar to early humans' tool discovery, which was limited to simply finding rocks and natural implements that could be used for helpful purposes. Now that we can design drugs to carry out precise missions at the molecular level, we are in a position to overcome age-old afflictions. The scope and scale of these efforts is vast; the examples in this book are only a small sampling of the most promising ideas. We'll provide additional compelling examples in the chapters ahead.

NOT JUST DESIGNER BABIES, BUT DESIGNER BABY BOOMERS

Gene technologies will comprise three stages: (1) influencing the metabolic expression of genes, (2) blocking or modifying gene expression, and (3) somatic gene therapy. Let's discuss how these imminent technologies might impact your personal voyage into the future.

Influencing the metabolic expression of genes. Science does not yet have the ability to change your genes (although this is starting to work), but by knowing what genes you have, you can make appropriate lifestyle choices and engage in preventive strategies to influence their impact. As we'll discuss in chapter 11, you already have the tools to read a portion of your personal genetic makeup and use this information to guide your lifestyle, nutritional, and supplement choices. You can use this information to design an individualized protocol to avoid diseases and progressive degenerative conditions for which you are genetically predisposed.

Blocking or modifying gene expression. Although we do not yet have the means to alter genes themselves, we are beginning to be able to alter their expression. Gene expression is the process by which your genetic blueprint is read and its instructions are implemented. Every cell in your body has a full set of all your genes. But a specific cell, such as a skin cell or a pancreatic islet cell, gets its characteristics from only a small fraction of all the

genetic material it carries—the portion of genetic information relevant to that particular type of cell.³ Since it is possible to control this process outside the cell nucleus, it's easier to implement these genetic blocking strategies than therapies that require access to the inside of the nucleus.

Gene expression is controlled by *peptides*, molecules made up of sequences of amino acids and short RNA strands. Scientists are just beginning to learn how these processes work.⁴ Many new therapies now in development and testing are based on manipulating this gene expression process to either turn off the expression of disease-causing genes or turn on desirable genes that may otherwise not be expressed in a particular type of cell.

Two evolving therapies for blocking or modifying gene expression are antisense therapy and RNA interference. The target of this therapy is the messenger RNA (mRNA), which is transcribed (copied) from DNA and then translated into proteins. For damaged or mutated genes, researchers are exploring ways to block the mRNA created by these genes so that they are unable to make undesired proteins. The repair process uses mirror-image sequences of RNA, called antisense RNA. These sequences stick to the abnormal protein-encoding RNA, preventing it from being expressed.⁵

In the RNAi (RNA interference) approach, researchers construct short double-stranded RNA segments containing both the “sense” and “antisense” strands. These match and lock on to portions of the RNA that are transcribed from mutated genes. This blocks the native RNA segment's ability to create proteins, effectively silencing the defective gene. In recent tests, using both RNA strands in this way has been dramatically more effective than using just the antisense strand. In many genetic diseases, only one copy of a given gene is defective. Because you get two copies of each gene, one from each parent, this approach leaves one healthy gene to make the necessary protein.⁶

Somatic gene therapy. This is the holy grail of bioengineering. This third stage will effectively change the genes inside the nucleus by “infecting” the nucleus with new DNA, essentially creating new genes.⁷ The concept of changing the genetic makeup of humans is often associated with the idea of “designer babies.” But the real promise of gene therapy is to actually change our *adult* genes.⁸ These new genes can be designed to either block undesirable disease-producing genes or introduce new ones that slow down and reverse aging processes.

Animal studies began in the 1970s and 1980s, and now a range of “transgenic” animals, including cattle, chickens, rabbits, and sea urchins, has been successfully produced. The year 1990 marked the first attempts at human gene

therapy. The challenge remains to transfer therapeutic DNA into target cells so that the DNA will then be expressed in the right amounts and at the right time.

Let's look first at how transfer of new genetic material occurs. A virus is often the vehicle of choice. Long ago, viruses developed the ability to deliver their genetic material to human cells, often resulting in disease. Researchers now simply remove the virus's harmful genes and insert therapeutic genes instead, so the virus then "infects" human cells with these beneficial genes. This approach is relatively straightforward, but viral genes are often too large to pass into many types of cells, such as brain cells. Other limitations of this process include the length of DNA that can be transferred. The precise location where the new viral DNA is integrated into the target cell's DNA sequence has also been difficult to control. In addition, such "infections" can trigger an immune response, resulting in rejection of the new genetic material.⁹

The deaths of two participants in gene therapy trials a few years ago caused a temporary setback, although research has since resumed. One patient died from an immune response to the virus vector. The second patient, suffering from "bubble boy" disease—essentially, he was born without an immune system—developed leukemia, which was triggered by the improper placement of the gene transferred into his cells.¹⁰ This second death points to two major hurdles that must be crossed for gene therapy to succeed: how to properly position the new genetic material on the patient's DNA strands and how to monitor the gene's expression. One possible solution is to deliver an imaging "reporter" gene along with the therapeutic gene. The reporter gene provides image signals that allow the gene therapy to be closely monitored. The process is permitted to proceed only if the placement of the new gene is verified as correct.¹¹

Gene Therapy Starts to Work

A team led by University of Glasgow researcher Dr. Andrew H. Baker has successfully used adenoviruses to bypass the liver and "infect" specific organs or regions within organs. For example, the researchers were able to direct gene therapy at the endothelial cells lining the inside of blood vessels. Baker said that his work could "improve the selectivity, efficiency, and safety of gene delivery to the cardiovascular system."

Another approach is being pioneered by a research team led by Craig Venter, the head of the private effort that successfully transcribed the human genome, which has already demonstrated the ability to create synthetic viruses from genetic information.¹² A primary application is designing viruses to deliver new genetic information for gene therapy.

Physical injections of inhibitory experimental means of transfer, some, can be used. This opens the door to epilepsy.¹³ Electrophoretic including drug delivery. One option is immunomodulation. Impact.¹⁵ Cystic fibrosis. Recombinant gene packaged. Yet another. Ultrasonic waves through cell membranes.

RECOMBINANT BETTING

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Physical injection (microinjection) of DNA into cells is possible but prohibitively expensive. Exciting advances have recently been made in other means of transfer. For example, fatty spheres with a watery core, called liposomes, can be used as a molecular Trojan horse to deliver genes to brain cells. This opens the door to treatment of disorders such as Parkinson's disease and epilepsy.¹³ Electric pulses can also be used to deliver a range of molecules, including drug proteins, RNA, and DNA, to cells.¹⁴

One option is to pack DNA into ultratiny (25-nanometer) nanoballs for maximum impact.¹⁵ This approach is already being tested on human patients with cystic fibrosis. Researchers reported a "6,000-fold increase in the expression of a gene packaged this way, compared with unpackaged DNA in liposomes."

Yet another approach uses DNA combined with microscopic bubbles. Ultrasonic waves are used to compress the bubbles, enabling them to pass through cell membranes.

RECOMBINANT TECHNOLOGY: BETTING THE FAMILY PHARM

We are already using gene therapy in other species. By modifying the genes of bacteria, plants, and animals, we can cause them to create the substances we need to combat human diseases. Recombinant proteins made by combining DNA from more than one organism are now being manufactured by bacteria, a novel biotech appropriately referred to as *pharming*. In recombinant technology, the genetic material that codes for a desired protein is spliced into the DNA of certain species of bacteria, which then go to work making this protein. Given how fast bacteria multiply, it's easy to create significant amounts of proteins this way. Insulin was the first molecule to be created synthetically by recombinant technology, so that insulin-dependent diabetics are no longer reliant on injections of beef or pork insulin. Many diabetics developed allergic reactions or high levels of antibodies against the foreign proteins found in the beef- and pork-derived insulin preparations. With recombinant *human* insulin, this is no longer a problem.

Children with growth hormone deficiency (dwarfs) used to rely on injections of hGH (human growth hormone) derived from the pituitary glands of human cadavers. It took a lot of cadavers to provide enough hGH for just one child for a year. There was also the risk of certain infections. Recombinant hGH has solved this problem and substantially lowered the price of this therapy. It has enabled adults with growth hormone deficiency to be treated as well.

Genes from proteins have also been spliced into "immortalized" human kidney cells and are now being pharmed to create proteins found useful in treating patients who have suffered strokes, as well as numerous other illnesses.¹⁶ Patients with chronic kidney disease are deficient in a protein made by the kidneys called erythropoietin. Without erythropoietin, severe anemia results and frequent transfusions are needed. By inserting the genes that code for this protein into hamster cells, drug companies have been able to create enough erythropoietin to avoid the need for transfusion for many dialysis patients.

New methods involving traditional farm animals are also being found. Cows produce large amounts of milk, so splicing DNA into the genes that code for milk is a valuable technique. The DNA that codes for egg protein is now being used so that the eggs of transgenic (containing a gene or genes artificially inserted from a different species) chickens will contain useful proteins. In the near future we will have pharms where the animals have had their genes altered so that their milk, eggs, or even semen will produce recombinant proteins to help treat currently untreatable or only partially treatable conditions, such as multiple sclerosis, Parkinson's disease, Alzheimer's disease, hepatitis C, and AIDS.

Pharmers won't be restricted to using animals. Plants, particularly types with high protein content such as corn or tobacco, can be reprogrammed to produce substances of great value. In Japan, for instance, a strain of genetically modified rice contains a protein that will kill the hepatitis B virus.

THERAPEUTIC CLONING

One of the most powerful methods of applying life's own machinery to improve and extend life involves harnessing biology's reproductive mechanisms in the form of cloning. Cloning is an extremely important technology, not for cloning complete humans but for life extension purposes. Therapeutic cloning creates new tissues to replace defective tissues or organs.

All responsible ethicists, including these authors, consider human cloning at the present time to be unethical, yet our reasons have little to do with the slippery (slope) issues of manipulating human life. Rather, the technology today simply does not yet work reliably. The current technique involves fusing a cell nucleus from a donor to a recipient egg cell using an electric spark and causes a high level of genetic errors.¹⁷

This is the primary reason most of the fetuses created in this way so far have not made it to term. Even those that do survive have genetic defects. Dolly the Sheep developed an obesity problem in adulthood, and most of the cloned an-

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imals produced thus far have had unpredictable health problems. Scientists have
 a number of ideas for perfecting this process, including using alternative ways
 of fusing the nucleus and egg cell without the destructive electrical spark. Until
 the technology is demonstrably safe, however, it would be unethical to create
 a human life with such a high likelihood of severe health problems.

However, the most valuable applications of cloning technology are *not* for
 the purpose of cloning entire human beings but to create human organs, such
 as hearts or kidneys. This uses germ line cells—those in the prefetal stage (be-
 fore implantation of a fetus). These germ line cells go through differentiation,
 which can then be developed into specific organs. Because differentiation takes
 place during the prefetal stage, most ethicists believe that this process does not
 raise ethical concerns, although this issue has been highly contentious.¹⁸

A team of researchers led by Woo Suk Hwang and Shin Yong Moon of
 Seoul National University in South Korea has taken an important step forward
 toward perfecting this technology. In an article published in *Science*, they an-
 nounced they had successfully cloned a line of human pluripotent stem cells,
 the type that has the potential to turn into any type of cell the body needs.
 Their cell line had already undergone 70 reproductions without incident.¹⁹
 This research paves the way for significant gains in the production of healthy
 human-replacement tissues and organs derived from a cloned stem cell line.

Defeating programmed cell death. Therapeutic cloning relates to
 telomeres, which are strings of a repeating code at the end of each DNA
 strand. These repeating codes are like a string of beads, in which one "bead"
 falls off each time a cell divides. This places a limit on the number of times a
 cell can replicate—the so-called Hayflick limit. Once these DNA beads run
 out, a cell is programmed for death. Recently, it was discovered that a single
 enzyme called telomerase can extend the length of the telomere beads,
 thereby overcoming the Hayflick limit. Germ line cells create telomerase and
 are immortal. Cancer cells also produce telomerase, which allows them to
 replicate indefinitely. The identification of this single enzyme creates impor-
 tant opportunities to manipulate this process to either extend the longevity
 of healthy cells or terminate the longevity of pathological cells, such as cancer.

It is interesting to reflect on the remarkable stability of the immortal germ
 line cells, which link all cell-based life on Earth. The germ line cells avoid
 destruction through the telomerase enzyme, which rebuilds the telomere
 chain after each cell division. This single enzyme makes the germ line cells
 immortal, and indeed these cells have survived from the beginning of life on
 Earth billions of years ago. This insight opens up the possibility of future
 gene therapies that would return cells to their youthful, telomerase-extended

state. Animal experiments have shown telomerase to be relatively benign, although some experiments have resulted in increased cancer rates.

There are also challenges in transferring telomerase into cell nuclei, although the gene therapy technology required is making solid progress. Scientists such as Michael West, president and CEO of Advanced Cell Technology Inc., have expressed confidence that new techniques will provide the ability to transfer telomerase into cell nuclei and overcome the cancer issue. Telomerase gene therapy holds the promise of indefinitely rejuvenating human somatic (non-germ line) cells—that is, all human cells.

Progress in growing new tissues and organs from stem cells is developing rapidly. Robert Langer's team at MIT has grown primitive versions of human organs such as liver, cartilage, and neural tissues. Their technique involves growing cells on specially designed biodegradable polymer scaffolds, which are spongelike structures with the approximate shape of the desired organ. Langer and his team wrote, "Here we show for the first time that polymer scaffolds . . . promoted proliferation, differentiation and organization of human embryonic stem cells into 3D structures."

One of the challenges in growing new human organs in this way is creating a functioning system of new blood vessels. Researchers at MIT and Harvard Medical School have constructed a working synthetic vascular system using two computer-etched biodegradable polymers sandwiched together to create capillaries only 10 microns (millionths of a meter) wide, as well as arteries and veins up to 300 times wider.²⁰

One exciting approach that bypasses the ethical controversy of using fetal tissue, while also providing a substantial source of stem cells, which are currently limited in quantity, is parthogenesis, or so-called virgin birth. Adding certain chemicals to unfertilized human egg cells can turn them into embryos, which might then act as a source of new stem cells.²¹ These embryos, called parthenotes, can never become babies, so there should not be an ethical issue in destroying tissue that is destined for destruction anyway. Another intriguing idea is for a woman to create parthenotes from her own egg cells to create stem cells with her own DNA, thereby avoiding potential rejection of foreign cells by a patient's immune system.

Human somatic cell engineering. This is an even more promising approach that entirely bypasses the controversy of using fetal stem cells. These emerging technologies, also called transdifferentiation, create new tissues with a patient's own DNA by converting one type of cell (such as a skin cell) directly into another (such as a pancreatic islet cell or a heart cell) without the use of fetal stem cells.²² There have been recent breakthroughs in this

area. Scientists have converted human embryonic stem cells into heart muscle. Hematech is working on converting human embryonic stem cells into a primitive brain.

Consider the possibility of other types of stem cells. As discussed above, the use of stem cells to repair RNA fragments and manipulate the genome is a promising area.

Perfecting the use of stem cells and political and ethical perspectives. If we can produce a new heart, we can produce a new germ line. This is a new way of thinking about the future of human life.

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Growing You

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Even more exciting is the possibility of their "young" stem cells. These cells are introduced into the body to produce new tissue. It is a new way of thinking about the future of human life. It is a new way of thinking about the future of human life. It is a new way of thinking about the future of human life.

area. Scientists from the United States and Norway have successfully converted human skin cells directly into immune system cells and nerve cells.²³ Hematech, a biotechnology company, has reprogrammed fibroblast cells back into a primordial state where they can be converted into other types of cells.

Consider the question: What is the difference between a skin cell and any other type of cell in the body? After all, they all have the same DNA. As noted above, the differences are found in protein signaling factors. These include short RNA fragments and peptides, which we are now beginning to understand. By manipulating these proteins, we can turn one type of cell into another.²⁴

Perfecting this technology would not only defuse a contentious ethical and political issue, it would also offer an ideal solution from a scientific perspective. If you need pancreatic islet cells or kidney tissues—or even a whole new heart—to avoid autoimmune reactions, you would strongly prefer to produce these from your own DNA, not the DNA from someone else's germ line cells. And this approach uses your own plentiful skin cells rather than your rare and precious stem cells.

This process would directly grow an organ with your genetic makeup, and the new organ could have its telomeres fully extended to their original youthful length, effectively making the new organ young again.²⁵ That means an 80-year-old man could have his heart replaced with the same heart he had when he was, say, 25.

The master gene that enables stem cells to remain youthful and pluripotent (able to differentiate into virtually any type of other cell) has been dis-

Growing Younger

Scientists at the European Molecular Biology Laboratory and the University of Rome have identified a protein called mIGF-1 that induces stem cells from other parts of the body to quickly migrate to muscles damaged from disease or injury. Our ability to produce mIGF-1 declines with age, but this age-related process can be reversed by administering the protein. This may be a key step in stem cell therapy.

Even more exciting is the prospect of replacing one's organs and tissues with their "young" replacements without surgery. Cloned telomere-extended cells introduced into an organ will integrate themselves with the older cells. Through repeated treatments over a period of time, the organ will end up being dominated by the younger cells. We normally replace our own cells on a regular basis anyway, so why not do so with youthful telomere-extended cells rather than older telomere-shortened ones? There's no reason why we couldn't eventually do this with every organ and tissue in our body. We would thereby grow progressively younger.

covered and named *nanog* by a team at the Institute for Stem Cell Research in Edinburgh, Scotland.²⁶ "Nanog seems to be a master gene that makes embryonic stem cells grow in the laboratory," says Ian Chambers, one of the team's scientists. "In effect this [gene] makes stem cells immortal." The insight is a big step in being able to turn any cell, such as a skin cell, into a pluripotent cell, which can then be transformed into any other type of cell.

REVERSING HUMAN AGING

Our understanding of the principal components of human aging is growing rapidly. Strategies have been identified to halt and reverse each of the aging processes. Perhaps the most energetic and insightful advocate of stopping the aging process is Aubrey de Grey, a scientist with the department of genetics at Cambridge University. De Grey describes his goal as "engineered negligible senescence"—stopping us from becoming more frail and disease-prone as we get older.²⁷

According to de Grey, "All the core knowledge needed to develop *engineered negligible senescence* is already in our possession—it mainly just needs to be pieced together."²⁸ He believes we'll demonstrate "robustly rejuvenated" mice—mice that are functionally younger than before being treated, and with the life extension to prove it—within 10 years, and points out that this demonstration will have a dramatic effect on public opinion. Showing that we can reverse the aging process in an animal that shares 99 percent of our genes will profoundly transform the common wisdom that aging and death are inevitable. Once demonstrated in an animal, robust rejuvenation in humans is likely to take an additional 5 to 10 years, but the advent of rejuvenated mice will create enormous competitive pressure to translate these results into human therapies.

Earlier in the evolution of our species (and precursors to our species), survival was not aided—indeed, it would have been hurt—by individuals living long past their child-rearing years. As a result, genes that supported significant life extension were selected against. In our modern era of abundance, all generations can contribute to the ongoing expansion of human knowledge. "Our life expectancy will be in the region of 5,000 years . . . by the year 2100," says de Grey. By following the three bridges described in this book, you should be able to reach the year 2100, and then, according to de Grey, extend your longevity indefinitely.

De Grey describes seven key aging processes that currently encourage senescence and has identified strategies for reversing each. Here are four of de Grey's key strategies:

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Chromosomal (nuclear) mutations and "epimutations."²⁹ Almost all of our DNA is in our chromosomes, in the nucleus of the cell. (The rest is in the mitochondria, which we'll come to in a moment.) Over time, mutations occur, that is, the DNA sequence becomes damaged. Additionally, cells accumulate changes to "epigenetic" information that determine which genes are expressed in different cells. These changes also matter because they cause cells to behave inappropriately for the tissue they're in. Most such changes (of either sort) are either harmless or just cause the cell to die and be replaced by division of a neighboring cell. The changes that matter are primarily ones that result in cancer. This means that if we can cure cancer, nuclear mutations and epimutations should largely be harmless. De Grey's proposed strategy for curing cancer is pre-emptive: It involves using gene therapy to remove from all our cells the genes that cancers need to turn on in order to maintain their telomeres when they divide. This will not stop cancers from being initiated by mutations, but it will make them wither away before they get anywhere near big enough to kill us. Strategies for deleting genes in this way are already available and are rapidly being improved.

Toxic cells. Occasionally, cells get into a state where they're not cancerous, but still it would be best for the body if they died. Cell senescence is an example, and so is having too many fat cells. In these cases we need to kill those cells (which is usually easier than reverting them to a healthy state). Methods are being developed to target "suicide genes" to such cells, and also to make the immune system kill them.

Blocking the telomerase enzyme is one of many strategies being pursued against cancer. Doing this would prevent cancer cells from replicating more than a certain number of times, effectively destroying the cancer's ability to spread. There are many other strategies being intensely pursued to overcome cancer. Particularly promising are cancer vaccines designed to stimulate the immune system to attack cancer cells. These vaccines could be used to prevent cancer, as a first-line treatment, or to mop up cancer cells after other treatments.³⁰ We'll discuss Bridge Two strategies against cancer in more detail in chapter 16, "The Prevention and Early Detection of Cancer."

Mitochondrial mutations. Another aging process identified by de Grey is accumulation of mutations in the 13 genes in the mitochondria, the energy factories for the cell.³¹ The mitochondrial genes undergo a higher rate of mutations than those in the nucleus and are critical to the efficient functioning of our cells. Once we master somatic gene therapy, we could put multiple copies of these 13 genes within the relative safety of the cell nucleus, thereby providing redundancy (backup copies) for this vital genetic information. The mechanism already exists in cells for nucleus-encoded proteins to be imported into the mi-

tochondria, so it is not necessary for these proteins to be produced in the mitochondria itself. In fact, most of the proteins needed for mitochondrial function are already coded by the nuclear DNA. There has already been successful research in transferring mitochondrial genes into the nucleus in cell cultures.

Cell loss and atrophy. Our body's tissues have the means to replace worn-out cells, but this ability is limited in certain organs, says de Grey. For example, the heart is unable to replace cells as quickly as needed as we get older, so it compensates by enlarging surviving cells using fibrous material. Over time, this causes the heart to become less supple and responsive. A primary strategy here is to deploy therapeutic cloning of our own cells, as described on page 22.

Evidence from the genome project indicates that no more than a few hundred genes are involved in the aging process. By manipulating these genes, radical life extension has already been achieved in simpler animals. For example,

A Panoply of Emerging Therapies

A broad variety of hybrid biotechnology strategies is emerging. Consider this small sample of additional research under way:

- Chemists from the Scripps Research Institute have identified a molecule they call reversine that appears to reprogram aging cells to make them youthful.³³ It may be an alternative to stem cell therapies to regenerate cells and tissues that need replacement.
- Researchers have demonstrated a method of creating dried stem cells that are revived just by adding water, providing indefinite shelf life to cells that can be used to re-create tissues such as bone, blood, and organs.³⁴
- One of the major challenges in medicine is getting needed nutrients, supplements, and medications into the bloodstream without having to go through the gastrointestinal tract, which often interferes dramatically with a drug's effectiveness (and may also cause digestive upset). Many medications, such as insulin, human growth hormone, and therapeutic DNA, must be introduced through painful daily injections that adversely affect a patient's quality of life. Researchers at Johns Hopkins University have developed plastic polymer spheres that surround tiny doses of medications and can be inhaled. The polymers dissolve inside the lungs, releasing their therapeutic cargo at the correct rate. All of the materials used are already FDA-approved, so it is likely that the approval process for this application will be simplified. Ultimately, we will have the means to easily send optimal levels of all nutrients directly into the bloodstream without requiring pills or injections.

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by modifying genes in the *C. elegans* worm that control insulin and modifying sex hormone levels, the life span of the test animals was expanded sixfold, the equivalent of a 500-year life span for a human.³² As we gain the ability to understand and reprogram gene expression, reprogramming the aging process in humans will become increasingly feasible. The idea that aging and dying are inevitable is deeply rooted, but this age-old perspective will gradually change as gene therapies are successfully demonstrated over the next two decades.

BRIDGE THREE: NANOTECHNOLOGY AND ARTIFICIAL INTELLIGENCE

As we "reverse engineer" (understand the principles of operation behind) our biology, we will apply our technology to augment and redesign our

- The human genome on a chip is now available. An integrated "gene chip" allows researchers to determine exactly which genes are expressed in a diseased organ, compared with a healthy one, which will greatly accelerate drug discovery and the prediction of drug effects.
- We are in the early stages of creating simulated biology to be able to discover and test drugs and other therapies *in silico* (in chips). There are already detailed systems that can simulate organs such as the heart using cell-by-cell simulations. The Defense Advanced Research Projects Agency (DARPA) is developing a program that will provide a virtual army of simulated test subjects to automatically test drugs, procedures, even weapons. The goal is to simulate every aspect of the human body, incorporating all genetic and proteomic (protein expression) information on a molecular level. One of DARPA's objectives is to place a digital version of each soldier's complete body on a dog tag. If that soldier needed emergency treatment, medics would access the "virtual soldier program" on the dog tag to immediately make lifesaving decisions. Howard Asher, director of global life sciences for Sun Microsystems, states, "We believe in 10 years we can eliminate the need for all animal studies, we can eliminate phase one and phase two clinical studies, so computationally we can model a drug or therapeutic agent in the computer against the genomic data."

bodies and brains to radically extend longevity, enhance our health, and expand our intelligence and experiences. Much of this technological development will be the result of research into nanotechnology, a term originally coined by K. Eric Drexler in the 1970s to describe the study of objects whose smallest features are less than 100 nanometers (billionths of a meter). A nanometer equals roughly the diameter of five carbon atoms.

Robert A. Freitas Jr., a nanotechnology theorist, writes, "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."³⁵

Freitas points out that if "the idea of placing millions of autonomous nanobots (blood cell-sized robots built molecule by molecule) inside one's body might seem odd, even alarming, the fact is that the body already teems with a vast number of mobile nanodevices." Biology itself provides the proof that nanotechnology is feasible. As Rita Colwell, director of the National Science Foundation, has said, "Life is nanotechnology that works." Macrophages (white blood cells) and ribosomes (molecular "machines" that create amino acid strings according to information in RNA strands) are essentially nanobots designed through natural selection. As we engineer our own nanobots to repair and extend biology, we won't be constrained by biology's toolbox. Biology uses a limited set of proteins for all of its creations, whereas we can create structures that are dramatically stronger, faster, and more intricate.

One application we'll discuss further in chapter 7, on digestion, is to disconnect the sensory and pleasurable process of eating from the biological purpose of obtaining optimal nutrition. Billions of tiny nanobots in the digestive tract and bloodstream could intelligently extract the precise nutrients we require, call for needed additional nutrients and supplements through our body's personal wireless local area network (nanobots that communicate with one another), and send the rest of the food we eat on its way to elimination.

BioMEMS. If this seems particularly futuristic, keep in mind that intelligent machines are already being injected into our bloodstreams today. There are dozens of projects under way to create bloodstream-based biological microelectromechanical systems (bioMEMS) with a wide range of diagnostic and therapeutic applications.³⁶ There are already four major conferences devoted to these projects.³⁷ BioMEMS devices are being designed to intelligently scout out pathogens and deliver medications in precise ways.

For example, nanoengineered blood-borne devices that deliver hormones

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such as insulin have been demonstrated in animals.³⁸ Similar systems could precisely deliver dopamine to the brain for Parkinson's patients, provide blood-clotting factors for patients with hemophilia, and deliver cancer drugs directly to tumor sites. One new design provides up to 20 separate reservoirs that can release the different substances at programmed times and locations in the body.³⁹

Kensall Wise, a professor of electrical engineering at the University of Michigan, has developed a tiny neural probe that provides precise monitoring of the electrical activity of patients with neural diseases.⁴⁰ Future designs are expected to deliver drugs to precise locations in the brain as well. Kazushi Ishiyama at Tohoku University in Japan has developed micromachines that use microscopic spinning screws to deliver drugs directly into small cancerous tumors.⁴¹

A particularly innovative micromachine developed by Sandia National Labs has actual microteeth with a jaw that opens and closes to trap individual cells and then implant them with substances such as DNA, proteins, or drugs.⁴²

Complex structures at the molecular level have already been constructed. In some cases, building blocks are borrowed from nature. In fact, copying or manipulating naturally occurring molecules to accomplish specific goals is a cornerstone of present-day nanotech research. DNA turns out to be a useful structural tool because the unzipped strands can be organized into structures such as cubes, octahedrons, and more complicated designs. A team at Cornell University used portions of a natural enzyme, ATPase, to build a nanoscale motor. Another team at the CNRS Institute in Strasbourg, France, has successfully used carbon nanotubes to deliver a peptide into the nuclei of fibroblast cells. Many approaches are being developed for micro- and nanosize machines to perform a broad variety of tasks in the body and bloodstream.

Programmable blood. One pervasive system that has already been the subject of a comprehensive conceptual redesign is our blood. In chapter 15, "The Real Cause of Heart Disease and How to Prevent It," we will discuss a series of remarkable conceptual designs by Freitas for robotic replacements of our red blood cells, white blood cells, and platelets. Detailed analyses of these designs demonstrate that these tiny robots would be hundreds or thousands of times more capable than their natural counterparts.

Nanopower. Developing power sources for these tiny devices has already received significant research attention. MEMS (microelectronic mechanical systems) technology is being applied to create microscopic hydrogen fuel cells to power portable electronics and, ultimately, nanobots that will be introduced into the human body. One strategy is to use the same energy

sources—glucose and ATP—that power our natural nanobots, such as macrophages, a type of white blood cell that is designed to destroy harmful bacteria and viruses. A Japanese research team has developed a “bio-nano” generator that creates power from glucose in the blood. Another team at the University of Texas at Austin has developed a fuel cell that uses both glucose and oxygen in human blood.⁴³

Continual monitoring. Sensors based on silicon nanowires have shown the potential to detect disease almost instantly.⁴⁴ Using any bodily fluid, such as urine, saliva, or blood, diseases including cancer can be detected at very early stages. According to the study leader, Charles M. Lieber, professor of chemistry at Harvard University, this technology will enable you to “give a drop of blood from a pinprick on your finger and, within minutes, find out whether you have a particular virus or genetic disease, or your risk for different diseases or drug interactions.” This approach can also be used for detection of bioterrorism threats.

Within several years, we will have the means of continually monitoring the status of our bodies to fine-tune our health programs as well as provide early warning of emergencies such as heart attacks. The authors are working on this type of system with biomedical company United Therapeutics, using miniaturized sensors, computers, and wireless communication. Researchers at Edinburgh University are developing spray-on nanocomputers for health monitoring. Their goal: a device the size of a grain of sand that combines a computer, a wireless communication system, and sensors for heat, pressure, light, magnetic fields, and electrical currents. In another development, a research team headed by Garth Ehrlich of the Allegheny Singer Research Institute in Pittsburgh is developing MEMS-based sensor robots that can be implanted inside the body to detect infection, identify the pathogen, and then dispense the appropriate antibiotic from the device’s internal containers.⁴⁵

One application they envision is preventing bacterial infections, a major cause of hip joint replacement failure. Ehrlich points out that today, “the only recourse for such patients is the traumatic removal of the implant, which results in additional bone loss, extensive soft tissue destruction, months of forced bed rest with intravenous antibiotics, and significant loss of quality of life due to complete loss of mobility.”

Nanosurgery. Nanobots will make great surgeons. Teams of millions of nanobots will be able to restructure bones and muscles, destroy unwanted growths such as tumors on a cell-by-cell basis, and clear arteries while restructuring them out of healthy tissue. Nanobots would be thousands of times more precise than the sharpest surgical tools used today,

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would leave no scars, and could provide continual follow-up after certain surgical procedures. Nanobot surgeons could even perform surgery on structures within cells, such as repairing DNA within the nucleus. These nanobots will require distributed intelligence. Like ants in an ant colony, their actions will need to be highly coordinated, and the entire "colony" of nanobots will need to display flexible intelligence. Distributed systems that display intelligent coordination is one of the key goals of research in artificial intelligence—developing computers that emulate human intelligence.

One of Freitas's more advanced conceptual designs is a DNA repair robot. Billions or even trillions of such robots could go inside all of your cells and make repairs as well as improvements to the DNA in the genes. Freitas points out that it may be more efficient to just replace all the DNA in a gene with a new corrected copy rather than attempt to make changes to individual nucleotides.

Here's an original idea: replace the genetic machinery altogether (the cell nucleus, ribosomes, and related structures) with a small computerized robot. The computer would store the genetic code, which is only about 800 megabytes of information, or about 30 megabytes using data compression. The computerized system replacing the nucleus would then perform the function of the ribosomes by directly assembling strings of amino acids according to the computerized genetic information. These computers would all be on a wireless local area network, so improvements to the genetic code could be quickly downloaded from the Internet. It would not be necessary for the computer replacing each cell nucleus to have a complete copy of the genetic code, since these computers will be able to share their information. One major advantage of this approach is that undesirable replication

Harnessing the Heat of the Sun

Experiments by a Harvard team led by physicist Eric Mazur have shown the feasibility of using sharply focused laser light to perform surgical procedures from outside the patient, including destroying small structures inside cells without otherwise affecting them.⁴⁶ "It's a microscopic James Bond type of scenario," according to project contributor and Harvard cell biologist Donald Ingber. "It generates the heat of the sun, but only for quintillionths of a second, and in a very small space." The team has already demonstrated the ability of performing their laser-based nanosurgery from outside an animal and successfully manipulated the sense of smell of the worm *Caenorhabditis elegans*.

processes—for example, of pathological viruses or cancer cells—could be quickly shut down.

Intelligent cells. A hybrid scenario involving both biotechnology and nanotechnology contemplates turning biological cells into computers. These “enhanced intelligence” cells could then detect and destroy cancer cells and pathogens, or even regrow human body parts such as organs and limbs. Princeton biochemist Ron Weiss has modified cells to incorporate a variety of logic functions that are used for basic computation.⁴⁷ Boston University’s Timothy Gardner has developed a cellular logic switch, another basic building block for turning cells into computers.⁴⁸ And scientists at the MIT Media Lab have developed ways to use wireless communication to send messages, including intricate sequences of instructions, to computers inside modified cells.⁴⁹ By attaching gold crystals comprised of less than 100 atoms to DNA, they were able to use the gold as antennae and selectively cause the double-stranded DNA to unzip without affecting nearby molecules. The technique could ultimately be used to control gene expression through remote control. Weiss points out that “once you have the ability to program cells, you don’t have to be constrained by what the cells know how to do already. You can program them to do new things, in new patterns.”

We are also making exponential progress in understanding the principles of operation of the human brain. Our tools for peering inside the brain are accelerating in their price-performance, and the ability to see small features and fast events. An emerging generation of brain-scanning tools is providing the means for the first time to monitor individual interneuronal connections in real time in clusters of tens of thousands of neurons. We already have detailed models and simulations of several dozen regions of the human brain, and we believe that it is a conservative projection to anticipate the completion of the reverse engineering of the several hundred regions of the brain within the next two decades. 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. With a measure of intelligence, the nanobots coursing through our bloodstream, bodily organs, and brain will be able to overcome virtually any obstacle to keeping us healthy. Ultimately, we will merge our biological thinking with advanced artificial intelligence to vastly expand our abilities to think, create, and experience.

rather than vitamin or mineral supplementation, and do not account for unusual requirements due to disease or environmental stress. See www.blionline.com/HDB/NutritionalStandardsRDAUSRDAAndRDI/AntioxidantsBooklet.htm.

13 O. W. Rasmussen et al. 1993. "Effects on blood pressure, glucose and lipid levels of a high-monounsaturated fat diet compared with a high-carbohydrate diet in NIDDM subjects." *Diabetes Care*. 16: 1565-1571.

14 On the Web site for the American Diabetes Association is found the "Diabetic Food Pyramid." Interestingly, it is essentially identical to the Department of Agriculture's Food Pyramid recommended for the general public. The same reliance on a starch- and grain-based diet with 30 percent of calories coming from fat is recommended. See www.diabetes.org/main/health/nutrition/article031799.jsp.

15 D. Ornish. "Can lifestyle changes reverse coronary heart disease?" 1990. *Lancet*. 336: 129-133.

16 E. G. Vermeulen et al. 2000. "Effect of homocysteine-lowering treatment with folic acid plus vitamin B₆ on progression of sub clinical atherosclerosis: a randomized, placebo-controlled trial." *Lancet*. Feb 12;355(9203): 517-522. Also, in an editorial accompanying A. D. Kuczyński. 2002. "Homocysteine, Stroke, and Dementia," *Stroke*. 33: 2343-2344. Dr. Kuczyński of Tel-Aviv University Medical School in Ramat-Aviv, Israel, says, "Since dietary habits are so different among people, it may be appropriate to recommend 2 to 5 mg folic acid and a similar dose of vitamin B₁₂ daily. This recommendation is based on the known safety of both vitamins, which do not have side effects even if used in excessive amounts, and their low cost."

CHAPTER 2

1 Nanotechnology is "thorough, inexpensive control of the structure of matter based on molecule-by-molecule control of products and byproducts; the products and processes of molecular manufacturing, including molecular machinery." (E. Drexler and C. Peterson. 1991. *Unbounding the Future: The Nanotechnology Revolution*. New York: William Morrow and Company.) According to the authors (chapter 1): "Technology has been moving toward greater control of the structure of matter for millennia . . . [P]ast advanced technologies—microwave tubes, lasers, superconductors, satellites, robots, and the like—have come trickling out of factories, at first with high price tags and narrow applications. Molecular manufacturing, though, will be more like computers: a flexible technology with a huge range of applications. And molecular manufacturing won't come trickling out of conventional factories as computers did; it will replace factories and replace or upgrade their products. This is something new and basic, not just another twentieth-century gadget. It will arise out of twentieth-century trends in science, but it will break the trend-lines in technology, economics, and environmental affairs."

Drexler and Peterson outline the following possible scenarios to explain the scope of the revolution: efficient solar cells "as cheap as newspaper and as tough as asphalt," molecular mechanisms that can kill cold viruses in six hours before biodegrading, immune machines that destroy malignant cells in the body at the push of a button, pocket supercomputers, the end of the use of fossil fuels, space travel, and restoration of lost species. Also see another book by K. E. Drexler, *Engines of Creation* (Anchor Books, 1986). Foresight Institute has a useful list of nanotechnology FAQs (www.foresight.org/NanoRev/FIFAQ1.html) and other information. Other Web resources include the National Nanotechnology Initiative (www.nano.gov), www.nanotechweb.org, Dr. Ralph Merkle's Nanotechnology page (www.zyvex.com/nano/), and *Nanotechnology* (an online journal: www.iop.org/EJ/journal/0957-4484).

Extensive material on nanotechnology can be found on Ray Kurzweil's Web site, www.kurzweilai.net.

2 Nanotechnology is technology in which objects are built from individual atoms or molecules, or where one or more dimensions are on a scale of nanometers (billionths of meter). For further information, see K. E. Drexler's 1986 classic *Engines of Creation*; www.kurzweilai.net/meme/frame.html?m=8.

3 Besides the functions of different types of cells, two other causes for cells to control the expression of genes are environmental cues and developmental processes. Even simple organisms such as bacteria can turn on and off the synthesis of proteins, depending on environmental cues. *E. coli*, for example, can turn off the synthesis of proteins that allow it to fix nitrogen gas from the air when there are other, less-energy-intensive sources of nitrogen in its environment. A recent study of 1,800 strawberry genes found that the expression of 200 of those genes varied during different stages of development (E. Marshall. 1999. "An array of uses: expression patterns in strawberries, Ebola, TB, and mouse cells." *Science*. 286(5439): 445).

4 Along with a protein-encoding region, genes include regulatory sequences called promoters and enhancers that control where and when that gene is expressed. Promoters are located "upstream" (on base pairs nearby the transcription site) on the DNA molecule. An enhancer activates a promoter, thereby controlling

the rate of gene expression. To be expressed, most genes require enhancers; enhancers determine when genes are expressed and for which target protein cell type. Each gene can have several different enhancer sites linked to it (S. F. Gilbert. 2000. *Developmental Biology*, 6th ed. Sunderland, Massachusetts: Sinauer Associates; searchable online at www.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View.ShowTOC&rid=dbio.TOC&depth=2).

By binding to enhancer or promoter regions, transcription factors start or repress the expression of a gene. New knowledge of transcription factors has transformed our understanding of gene expression. Per S. F. Gilbert in the chapter "The Genetic Core of Development: Differential Gene Expression," "The gene itself is no longer seen as an independent entity controlling the synthesis of proteins. Rather, the gene both directs and is directed by protein synthesis. Natalie Anger (1992) has written, 'A series of discoveries suggests that DNA is more like a certain type of politician, surrounded by a flock of protein handlers and advisors that must vigorously massage it, twist it and, on occasion, reinvent it before the grand blueprint of the body can make any sense at all.'"

5 Many antisense RNAs "have shown convincing in vitro reduction in target gene expression and promising activity against a wide variety of tumors." A. Biroccio, C. Leonetti, and G. Zupi. 2003. "The future of antisense therapy: combination with anticancer treatments." *Oncogene*. Sep 29;22(42): 6579-6588. See also "Subtle gene therapy tackles blood disorder." October 11, 2002, *NewScientist.com*; www.newscientist.com/news/news.jsp?id=ns99992915; X. Jiang et al. 2003. "Inhibition of MMP-1 expression by antisense RNA decreases invasiveness of human chondrosarcoma." *J Orthop Res*. Nov;21(6): 1063-1070.

6 B. Holmes. "Gene therapy may switch off Huntington's." *NewScientist.com*, March 13, 2003; www.newscientist.com/news/news.jsp?id=ns99993493.

"Emerging as a powerful tool for reverse genetic analysis, RNAi is rapidly being applied to study the function of many genes associated with human disease, in particular those associated with oncogenesis and infectious disease." J. C. Cheng, T. B. Moore, and K. M. Sakamoto. 2003. "RNA interference and human disease." *Mol Genet Metab*. Oct;80(1-2): 121-128. RNAi is a "potent and highly sequence-specific mechanism" (L. Zhang, D. K. Fogg, and D. M. Waisman. 2003. "RNA interference-mediated silencing of the S100A10 gene attenuates plasmin generation and invasiveness of Colo 222 colorectal cancer cells." *J Biol Chem*. Oct 21 [e-pub ahead of print]).

7 Gene transfer to somatic cells affects a subset of cells in the body for a period of time. It is theoretically possible to also alter genetic information in egg and sperm (germ line) cells, for the purpose of passing on those changes to the next generations. Such therapy poses many ethical concerns and has not yet been attempted.

8 Genes encode proteins, which perform vital functions in the human body. Abnormal or mutated genes encode proteins that are unable to perform those functions, resulting in genetic disorders and diseases. The goal of gene therapy is to replace the defective genes so that normal proteins are produced. This can be done in a number of ways, but the most typical way is to insert a therapeutic replacement gene into the patient's target cells using a carrier molecule called a vector. "Currently, the most common vector is a virus that has 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 take advantage of this capability and manipulate the virus genome to remove the disease-causing genes and insert therapeutic genes." (Human Genome Project, "Gene Therapy," www.ornl.gov/TechResources/Human_Genome/medicine/genetherapy.html). See the Human Genome Project site for more information about gene therapy and links. Gene therapy is an important enough area of research that there are currently six scientific peer-reviewed gene therapy journals and four professional associations dedicated to this topic.

9 K. Smith. 2002. "Gene transfer in higher animals: theoretical considerations and key concepts." *J Biotechnol*. Oct 9;99(1): 1-22.

10 "'Miracle' gene therapy trial halted." *NewScientist.com*, October 3, 2003; www.newscientist.com/news/news.jsp?id=ns99992878; Human Genome Project. "Gene therapy," www.ornl.gov/TechResources/Human_Genome/medicine/genetherapy.html.

11 L. Wu, M. Johnson, and M. Sato. 2003. "Transcriptionally targeted gene therapy to detect and treat cancer." *Trends Mol Med*. Oct;9(10): 421-429.

12 S. Westphal. "Virus synthesized in a fortnight." *NewScientist.com*, November 14, 2003; www.newscientist.com/news/news.jsp?id=ns99994383.

13 A. Ananthaswamy. "Undercover genes slip into the brain." *NewScientist.com*, March 20, 2003; www.newscientist.com/news/news.jsp?id=ns99993520.

14 A. E. Trezise et al. 2003. "In vivo gene expression: DNA electrotransfer." *Curr Opin Mol Ther*. Aug;5(4): 397-404.

15 S. Westphal. "DNA nanoballs boost gene therapy." *NewScientist.com*, May 12, 2002; www.newscientist.com/news/news.jsp?id=ns99992257.

16 B. Dekel et al. 2003. "Human and porcine early kidney precursors as a new source for transplantation." *Nature Med*. Jan 1;(9): 53-60.

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- 17 Here is one possible explanation: "In mammals, female embryos have two X-chromosomes and males have one. During early development in females, one of the X's and most of its genes are normally silenced or inactivated. That way, the amount of gene expression in males and females is the same. But in cloned animals, one X-chromosome is already inactivated in the donated nucleus. It must be reprogrammed and then later inactivated again, which introduces the possibility of errors." "Genetic defects may explain cloning failures." *CBCNews*, May 27, 2002; www.cbc.ca/storview/CBC/2002/05/27/cloning_errors020527. That story reports on F. Xue et al. 2002. "Aberrant patterns of X chromosome inactivation in bovine clones." *Nat Genet*. Jun;31(2): 216-220.
- 18 J. B. Gurdon and A. Colman. 1999. "The future of cloning." *Nature*. 402: 743-746; G. Stock and J. Campbell, eds. 2000. *Engineering the Human Germline: An Exploration of the Science and Ethics of Altering the Genes We Pass to Our Children*. New York: Oxford University Press.
- 19 W. S. Hwang. 2004. "Evidence of a Pluripotent Human Embryonic Stem Cell Line Derived from a Cloned Blastocyst." *Science*. Mar 12;303(5664): 1669-1674.
- 20 G. Vince. "Nanotechnology may create new organs." *NewScientist.com*, July 8, 2003; www.newscientist.com/news/news.jsp?id=ns99993916.
- 21 S. Westphal. "'Virgin birth' method promises ethical stem cells." *NewScientist.com*, April 3, 2003; www.newscientist.com/news/news.jsp?id=ns99993654.
- 22 Liver stem cells have been transformed into pancreatic cells (L. Yang et al. 2002. "In vitro transdifferentiation of adult hepatic stem cells into pancreatic endocrine hormone-producing cells." *Proc Natl Acad Sci USA*. Jun 11;99(12): 8078-8083). Adult muscle stem cells can be transformed into muscle, neural tissue, and blood vessels. Z. Qu-Petersen et al. 2002. "Identification of a novel population of muscle stem cells in mice: potential for muscle regeneration." *J Cell Biol*. May;157: 851-864.
- 23 A. M. Hakelien et al. 2002. "Reprogramming fibroblasts to express T-cell functions using cell extracts." *Nature Biotechnology*. May;20: 460-466.
- 24 See the description of transcription factors in note 3, page 380.
- 25 R. P. Lanza et al. 2000. "Extension of cell life-span and telomere length in animals cloned from senescent somatic cells." *Science*. Apr 28;288(5466): 665-669. See also J. C. Ameisen. 2002. "On the origin, evolution, and nature of programmed cell death: a timeline of four billion years." *Cell Death & Differentiation*. Apr;9(4): 367-393; M. E. Shay. "Transplantation without a donor." *Dream: The magazine of possibilities*, Children's Hospital Boston, Fall 2001; www.childrenshospital.org/about/dreamfall01.pdf.
- 26 S. Bhattacharya. "Stem cell 'immortality' gene found." *NewScientist.com*, May 30, 2003; www.newscientist.com/news/news.jsp?id=ns99993786.
- 27 A. D. de Grey. 2003. "The foreseeability of real anti-aging medicine: focusing the debate." *Exp Gerontol*. Sep;38(9): 927-934; A. D. de Grey. 2003. "An engineer's approach to the development of real anti-aging medicine." *Sci SAGE KE*. Jan 8;2003(1): VP1; A. D. de Grey et al. 2002. "Is human aging still mysterious enough to be left only to scientists?" *Bioessays*. Jul;24(7): 667-676.
- 28 A. D. de Grey. "Engineering negligible senescence: rational design of feasible, comprehensive rejuvenation biotechnology," at www.gen.cam.ac.uk/sens/sensovp.ppt.
- 29 A. D. de Grey et al. 2004. "Total deletion of in vivo telomere elongation capacity: an ambitious but possibly ultimate cure for all age-related human cancers." *Annals NY Acad Sci*. 1019: 147-170.
- 30 O. J. Finn. 2003. "Cancer vaccines: between the idea and the reality." *Nat Rev Immunol*. Aug;3(8): 630-641; R. C. Kennedy and M. H. Shearer. 2003. "A role for antibodies in tumor immunity." *Int Rev Immunol*. Mar-Apr;22(2): 141-172.
- 31 A. D. de Grey. 2002. "The reductive hotspot hypothesis of mammalian aging: membrane metabolism magnifies mutant mitochondrial mischief." *Eur J Biochem*. Apr;269(8): 2003-2009; P. F. Chinnery et al. 2002. "Accumulation of mitochondrial DNA mutations in ageing, cancer, and mitochondrial disease: is there a common mechanism?" *Lancet*. Oct 26;360(9342): 1323-1235; A. D. de Grey. 2000. "Mitochondrial gene therapy: an arena for the biomedical use of inteins." *Trends Biotechnol*. Sep;18(9): 394-399.
- 32 S. Graham. "Methuselah worm remains energetic for life." *ScientificAmerican.com*, October 27, 2003; www.sciam.com/article.cfm?chanID=sa003&articleID=000C601F-8711-1F99-86FB83414B7F0156.
- 33 P. Ball and H. Pearson. "Drug may give cells a fresh start." *Nature Science Update*, January 30, 2004; www.nature.com/nsu/040126/040126-14.html.
- 34 H. Pearson. "Instant stem cells—just add water." *Nature Science Update*, December 19, 2003; www.nature.com/nsu/031215/031215-11.html.
- 35 R. A. Freitas Jr. *Nanomedicine, Volume I: Basic Capabilities*, first in an anticipated four-volume *Nanomedicine* technical book series. Freitas offers a pioneering and fascinating glimpse into a molecular-nanotechnology future with far-reaching implications for the medical profession—and ultimately for the radical improvement and extension of natural human biological structure and function.

36 Sensors and diagnostic tools are important applications of nanotechnology because the devices can be placed in direct contact with cells and the molecules in it. Another option is nanoimaging, in which nanocrystals would seek out different types of molecules, such as cancer cells. When stimulated by a laser, the crystals would emit light. These applications are just the "tip of the nano-iceberg" (P. Balasubramanian and S. Japa. 2003. "Nanosensing," *Stanford Biomedicine Quarterly*. Spring, p. 13).

37 For activities of the International Society for BioMEMS and Biomedical Nanotechnology, see its site (www.bme.ohio-state.edu/isb/). You can also find BioMEMS conferences listed on the SPIE site (www.spie.org/Conferences).

38 As reported in the *Stanford Biomedicine Quarterly* article in note 36 above, researchers used a gold nanoparticle to monitor blood sugar in diabetics. Y. Xiao et al. 2003. "Plugging into enzymes": Nanowiring of redox enzymes by a gold nanoparticle." *Science*. Mar 21;299(5614): 1877-1881. "One might even speculate on the design of an 'artificial pancreas,' an implant that would release appropriate levels of insulin into the blood from moment to moment according to the blood sugar readings provided by this nanosensor system" (p. 12).

39 Dr. Michael Cima at MIT is one researcher examining in vivo drug release from implantable MEMS arrays. He is one of the authors on G. Voskerician et al. 2002. "Biocompatibility and biofouling of MEMS drug delivery devices." *Biomaterials*. 24: 1959-1967.

40 According to Wise, one reason for relatively slow advances over the past thirty years is because of the "aggressive saltwater environment" of living tissue. (Quoted in D. Lammers. "Micro medical devices could transform health care." *EE Times*, June 21, 2002; www.eetimes.com/at/news/OEG20020620S0060.) See also the discussion of Wise's work in J. DeGaspari. "Tiny, tuned, and unattached." *Mechanical Engineering*, July 1, 2001; www.memagazine.org/backissues/july01/features/tinytune/tinytune.html.

41 "A team of scientists from Japan have developed tiny spinning screws that can swim along veins. The screws could then be used to ferry drugs to infected tissues or even burrow into tumours to kill them off with a hot lance." "'Microbots' hunt down disease." *BBC News*, June 13, 2001; <http://news.bbc.co.uk/1/hi/health/1386440.stm>. The micromachines are based on cylindrical magnets. (K. Ishiyama, M. Sendoh, and K. I. Arai. 2002. "Magnetic micromachines for medical applications." *J Magnetism Magnetic Materials*. 242-245(P1): 41-46.)

42 See the Sandia National Laboratories August 15, 2001, press release "Pac-Man-like microstructure interacts with red blood cells," www.sandia.gov/media/NewsRel/NR2001/gobbler.htm. For an industry trade article in response, see D. Wilson. "Microteeth have a big bite." August 17, 2001; www.e4engineering.com/item.asp?ch=e4_home&type=Features&id=42543.

43 P. Ball. "Chemists build body fluid battery." *Nature Science Update*, November 12, 2002; www.nature.com/nsu/021111/021111-1.html.

44 M. Bernstein. "Tiny nanowire could be next big diagnostic tool for doctors." *EurekAlert*, December 16, 2003; www.eurekalert.org/pub_releases/2003-12/acs-nc121603.php.

45 J. Sliwa. Researchers envision intelligent implants." *EurekAlert*, July 8, 2003; www.eurekalert.org/pub_releases/2003-07/asfn-rei070303.php.

46 J. Whitfield. "Lasers operate inside single cells," *Nature Science Update*, October 6, 2003; www.nature.com/nsu/030929/030929-12.html.

47 Ron Weiss's home page at Princeton University (www.ee.princeton.edu/~rweiss/) lists his publications, such as 2003. "Genetic circuit building blocks for cellular computation, communications, and signal processing." *Natural Computing, an International Journal*. (2): 47-84.

48 S. L. Garfinkel. "Biological computing." *Technology Review*, May/June 2000; www.simson.net/clips/2000.TR.BiologicalComputing.htm.

49 Ibid. See also the list of current research on the MIT Media Lab Web site; www.media.mit.edu/research/index.html.

CHAPTER 3

1 Great Smokies Diagnostic Laboratory. "Integrative Medicine," at www.gsdl.com/gsdl/functional_med.html.

2 Terry Grossman's personal experience is by no means unique. In a recent article in *JAMA*, the official journal of the American Medical Association, 46.3 percent of American people consulted a practitioner of alternative medicine in 1997. (D. M. Eisenberg et al. "Trends in alternative medicine use in the United States, 1990-1997: results of a follow-up national survey." 1998. *JAMA*. Nov 11;280(18): 1569-75.)

3 N. M. Bressler et al. 2003. "Potential public health impact of Age-Related Eye Disease Study results: AREDS report no. 11." *Arch Ophthalmol*. Nov;121(11): 1621-1624.

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