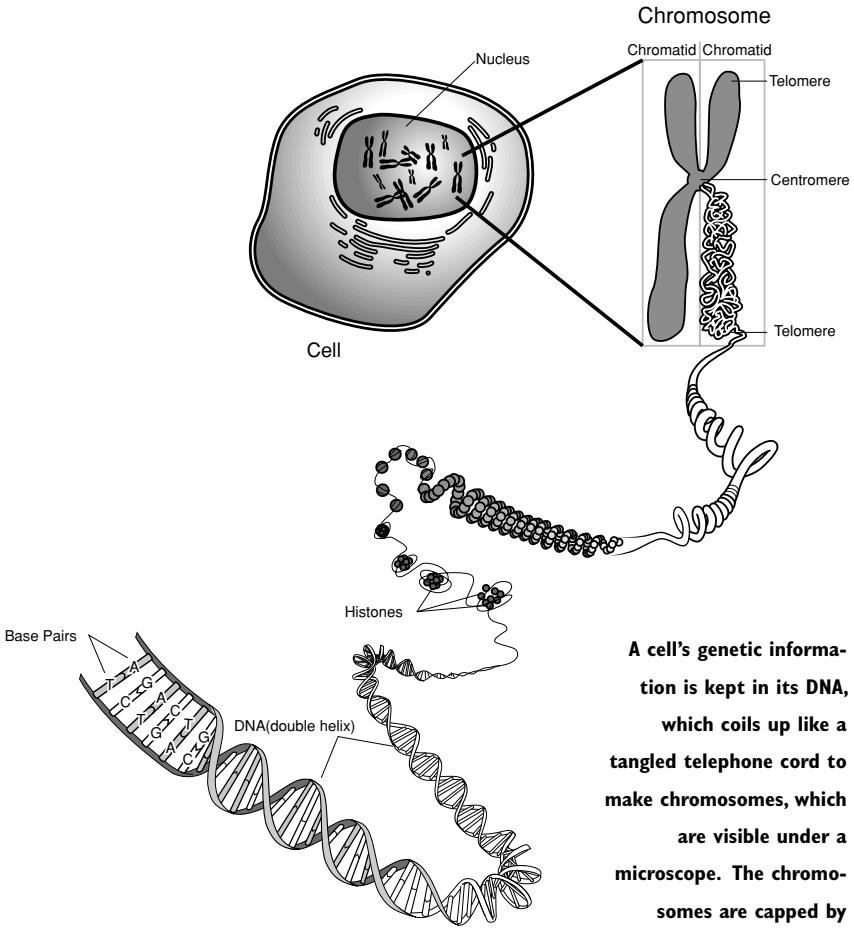
The Core 1 Science Writing course, introduced in the winter term of 1999–2000 as an elective, is now required of all juniors. All of the student papers can be found on-line at http://www.its.caltech.edu/~sciwrite/; we present two of the best here.

Immortality Under the Microscope

by Alisa Ching



A cell's genetic information is kept in its DNA, which coils up like a tangled telephone cord to make chromosomes, which are visible under a microscope. The chromosomes are capped by special stretches of DNA called telomeres, which may play a vital role in cellular aging. Graphic by Darryl Leja, National Human Genome Research Institute.

Since the Age of Exploration, the search for worldly riches has coexisted with another quest, for the secret to an eternal earthly life. Some of us fear death. Others fear growing old and not being able to live life. And we dream of being forever young. The fountain of youth seems a silly notion to us today, but only because the conquistadors searched for it across the map of the world, and not through the map of our biology. The search continues, but more profitably today, because today it is directed inward.

Aging, the process that leads inevitably to an organism's death, can be defined as the general decline in the function of organs and tissue over time. In trying to understand the mechanisms of aging of the organism as a whole, many scientists are now looking for explanations on the cellular level. The belief that aging of individual cells leads to aging of the organism was made stronger recently when it was found that a segment of DNA once thought to be insignificant plays a crucial role in cellular aging.

This small piece of DNA is known as a telomere, a name derived from the Greek words *telos* meaning "end" and *meros* meaning "part." Telomeres, also known as chromosomal "caps," are long, repetitive DNA sequences found at each end of every linear chromosome. They carry no information in the genetic sense; however, their physical characteristics provide the cell with vital instructions. By bending back on themselves, they create a loop that may prevent fraying of the chromosome. Therefore telomeres allow the cell to easily differentiate between a chromosome and a broken piece of DNA. But they serve another more vital role. Telomeres can be thought of as cellular biological clocks. During mitosis, or cellular division, the cell is unable to replicate a small portion at the end of the telomere; therefore, these telomeres get shorter and shorter, until eventually the cell is no longer able to divide without losing part of the DNA encoding important gen-

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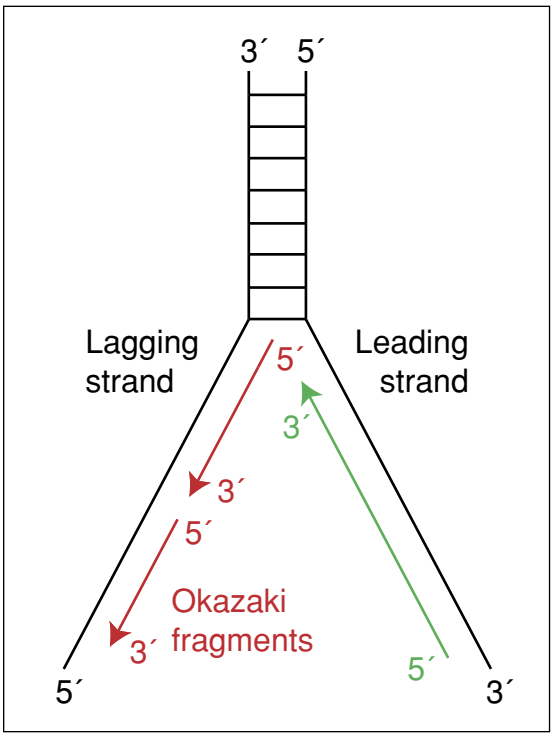
etic information. At this point, known as crisis, the cell simply stops dividing. From crisis, the cell normally enters into an inactive state known as senescence, which eventually leads to cell death.

Telomeres are a relatively recent discovery. In 1881, the German biologist August Weismann postulated that, contrary to the popular belief of the time, cells could only undergo a finite number of divisions. His theory could not be substantiated until 1961, when the biologist Leonard Hayflick, carrying out research at the Wistar Institute in Philadelphia, observed that, in culture, lung cells ceased to divide after about 50 divisions. Even if the tissue were frozen after 25 divisions, upon revival the cells would only divide until the 50-division limit was reached. This indicated that the number of divisions, not elapsed time, determines a cell's mortality. This finite limit to cellular replication has since been known as the Hayflick Limit. Hayflick, however, did not propose a mechanism to explain what he had seen. In 1971, closer observations by Alexi Olovnikov, a Russian scientist, found that telomeres got shorter with each mitotic division. Olovnikov proposed that telomere shortening was somehow related to cellular senescence. Finally, in 1990, Carol Greider and Bruce Fletcher at the Cold Spring Harbor Laboratory in New York experimentally proved that telomere length correlates with cellular aging.

Although many factors contribute to the aging of an organism, evidence suggests that it is directly related to the aging of the cell, and thus to telomere shortening. By understanding these factors' regulation, perhaps someday we will be able to slow or even stop the aging process. Since the length of a telomere determines the number of divisions a cell can undergo, perhaps by extending telomere length we can thereby extend the Hayflick limit, or even immortalize the cell. The implications and possibilities are innumerable.

In order to understand the purpose of telomeres, it is necessary to have a basic understanding of DNA replication. DNA is composed of a series of sugars stacked on top of each other to form the backbone of the strand, and bases attached to each sugar that form base pairs with bases of the adjacent strand of DNA. Each sugar-base complex is known as a nucleotide. In DNA four bases are used; they are abbreviated by one-letter codes: adenine (A), guanine (G), thymine (T), and cytosine (C). Bonds are formed between the bases so that A binds with T, and C binds with G. The two strands of nucleotides wind around each other to form a double helix. The long double strand of DNA condenses to form a very compact structure known as a chromosome.

Each strand of DNA has a polarity associated with it; one end is known as the 3′ (three-prime) end and the other as the 5′ (five-prime) end. The nucleotide strands bind in such a way that they line up antiparallel to each other—the 5′ end of one strand is next to the 3′ end of the other strand, as shown in the figure on the next page. When a cell divides, it needs to make a copy of each chromosome so that each new cell has all the necessary information. An enzyme known as a DNA polymerase is responsible for replicating DNA. The polymerase binds to the 3′ end of one DNA strand, known as the leader strand, and unzips the double helix DNA template as it synthesizes the new strand. However, polymerase can only synthesize DNA in one direction: from the 5′ end to the 3′ end. Since the DNA strands run antiparallel to each other, the other strand, known as the lagging strand, is replicated in segments, known as Okazaki fragments, that later get fused together. Near the end of the chromosome, the polymerase may not have enough room to bind and copy the very last nucleotides on the lagging strand, so therefore the end does not get replicated. This unreplicated portion is known as the 3′ overhang and is eventually lost. Thus chromosome shortening occurs every time DNA is replicated for mitotic division of the cell.



When DNA replicates, it unzips and an enzyme called DNA polymerase "reads" the exposed information from the 3´ end toward the 5´ end. Since the strands are antiparallel, the copy thus produced runs from the 5´ end to the 3´ end. The DNA on the leading strand can be read off in one fell swoop as it unwinds, but DNA on the lagging strand must be copied piecemeal, in so-called Okazaki fragments, which are then reassembled. The last few letters on the lagging strand don't get copied, because the DNA polymerase has nothing beyond them to bind to while copying them, and they are thus lost.

Approximately 50 to 200 base pairs of DNA are lost with each division. In viable cells this process doesn't affect the core DNA, since the overhang is part of the telomeres.

Telomeres, which are simply long repeat sequences of the bases TTAGGG, serve as a buffer to allow the cell to divide many times. After some number of divisions, the telomeres get depleted. The ends of the chromosomes get too close to the genetic material and the cell enters senescence. Compared to the rest of the chromosome, telomeres are relatively small. The average human chromosome is 130,000,000 base pairs long. At conception, telomeres are about 10,000 base pairs long and at birth they have already shortened to about 5,000 base pairs. The age of the human correlates to the length of their telomeres, with the exception that humans with premature aging diseases, known as progeria, exhibit unusually shortened telomeres.

There are several solutions to the end-replication problem. The first solution is to not have any ends at all. This is seen in many bacteria and viruses that have circular DNA. These single-celled organisms can divide forever and never lose any DNA during replication. The second solution is to have special proteins at the ends of the chromosome that specify the starting point for replication, thereby assuring that the ends will be copied. This is seen in some viruses such as adenoviruses. In this way, the ends of the chromosome can be copied. The third solution is to use an enzyme to reextend the end part of the DNA that is lost. This solution is found in all plants and animals.

In humans, certain types of cells do not exhibit a replicative limit. Stem cells (cells that give rise to skin, intestine, and blood cells), germ cells (cells such as sperm or egg that give rise to progeny), and cancer cells (mutant cells that have become immortalized) can all divide indefinitely. The common factor found in all of these immortalized cells is telomerase, a ribonucleic enzyme that synthesizes telomeric DNA (TTAGGG sequences) on the ends of chromosomes, replenishing the material lost to cell division. Telomerase is not normally expressed (or activated) in human somatic tissue (cells that compose the majority of the body, such as skin, intestine, and blood cells—the cells derived from stem cells, in other words) but is expressed in germ cells, stem cells, and cancer cells, where unlimited division is needed.

Studies done on telomeres have all shown that the length of a telomere has many effects on the cell, determining, in particular, the expression of many cellular proteins. It is thought that changes resulting from these processes may contribute to some of the age-related changes of the entire organism. In 1999 a pivotal study was done by Karl Rudolph, Carol Greider, and others at the Dana-Farber Cancer Institute in Boston, in which mice were bred that lacked telomerase. The progeny of these mice contained critically shortened telomeres, which got shorter with each generation. By the sixth generation, the telomeres were so short that the mice could no longer reproduce. It was observed that these mice had much shorter life spans than normal mice, and exhibited symptoms similar to those seen in elderly humans. The mice were graying and balding, they suffered weight loss and ulcers, they took longer to heal wounds, and they experienced an increase in cancer, atherosclerosis, and osteoporosis, as well as a general decrease in their ability to respond to stress. The severity of these symptoms increased with shorter telomere length. The findings from this study demonstrate a direct link between shortened telomeres and aging of the organism.

Still, there are many differences between humans and mice. First, these symptoms are not usually seen in mice at all. Since mice have relatively short life spans and die of predation or environmental stress, they never normally show any of these signs of aging. Also, mice have much longer telomeres than would ever be used in their lifetimes, and express telomerase in somatic cells; therefore telomere shortening does not play a vital role in mice. However, humans do not have telomerase expression in somatic cells and have much longer life spans. Consequently, telomere shortening greatly affects elderly humans, more so than it affects any other organism, since modern medicine perpetually finds ways to prolong human life.

Studies are also being done on humans, especially on humans who exhibit progeroid syndromes—diseases in which children age prematurely. Children with conditions such as Werner's

syndrome and Hutchinson-Gilford's syndrome exhibit faster telomere shortening, decreased cellular divisions, and decreased ability to cope with stress. Some afflicted five-year-olds have telomeres comparable to those of an 80- or 90-year-old. These diseases are rare; their further study could provide valuable insight into the details of organismal aging.

An understanding of how telomerase affects the aging process promises new advances in tissue engineering. Biologists currently look for ways to synthesize organs for transplantation into ill patients. Using telomerase, however, cells within a patient's body could be treated and rejuvenated so that tissue transplants would not be necessary. This has almost an infinite number of applications, including bone-marrow transplants, skin grafts, and cosmetic applications, as well as improving general immunity in older patients, or patients with AIDS or blood disorders.

Such therapies also come with worries. One major concern is that prolonging the life of cells with damaged DNA would lead to further accumulation of mutations and an increase in the possibility of cancer. It is generally accepted that cancer arises from mutated cells that exhibit accelerated growth. Since it takes many divisions for the cell to accumulate enough mutations to become cancerous, cells that can only undergo a finite number of divisions are less likely to become malignant. Runaway cells will quickly come to the ends of their telomeres and die off. In this way the presence of telomeres acts to protect against early development of cancer.

This is also evident in mouse experiments. In the Dana-Farber study, the telomerase-deficient mice also had a high incidence of cancer. It is believed that their shortened telomeres cause a greater instability of their chromosomes, resulting in a higher susceptibility to cancer formation.

But telomerase can also abet cancer if it occurs in the wrong cell at the wrong time. Cancerous cells that find a way to express telomerase can overcome their replicative limit and undergo indefinite growth. Throughout the mid-20th century, many biologists noticed that, from time to time, immortal cells occasionally arose from normal, mortal cell cultures. It is now known that these cells were strains of cancer. When cells reach the Hayflick limit and enter crisis, they normally proceed to senescence and death. However, crisis is a genetically unstable stage where chromosomes, unprotected by telomeres, can randomly break and fuse. A cell in crisis is more prone to random mutation. If a chance mutation reactivates telomerase in such a cell, the cell can continue to divide, and can go on to form a tumor. For this reason, cancer is often found in elderly patients who have shortened telomeres. Most cancerous cells arise in this way, as indicated by the telomerase activity present in 85 to 90 percent of human tumors.

The fact that cancerous cells express telomerase is extremely important. The presence of telomerase in cells where it shouldn't be seen can be used as a tumor marker for early cancer diagnosis. It can also be used as a basis for a cure for cancer. Telomere inhibitors may someday be employed to deactivate telomerase in cancer cells, thereby impeding their ability to indefinitely divide. One potential problem with this method is that it may take too long to terminate a tumor's growth, and the death of the human may occur before the death of the cancerous cells. But current research looks very promising.

Telomeres also play a role in cloning. Observations of Dolly the sheep reveal that her telomeres are shorter than average for a sheep of her age. Dolly was cloned by taking the nucleus, which contains the genetic information, from a somatic cell of a six-year old ewe, and transferring it to an enucleated egg. (An enucleated egg is simply an egg from which the nucleus has been removed.) Since the DNA was from a six-year-old ewe, the chromosomes had telomeres that had already been shortened. This means that Dolly will most likely have a shorter life span. However, Dolly's offspring appear to be normal, and do not exhibit shortened telomeres. This indicates that their telomeres were elongated—most likely in Dolly's germ cells, and not during conception. Cloned mice, on the other hand, do not seem to have this problem. Because of the somatic expression of telomerase in mice, somatic-cell telomeres are not significantly shorter than germ-cell telomeres. There is a possibility that Dolly is simply an exception, and that not all sheep clones will exhibit shortened telomeres. However, if Dolly is not an exception, cloned humans will very likely exhibit shorter telomeres as well.

In short, telomeres and telomerase have several functions. They act to stabilize the chromosomes and prevent them from fraying. They are a solution to the end-replication problem of linear DNA. And, by limiting the number of times that each cell divides, they protect the organism from the accumulation of too many mutations. The consequences are that shortened telomeres result in the aging of the organism. And abnormal cells that find a way to express telomerase can lead to cancer.

Although many researchers seek a simple unified theory of aging, telomeres and telomerase are most likely not aging's only factors. Many theories attribute aging and longevity to meta-

These mice had much shorter life spans than normal mice, and exhibited symptoms similar to those seen in elderly humans... graying and balding, they suffered weight loss and ulcers, they took longer to heal wounds, and they experienced an increase in cancer, atherosclerosis, and osteoporosis.

bolic rate, changes in hormone production, mitochondrial damage, genes that determine longevity, accumulation of toxins, and free-radical oxidation.

One theory is that the number of divisions cells can undergo determines the longevity of the species. (Note that telomere length does not correlate with life span across different species.) It has been found that Galapagos tortoises live an average of 175 years and their cells undergo approximately 130 divisions. Humans have an average life span of about 80 years and human cells undergo around 50 divisions. And mice, which only live for a couple of years, have cells that divide about 30 times.

Another theory bases longevity on the total metabolic potential of the organism, measured as the total kilocalories used per gram of body weight per lifetime. For example, an elephant, which lives about 10 to 20 times longer than a mouse, has an average of 30 heartbeats per minute whereas a mouse has approximately 300 heartbeats per minute. Both species take about 200 million breaths in a lifetime and both species have a metabolic potential of about 200 kilocalories per gram. This figure is much the same for other mammals. Therefore life span simply depends on the rate at which this potential is used up. Humans are an exception, with a metabolic potential of 800 kilocalories per gram.

Another theory bases longevity on a species' ability to reproduce. After reproduction is complete, there is no longer any need for the organism. Therefore, since hormones regulate reproduction, a change in the production of hormones also regulates aging. For women, menopause represents a major change in estrogen levels that is often associated with age-related symptoms such as osteoporosis and a decline in cardiovascular health. For men, there is no one turning event, rather a gradual decline in testosterone levels with age.

Several theories base longevity on the amount of damage accumulated by the cell's DNA. One theory is based on free radicals, which are highly reactive chemical agents that oxidize membranes, DNA, and proteins. This damage accumulates over time and leads to nonfunctional cells. Similarly, toxins can accumulate in cells and disrupt their ability to function properly. Some think that damage done to mitochondrial DNA is more significant than damage done to "genomic" DNA, the DNA of the cell itself. Mitochondria are organelles within a cell that provide the energy for cellular activities. Mitochondria have their own DNA, but there are no mechanisms to repair mutated mitochondrial DNA as there are to repair genomic DNA. Therefore mitochondrial DNA accumulates mutations faster than genomic DNA.

Other theories base longevity on certain genes that help the organism cope with stress. By increasing resistance to stress, the organism can live longer. However, many genes aside from stress genes seem to play a role in longevity.

Despite this multiplicity of theories, it may be possible to indirectly correlate all aging with one specific event that is crucial to the cell's vitality. For example, the telomere theory of aging may apply to many age-related diseases that do not seem at first to be connected to shortened telomeres, such as myocardial (heart) cell death in atherosclerosis. Atherosclerosis is the most common cause of coronary-artery disease and is responsible for approximately one-third of all deaths in the United States. Myocardial cells do not divide; therefore death of myocardial cells in atherosclerosis is not directly due to telomere shortening. However, the endothelial cells of the coronary vessels, which supply the myocardial cells with oxygen-rich blood, do experience telomere shortening and death. The dead endothelial cells build up in the arteries, constricting the blood flow to the myocardial cells, thereby killing the myocardial cells through lack of oxygen.

It could also be argued that the neurons affected by Alzheimer's disease experience a similar fate. It is thought that, since neurons do not divide, their telomeres do not contribute to Alzheimer's disease. However, although there is as yet no evidence to support the possibility, Alzheimer's disease may result from the senescence of neighboring astroglial cells—cells that do divide, and that are necessary in the regulation of the neurons. Similar mechanisms may explain many age-related diseases that affect nondividing cells. More likely, however, there are many intermingled factors that together are sufficient to lead to aging.

In looking for the fountain of youth we look to all the causes of aging. Ultimately what leads to the death of an organism is almost as complex and intricate as what leads to the life of the organism. Even if we never achieve immortality by studying aging, our increased understanding of telomeres and telomerase may extend the life spans of humans and enhance our ability to live out the rest of our years as fully as possible. □

Alisa Ching is a senior in chemical engineering. Her mentor was Bruce Hay, assistant professor of biology, who studies the molecular genetics of cell death. She became interested in telomeres when Hay brought them up in his genetics class one day.

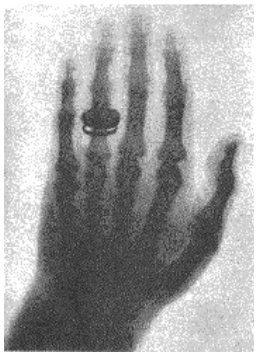
The Promise of Portable MRI

by John Ferguson

Introduction

In the summer of 1881, America's 20th president, James A. Garfield, lay on his bed slowly dying. Somewhere in his body was an assassin's bullet. Over a period of 80 days, 16 different doctors and surgeons tried to locate the bullet. They poked fingers and metal probes into the bullet hole, without success. Even the famous American inventor Alexander Graham Bell tried his hand at locating the bullet by creating a crude metal detector. After some time, he claimed he had found the bullet, and the doctors rushed to operate on Garfield to excise it. However, Bell did not realize that the president's bed contained metal springs. The doctors, of course, could not find the bullet, but created more complications which ultimately led to the president's death.

If this had happened fifteen years later, the doctors would have had no difficulty finding the bullet. A new technology had been discovered that revolutionized the world of medicine. The German physicist Wilhelm Roentgen discovered X rays by observing electric currents in a partially evacuated glass tube. These rays, now known to be high-energy electromagnetic radiation, would pass through objects that light could not. Roentgen experimented with the tube, observing metal and nonmetal objects. He could even see through doors. But more amazing than that were the results when he looked at his wife's hand. In this first medical X-ray image, her bones and metal wedding ring could be seen clearly.



X rays are still very common today. But with the development of computers, 3-D images can be reconstructed from signals received by X-ray detectors that rotate around the subject's body. This technique, known as CT (Computed Tomography) or, more popularly, "CAT scanning" (for Computed Axial Tomography) was introduced in 1972 by Godfrey Hounsfield, who was honored with a Nobel Prize in 1979 and a unit in his name, the Hounsfield, which measures the attenuation of X rays as they pass through tissue. A modern X-ray CT can collect and reconstruct a high-resolution "slice" of the body in half a second. Computers are also used to create images for Positron Emission Tomography (PET) and Single Photon Emission Computerized Tomography (SPECT). Both imaging techniques involve injecting the body with a radioactive tracer and monitoring the emissions as the radioactive substance travels around the body. However,

President Garfield is assassinated at a train depot. From *Frank Leslie's Illustrated Newspaper*, July 16, 1881.

A promising handheld MRI scanner is under development. If successful... [w]e would have a device very similar to the medical tricorder from *Star Trek*; it could measure anything, anywhere.

overexposure to ionizing radiation and X rays has been shown to be dangerous and unhealthy.

Two alternative imaging techniques have become immensely popular due to their mildness and versatility: ultrasound and MRI. These work through sound waves and magnetic fields respectively, which are safe for most people (although MRI scanners cannot be used on patients with pacemakers, cochlear implants, or aneurysm clips). Doctors can prescribe these diagnostic tests as frequently as desired, without concern about the patient's long-term health. However, the largest drawback of these two modalities is their size and their price. A common ultrasound scanner can be wheeled bed-to-bed around the hospital on a cart and costs $150,000, while an MRI scanner needs a shielded room dedicated to MRI and a cryogenic cooling system to operate a superconducting magnet, and costs about $2,000,000.

But on the horizon, two new products show the next direction of medical imaging: portable, nonionizing imaging devices at a fraction of the current prices. A highly portable ultrasound scanner is already being sold; a promising handheld MRI scanner is under development. If successful, the MRI scanner could revolutionize medicine by creating an incredible medical tool. We would have a device very similar to the medical tricorder from *Star Trek*; it could measure anything, anywhere.

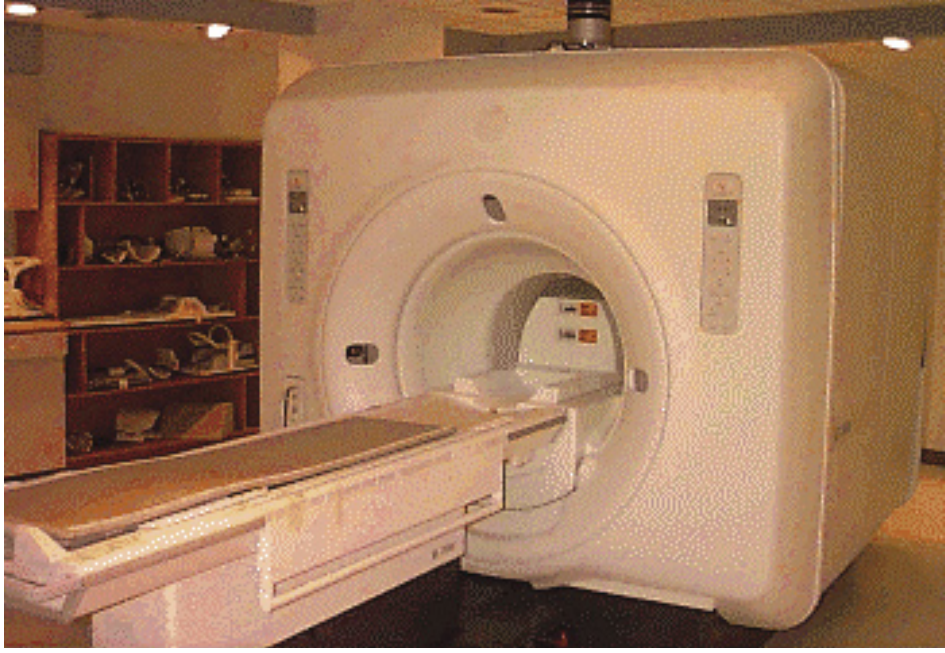
MRI History

But to see how this handheld device works and to realize its possibilities and limitations requires a good understanding of the history of the technology that led to its current state. Thousands of years ago, people in China and Greece independently discovered lodestones and used them for fortune-telling and navigation. However, their useful but seemingly magical motions were not understood until the 19th century. In 1802, the Italian scientist Gian Domenico Romagnosi found that a lodestone would move when a nearby wire conducted current; unfortunately, this result lay unnoticed for nearly 20 years, until Hans Christian Ørsted published the finding. Suddenly the floodgate was opened for scientific discovery. Countless people contributed findings to further the field of electromagnetism, including Ampere, Weber, Faraday, Hertz, Curie, and even the American patriot Ben Franklin. In 1873, James Clerk Maxwell combined all of these results into four simple equations that can be summarized as follows: electricity and magnetism are inescapably tied together. A moving charge (i.e., a current) creates a magnetic field; a changing magnetic field induces a current. The picture seemed complete and fully understood.

However, as in all of physics, the 20th century uprooted many firmly established ideas, giving rise to new possibilities. Quantum mechanics, as described by Wolfgang Pauli in 1924, gave a more complete explanation for the nature of electricity and magnetism. Nuclei of atoms display a property called spin, which is, in a sense, small-scale angular momentum. Normally, the orientation of these spins in a material is quite random. However, in the presence of a magnetic field, the nuclear spins line up parallel and antiparallel to the field, with a tiny excess—a few nuclei per million—lined up parallel. It is these few spins that can be detected, and the way they react to changing magnetic fields gives rise to the predecessor of MRI, Nuclear Magnetic Resonance (NMR).

The official birthday of NMR was in 1946, when a Stanford team led by Felix Bloch and a team from MIT led by Edward Purcell independently discovered that by adding an additional small field to the original magnetic field, interesting results would follow. By adding the second, oscillating, field, known as a radiofrequency (RF) pulse, at the proper frequency for a short period of time, some of the nuclei would absorb the energy, or resonate. After the RF pulse turned off, the nuclei would try to return to their original energies in a process called relaxation, giving off a signal that provided a great deal of information. The information included details of the sample's chemical composition and density, any movement of chemicals within the sample, and, with the use of a third, spatially varying magnetic field produced from gradient coils, the location of the chemicals within the field. Answers to what, how much, when, and where would be given without touching or damaging the sample. NMR remains to this day a premier instrument to investigate chemical structures. But it wasn't until 20 years after the discovery of NMR that the medical diagnostic possibilities were realized.

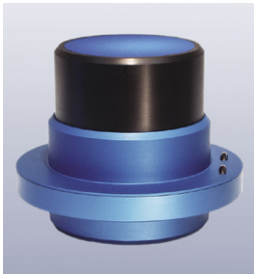
A short time after Bloch discovered NMR, he put his finger inside the magnet and noticed



A normal MRI full-body scanner. The patient lies on the table, which then slides into the hole in the doughnut-shaped magnet. Image courtesy of J. P. Hornak, The Basics of *MRI*, http://www.cis.rit.edu/htbooks/mri/.

a strong output signal. Unfortunately, he did not pursue this result any further. It wasn't until 1972 that a paper by Raymond Damadian, showing that tumors could be distinguished from normal tissue by their relaxation times, woke the world up to the possibilities of medical NMR. Another scientific floodgate opened. Numerous people started noticing all sorts of medically relevant phenomena that could be detected with NMR. In 1978, an imaging device was created based on the differences in relaxation times of different tissues. Instead of naming the new device "Nuclear Magnetic Resonance Imaging," the word "nuclear" was dropped, due to its negative connotations with nuclear warfare and nuclear radiation, and MRI was born. Now MRI scanners can be found in most hospitals and are frequently used to get detailed body images that also contain functional information. Since the first device in 1978, technological improvements in MRI have been true triumphs of both science and engineering.

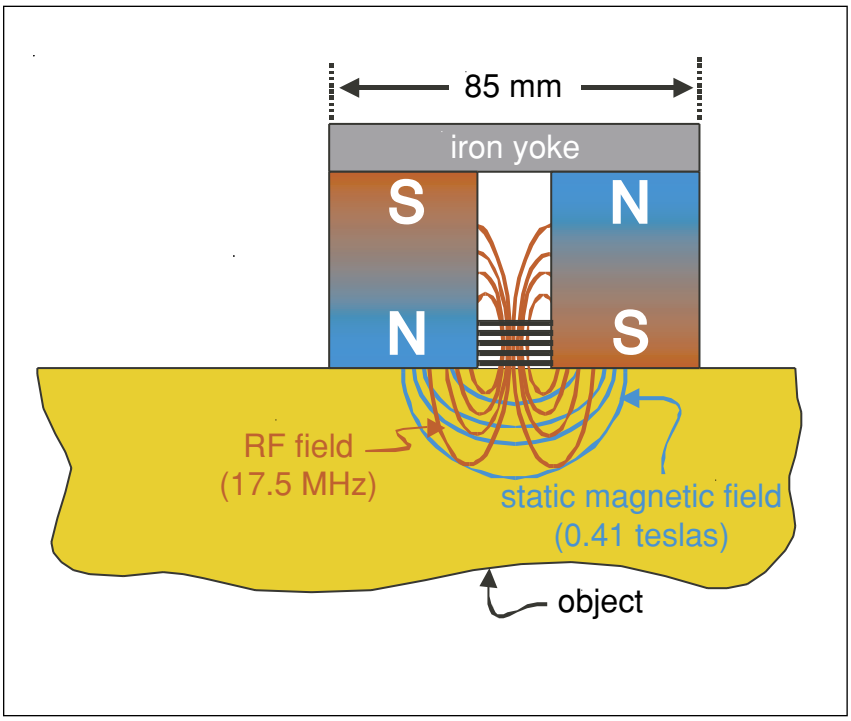
The main magnet, the most vital component of any MRI system, creates enormous design demands. The most common MRI scanner found in hospitals has a strength of 1.5 teslas, 30,000 times that of the earth's magnetic field. To get such a high field strength, a superconducting magnet is used that requires a sophisticated cooling system made from layers of liquid helium and vacuums. Precautions must be taken against a quench, which is a violent expansion of the helium due to insufficient cooling, and a safe-release system must be in place in case a quench occurs. Also, shielding must be constructed to protect neighboring rooms (and adjoining floors!) from the strong magnetic field, which can erase credit cards, affect computer memory and displays, and even kill people who have pacemakers. This shielding can involve about 20 tons of material to block the fields, as well as additional magnets that reduce the outside fields, and sacrifices some of the desired field strength inside the magnet. Other systems that involve complicated design are the shim system, which creates magnetic fields that are homogeneous; gradient systems, which give better spatial resolution and faster imaging; and RF systems that resonate the nuclei within given specifications. All of these issues contribute to the overwhelming cost of an MRI system, averaging $2,000,000 for a new 1.5-tesla installation with about $300,000 in yearly maintenance. In addition, many people believe that the best way to improve the MRI scanner is by increasing the field strength to 3 or 4 teslas. This would improve resolution and scan time, but with a significant increase in the system's size, complexity, protective equipment, and, of course, price.



The NMR-MOUSE is about the size of a prescription bottle. This is not your father's MRI!

The NMR-MOUSE

Enter the NMR-MOUSE (MObile Universal Surface Explorer). This handheld, one-kilogram unit holds promise as a portable MRI device that would cost less than $1,000. Its design is very simple: two antiparallel magnets, held apart by a block of iron and an RF coil, and two gradient coils in the gap between them. The two magnets are made of a rare-earth metal that generates a high magnetic-field strength for their size; the iron block, called a yoke, serves to increase the field strength. The RF and gradient coils serve the same purpose as in a normal MRI scanner—to stimulate the atomic nuclei within a specified region. However, the most important feature in the NMR-MOUSE is the absence of all the extra equipment found in a typical scanner. There are no shim coils, no shielding, and no cryogenic cooling system, since two permanent magnets are used instead of a superconducting magnet. This results from a philosophy entirely different from that of mainstream MRI—namely, that of using a smaller overall field strength, exploiting the stray



A schematic of the NMR-MOUSE being applied to the surface of a solid. The set of parallel black lines between the magnets is the RF coil.

field instead of the main field, and converting the "disadvantage" of inhomogeneity (where the magnetic field is not perfectly uniform) into an advantage.

The inventors of the NMR-MOUSE, Peter Blümler and Bernhard Blümich (both then at the RWTH in Aachen, Germany), were led to design and construction of the NMR-MOUSE in 1993 by two simple realizations: "typical MRI contrast (relaxation, diffusion) doesn't rely on homogeneous fields" and "localization procedures imply inhomogeneous fields." Instead of using the traditional approach of creating a completely homogeneous field and adding systemic variations, they found that a naturally inhomogeneous field with consistent responses would work as well. Unknowingly, they had just entered the world of so-called fringe-field NMR. The first few magnets that were used in NMR had significant inhomogeneities; scientists designed their experiments around this fact. However, as technology improved, the vast majority of researchers looked to bigger and more homogeneous magnets. Even so, a few people, most notably Jasper Jackson, did research with smaller magnetic fields—down to just using the earth's natural magnetic field—and strange combinations of magnets that would create regular fields outside of two magnets. These devices found applications in detecting signals in dangerous places—using the magnet to peer through a wall into a dangerous room, for example—or inaccessible ones, such as logging a well, in which an NMR device is dropped down a very deep borehole to make moisture measurements and detect oil in rocks miles below the surface. These instruments were providing solutions that the larger, superconducting NMR spectrometers could never attempt. So, what seemed like an original idea by Blümler and Blümich—to use a small system to make measurements outside of the main magnetic field—was actually closely related to work done 40 years before. Nevertheless, with the use of more powerful rare earth magnets and efficient computer-aided designs, new possibilities have opened up, most notably in imaging.

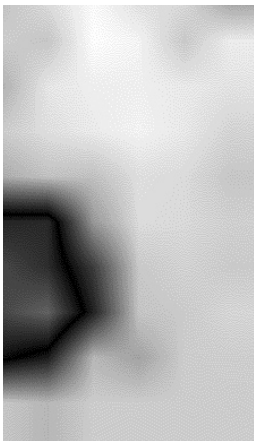
The NMR-MOUSE brings to the table a small yet potent design. With dimensions of 9 × 2 × 2 centimeters and a weight of 1.25 kilograms, it is truly handheld. All it needs to operate is a cable connecting it to a computer, so it is highly portable. The NMR-MOUSE can image an ellipsoid 16 × 1 × 2 centimeters. At the surface, a field strength of 0.5 teslas can be found. Incredibly, as an imaging tool, it can scan with 100-micron (0.1-millimeter) resolution. However, the NMR-MOUSE's biggest limitation is penetration depth; it can only image objects very close by. Currently, the maximum penetration depth is 5 millimeters, with closer objects generating stronger signals. This creates a large restriction on the types of objects the NMR-MOUSE can image, and on its general applications.

Even so, the NMR-MOUSE has found both traditional and novel uses. Blümler and Blümich see applications in nondestructive materials testing, process control, agriculture, food processing, and medicine. Theoretically, any material that contains protons can be detected by the NMR-MOUSE, but polymers (e.g., plastics), elastomers (e.g., tires), and biological materials (e.g., humans) give the best results. And two new applications are possible now, due to the portable and inhomogeneous-field nature of the detector. First, imaging can be done on substances that contain ferromagnetic materials, such as steel-belted tires. An ordinary NMR device would not be able to image such a thing without serious damage and/or signal interference occurring. In fact, strangely enough, the steel cords in tires have been shown to improve the signal for the NMR-MOUSE. Second, because the NMR-MOUSE can be placed in any desired position, directional patterns, called anisotropies, within the material can be measured. Tendons have dense collagen structures that are normally very difficult to measure using traditional NMR. Even so, the NMR-MOUSE has successfully performed accurate measurements on the Achilles tendon in human subjects. This is because the scanner can be manually adjusted to the "magic angle" of 54.7 degrees, where a robust measurement of anisotropies can be made. More experiments are required to develop these measurements into a useful diagnostic tool. Also, the NMR-MOUSE has produced a cross-sectional image of a pork leg, obtained from a butcher, where muscle, bone, and marrow can be easily distinguished. Of course, this is not on a par with modern MRI images, which take incredibly detailed pictures

A prototype of the NMR-MOUSE testing a tire.

of human structures. However, compared to older MRI images produced by multiton machines, the 1.25-kilogram NMR-MOUSE performs quite impressively.

There is another imaging modality that is enjoying success with its portability. Ultrasound has been used as a medical device since the 1950s. Since ultrasound uses sound waves, it is like MRI in being noninvasive and nonionizing. Ultrasound is safe enough to use for viewing the fetus inside a pregnant woman's body without any concern for the baby. It can detect solid structures in the human body and analyze the movements of fluids, such as blood. However, its biggest disadvantage is that it cannot see behind bone or gas—it can't see behind the air in your lungs, for example. A modern ultrasound scanner has two components: a transducer that emits and receives the sound waves and a computer-based data-processing unit. The transducer is handheld, while the computer is normally very large and needs a skilled technician to operate it. However, SonoSite has just developed an ultrasound scanner that weighs 2.5 kilograms for the transducer, computer, and display, is portable, and is easier to operate than traditional systems. Doctors can take the scanner anywhere to make measurements without carrying a large computer-based system. In addition, this new scanner costs only about $25,000, compared to the $150,000 to $300,000 price tag for larger scanners. How can the NMR-MOUSE compete with this new device?



A 5 × 3-centimeter cross section through a pork leg, as seen by the NMR-MOUSE. The black ring is bone; the gray within it, marrow; and the light gray outside it, meat.

At the moment, the NMR-MOUSE cannot compare with the new SonoSite scanner in terms of usage and portability. First of all, it is important to realize that ultrasound and MRI are different imaging modalities; they each have significant advantages and disadvantages. Also, even though SonoSite's ultrasound scanner is much better developed than the NMR-MOUSE, there is a large company behind SonoSite's new system that has provided all of the necessary capital to miniaturize the device. Recall that traditional ultrasounds have handheld transducers and big computers. SonoSite's main contribution has been to make the large computer smaller. They haven't changed the fundamental ultrasound technique. On the other hand, the NMR-MOUSE was developed through the intellectual curiosity of two scientists who had to develop new techniques and designs with minimal funding. They were trying to find alternatives to large and expensive MRI scanners. Fortunately, Bruker, a giant in the NMR and MRI industries, has shown interest in the NMR-MOUSE and has begun collaborating with the scientists. With this corporate sponsorship, the NMR-MOUSE has an opportunity to really blossom. New designs will minimize the penetration limitations that have given the NMR-MOUSE so many restrictions. Maybe in the near future, we will be diagnosed and treated with portable MRI and ultrasound devices by doctors in their offices without having to go to the hospital and be charged a few thousand dollars. Even though physicians will not carry *Star Trek* medical tricorders anytime soon, we are definitely a step closer. Now we just have to work on teleportation. □

John Ferguson is a senior in physics. His mentor was Michael Tyszka, a visiting associate in biology at Caltech and an assistant professor of research at the City of Hope, in whose lab Ferguson worked last summer. This summer took Ferguson farther afield: he was one of four Caltech undergrads to ride the "Vomit Comet" at NASA's Johnson Space Center (see Random Walk).