

Volume 6 Spring 2002

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MIT

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MIT

UNDERGRADUATE RESEARCH JOURNAL

Volume 6, Spring 2002

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Tech Talk.

Welcome to the spring 2002 issue of the *MIT Undergraduate Research Journal (MURJ)*. In this sixth issue of our interdisciplinary journal, we have included both research reports discussing new and exciting work in fields as varied as ecology and stem cell research and feature essays that explore several humanitarian and environmental crises such as the conditions of refugees in Eritrea and the dangers posed by the continuing use of land mines.

As always, the reports and essays in this issue are written in a manner that maximizes each report's accessibility to all members of the MIT community. We hope this will enable individuals from diverse fields to learn about research in disciplines other than their own and about the debates taking place both in the academic and public worlds on how science may be better applied to alleviate social concerns.

We strive to present to the MIT community a forum through which ideas about both scientific research and public policy may be exchanged and debated. We would like to thank all those who help us meet our goal: We acknowledge the thoughtful advice and assistance of our advisor, Dean Les Perelman, the professors who contribute valuable time and effort in reviewing our work, and the continued support of *The Tech*.

If you would like to contribute to future issues of *MURJ*, we invite you to join us or submit your reports for our Fall 2002 issue. All submissions for the next issue will be due at the beginning of September. Please e-mail murj-public@mit.edu or visit our web site, web.mit.edu/murj/www, if you have further questions or comments.

Sincerely,

The editors of *MURJ*

MIT Science News in Review

[Biological Sciences]

A Step In the Fight against Cancer

MIT researchers have unexpectedly come across a method to treat a rare abdominal cancer. Although research was intended to be on basic cancer study, Dr. David A. Tuveson, professor of biology at MIT, has found an existing drug that heals those afflicted with Gastrointestinal Stromal Tumor (GIST).

The drug, Gleevac, has been clinically tested and has dramatically helped people with GIST. Tuveson worked with other colleagues from MIT and other institutions to show that the drug ST1571 stopped GIST. Through an inhibition of genetic mutation in the c-KIT receptor and, in some instances, destruction of cancerous cells, their work has helped to eliminate the disease.

Treatment of leukemia with ST1571 had focused on stopping the kinase enzyme that is responsible for the disease—Tuveson and his colleagues hypothesized that the drug might be effective against a similar mechanism in GIST.

Indeed, the 5,000 Americans that are annually affected by GIST may now have hope. Before current research, GIST could not be treated by any traditional means besides surgery. However, for those in developed stages of illness, such surgery is nearly impossible, and thus they are left with little help for a cure.

The work emphasizes the importance of basic research in finding more effective medical solutions to various illnesses, while also highlighting the importance of using basic observation, analysis, and critical thinking to apply existing solutions to new situations. The application of ST1571 to leukemia also raises support for the targeted approach to cancer, namely, the explicit focus on cancerous cells rather than destroying all the cells.

Thermotherapy Provides New Hope for Breast Cancer Treatment

Radar technology, first developed at MIT to detect missiles, is now being applied to the treatment of breast cancer. According to initial results from a Phase II trial, microwave radiation can kill tumor cells without harming the skin.

This novel therapy—termed “thermotherapy”—is based on technology first invented by Dr. Alan J. Fenn, a senior staff member at MIT Lincoln Laboratory.

The radiation was originally used to detect missiles and to protect against enemy jamming. But its ability to selectively kill cancer cells suggests that it could supplement or even replace more conventional approaches like surgery, x-ray radiation, and chemotherapy, which are less effective and have serious side effects.

Thermotherapy is effective because tumor cells contain unusually large amounts of water and ions, making them more susceptible to microwave energy than normal cells. The cancer cells are therefore preferentially destroyed. “After thermotherapy treatment, we are seeing a significant number of breast cancer cells killed without damage to the skin,” said Dr. Robert A. Gardner, a breast surgeon at Columbia Hospital in Florida.

Forty-three women with early-stage breast cancer are participating in the Phase II trials at three hospitals: Martin Luther University (Germany), Harbor-UCLA Medical Center, and Columbia Hospital. The study should be completed in 2002.

Gene Therapy Corrects Sickle-Cell Disease in Mice

In the December 14, 2001, issue of *Science*, Assistant Professor Philippe Leboulch, research affiliate in the Harvard-MIT Division of Health Sciences and Technology, and colleagues reported the development of a gene therapy method that treats sickle-cell anemia in mice.

Sickle-cell disease is caused by a point mutation in the beta globin gene that contributes two protein units to hemoglobin. When the mutation is inherited from both parents, abnormal hemoglobin molecules result. In periods of low oxygen, the mutant protein chains interact and bind to each other, causing red blood cells to collapse into sickle shapes that get caught in blood vessels, blocking blood flow and leading to anemia, stroke, and organ damage.

The therapy utilizes a modified lentivirus (a retrovirus) as a vector to transport an antisickling beta globin gene variant into the resting stem cells in bone marrow. The lentivirus is modified to include a flap of DNA from the HIV-1 virus. This improves the delivery. Furthermore, expression regulation elements surrounding the gene were optimized to increase expression in red blood cells.

“Usually when a copy of a new gene lands in the genome this way, it is strongly influenced by its surroundings and often gets silenced. But when the expression level is very high, and spread evenly through the cells, as it is in this case, the gene can do its work,” Leboulch said.

Mice that underwent this treatment after having their bone marrow eliminated by radiation were found to have 99 percent of their red blood cells expressing very high levels of the new gene less than 10 months after transplantation.



Dr. David A. Tuveson

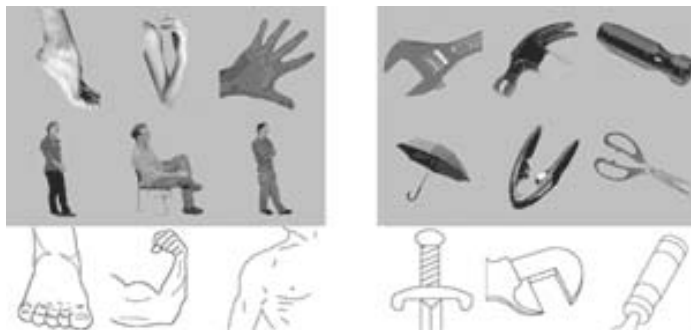
Two different models of sickle-cell disease were tested in mice. In one model the gene therapy caused an eightfold reduction in sickled cells. In the other model, sickled cells were completely eliminated. Other symptoms of sickle-cell disease were also corrected in mice, such as enlarged spleens, urine concentration defects, and dehydration of red blood cells.

Future research includes the development of large-scale production of nonreplicating viral vectors and the investigation into bypassing the toxic irradiation of bone marrow for the success of the therapy.

Brain Region Identified that Responds to Human Form

In consortium with the University of Wales, researchers at MIT have identified a region of the brain that responds strongly and primarily to images of the body and its parts.

The Extrastriate Body Area (EBA) is located in the lateral surface of the brain called the posterior superior temporal sulcus. It



may be part of a larger network of close areas that are key in social perception and cognition.

This discovery highlights why human brains have regions that process “faces, places, and bodies, but apparently not spiders, cars or food.” Neuroscientists are attempting to determine whether the mind exists as a single multipurpose system or as part of a complicated web of distinct systems for mental tasks.

Researchers are excited about the technology, which made possible the explorations of brain activity and are “now making progress at a historically unprecedented rate in understanding the functional organization of the mind and brain” (Professor Nancy Kanwisher).

[Physical Sciences]

MIT Researcher on Team for Possible 2006 Pluto Mission



Professor Richard P. Binzel of the Department of Earth, Atmospheric and Planetary Sciences was chosen by NASA as a member of the Pluto-Kuiper Belt (PKB) mission sciences team slated to visit Pluto and the Kuiper Belt in 2006.

Pluto is the last planet in the solar system to be visited by a spacecraft. The goal of the mission is to observe global geology and morphology, map the planetary surface composition, and characterize Pluto’s neutral atmosphere and its escape rates. “One of the most exciting aspects of this mission is that it will complete the first reconnaissance of our solar system by closely examining Pluto and one or more Kuiper Belt Objects,” Binzel said.

The PKB mission aims to reach Pluto before 2020, simply because as the planet moves farther from the sun its atmosphere may freeze out and to catch the planet before it moves into shadow, impeding the chance to take photographs in reflected sunlight. The 2006 launch date facilitates the slingshot trajectory of the spacecraft past Jupiter toward the outer solar system to fly by Pluto and Charon between 2016 and 2018. By 2026, the spacecraft will pass the Kuiper Belt, the distant home of comets believed to be the source of Earth’s water and the chemical building blocks of life. Kuiper Belt Objects (KBOs) are small, icy bodies with diameters of approximately 100 kilometers (62 miles), which make them difficult to study from Earth.

“Visiting Pluto and other Kuiper Belt Objects would be like visiting a deep freeze containing samples of the most ancient material in our solar system, the stuff that all the other planets including Earth were made of,” said Colleen Hartman, solar system exploration director in NASA’s Office of Space Science. “But the most exciting thing about going to an unexplored planet is what we may find there that we’re not expecting.”

MIT, NASA Scientists Team Up to Track Ice on Mars

Years ago, then-Vice President Dan Quayle made the humorous but inaccurate remark, “We have seen pictures where there are canals, we believe, and water [on Mars]. If there is water that means there is oxygen. If oxygen, that means we can breathe.” Although that remark appeared quite premature, MIT and NASA scientists have since investigated more about the “water” (actually ice and snow) on Mars and what it might implicate.

The team of David E. Smith of NASA’s Goddard Space Flight Center; Maria T. Zuber, professor of Earth, Atmospheric and Planetary Sciences (EAPS) at MIT; and EAPS research scientist Gregory A. Neumann has collaborated to provide for the first time measurements of the density and thickness of seasonal snow and frost on Mars. As published in the December 7 issue of *Science*, Smith, Zuber, and Neumann found that they could make extremely precise observations of seasonal frost deposits on Mars using NASA’s Mars Global Surveyor (MGS) spacecraft.

“Snow on Mars is denser than it is on Earth, being more ice-like than powdery,” Zuber told *Tech Talk* reporters. He and his colleagues chose the MGS craft so that they could use a laser-based altimeter and a radio tracking system to determine minute changes in elevation and gravity on Mars, allowing the team to make the first direct measurement of frost density on the planet. The group reported that over the course of one Martian year



(about 687 Earth days), about one-third of Mars' carbon dioxide atmosphere freezes in the northern and southern hemispheres. By measuring changes in the height of the Martian surface every two weeks, the NASA and MIT researchers showed that even minute changes in surface height correlate with the expected times of deposition and evaporation of carbon dioxide from the planet's surface. By tracking small changes in the gravity field of Mars, the team was also able to measure the density of surface frost deposits.

"Snow on Mars is composed of dry ice, and last year it reached a maximum depth of 1.5 to 2 meters near both the north and south poles," said Smith, who was lead author of the study. Smith's results, along with those of his colleagues, will likely provide a better understanding of Mars' atmosphere, as well as make it easier to design future spacecraft intended to land on the surface of Mars. The MGS spacecraft used in the experiment is already being used for this purpose and is now engaged in an extended mapping mission of the surface of Mars.

In addition to offering clues for future lander design, the results from this experiment offer the "first step toward understanding past climates on Mars," said Neumann. Using data from this study, scientists might be able to track what the atmosphere on Mars was like hundreds of years ago or even offer clues to the origins of Dan Quayle's notorious canals.

"Quantum weirdness" Provides More Accurate Measurement of Position

Instead of relying on the accuracy of researchers' measurements of the initiation and arrival times of a pulse, scientists can find the position of an object using quantum mechanics, the accuracy of which is based on how many photons can be prepared within a quantum pulse. Postdoctoral associates in MIT's Research Laboratory of Electronics call this process "quantum positioning system" (QPS).

Current techniques for locating the position of an object use clock synchronization; one can determine an object's position by sending pulses of light or sound from one place to another or by determining the arrival time of the pulses at a certain reference point.

According to Seth Lloyd, associate professor of mechanical engineering, "Counterintuitive features of quantum mechanics such as entanglement and squeezing can be employed to overcome the classical limits in these procedures."

Entanglement occurs when quantum correlations are greater than classical mechanics, while squeezing brings quantum noise levels below their original limit.

The accuracy of conventional techniques is proportional to the bandwidth of the pulse multiplied by the square root of the power in the pulse. Since it depends on the number of photons in a quantum pulse, in the "quantum quirk," 100 photons increased the result by 10 over the classical limit, and a million photons yields a thousand times better result.

Another use would be to implement quantum cryptographic schemes that would not allow an eavesdropper to obtain information on an object's position, benefiting high-security users. In

the near future, people could be using basic quantum building blocks in order to measure various objects' whereabouts.

Nepal Water Project

In 2000, some 1.7 billion people worldwide lacked access to clean drinking water, according to UNICEF. About 44,000 children under 5 die every year in Nepal from waterborne diseases. The poor quality of the water has caused developmental diseases in children. The women who run the families are saddled with carrying much needed water in rural areas, knowing that the very water they tote is causing illness in their families.

An MIT project in consortium with local Nepalese agencies and organizations is working to develop a solution to the water problem. Water engineer Susan Murcott spearheaded the project, which has become a large Masters of Engineering program with thesis projects in Nepal.

The problem has two main sides: removal of particles and microorganisms that cause diseases and finding a viable water-treatment system for a developing country with technical performance, "low or no" cost, sustainability, and social acceptance and adoption.

The search for a solution to the water contamination problem included exploring other MIT scientists' research. Amy Smith (MIT Edgerton Center instructor and graduate) invented a nonelectric-powered incubator for detecting microbial contamination. Nepal does not possess a reliable electrical source to power the standard microbial incubator. And Junko Sagara has studied the filtration methods in Nepal and examined the use of a stainless steel unit that works but is too expensive for the Nepalese to afford.

The best recommendation so far is SODIS (household solar disinfection). This is promising but still limited by the inclement weather in Nepal because the system runs on solar power. Work by other institutes includes a BioSand Water Filter (BSF) created by Professor David Manz of the University of Calgary, Canada. This system strains water through layers of sand, removing the sand and microbes; it is promising but requires much calibration and maintenance.

Carbon Credit Policy Examined

A feature of the Kyoto Protocol on Climate Change could irreversibly damage the welfare of the world's oceans. Carbon trading limits the amount of the greenhouse gas carbon dioxide that a country may emit. A country that has exceeded its quota can buy carbon credits from another country that has not reached its emissions quota. The purchase of such credits from commercial industries that have found ways to remove carbon from the atmosphere makes the credit policy dangerous.



One technique for removing atmospheric carbon is known as ocean fertilization. Experiments over the last 10 years show that fertilizing parts of the ocean increases phytoplankton, which as part of their normal life cycle remove carbon dioxide from the atmosphere.

MIT Professor Sallie W. Chisholm objects to this technique because “a fertilized part in turbulent ocean currents is not like a plot of land.”

She contests claims that ocean fertilization is easily controlled or a process that occurs naturally in nature or environmentally harmless in the long term. She worries about the slippery slope that the current interest in ocean fertilization would lead to. “If it’s profitable for one, it would be profitable for many, leading to exploitation and a classic tragedy of the commons,” she said.

Rhodium-Based Molecule Leads to Photosynthesis in a Beaker

The August 31, 2001, issue of *Science* covered the advent of a potentially cheap and clean future energy source through the creation of a rhodium-based molecule that produces hydrogen gas when submitted to a catalyst and a zap of light. “We have been seeking a future alternative fuel source by studying the principles that govern the conversion of photon energy into chemical potential,” said Professor of Chemistry Daniel G. Nocera and former MIT graduate student Alan F. Heyduk. “Our strategy is to use the energy of sunlight to drive reactants uphill to energy-rich products, thus harnessing the sun’s energy to create a renewable energy source in the future.”

When rhodium is dissolved in a hydrohalic acid solution and bombarded with light, the metal acts as a photocatalyst. The structure of the rhodium compound allows it to break chemical bonds in the hydrohalic acid to release hydrogen gas and halogen by-products. The halogen by-products are trapped and recycled into the reaction. “In the leaf, sugar and oxygen are energy-rich products. In our beaker, the sought-after fuels are hydrogen and a halogen, produced catalytically from the photochemical splitting of hydrohalic acid,” Nocera said.



Professor Daniel G. Nocera

The goal of the research reported in *Science* was to convert light into hydrogen by trapping photon energy in a structurally well-defined molecule. Although this system is not as complete or efficient as photosynthesis, it has surpassed the use of massive solid photocatalysts previously developed to achieve the goal of cleanly converting sunlight into chemical energy. “As it stands, we have performed half of the photosynthetic reaction by generating hydrogen. If we can now get the other half of the process to work [getting the halogen], we would have a framework for future energy production,” Nocera said.



[Technological Sciences]

2.009, a One-of-a-Kind Course

2.009 “Product Engineering Processes,” the mechanical engineering senior design course, is one of the most exciting and demanding courses at MIT. Working in teams, students are challenged to use both their engineering skills and their interpersonal skills to build several wireless, remote-controlled products. In addition to designing and building the products, the students are also required to draw upon their knowledge of business and marketing in order to present their products to a group of invited guests.

In this year’s 2.009 class, students from six different teams came up with a snowblower, a wheeled and turreted water gun, an amphibious tanklike toy that shoots foam discs, a water rescue vehicle, a bartending machine, and a rock-climbing device. Although the process of building these products can be grueling, students generally have a positive attitude toward the course. One of the 2.009 students, Greg Townsend, believes that the course is “an immense challenge, but it teaches you more than any of the other courses.”

The lead instructor is Professor David Wallace of mechanical engineering. The section instructors are professors Woodie Flowers and San-Gook Kim; lecturers Richard Fenner, Hamid Hashemi, David Meeker, and Doug Vincent; and visiting engineer Chris Magee. The course sponsors are the Lemelson Foundation, United Technologies, Ford Motor Co., and General Motors.

Unveiling the Myths behind the Collapse of the World Trade Center

The collapse of the World Trade Center (WTC) towers on September 11, 2001, was a tragic yet scientifically intriguing event. In its December, 2001, issue, *JOM: The Member Journal of The Minerals, Metals, Materials Society* attempts to elucidate the events that brought about the eventual complete destruction of the twin towers.

There were three major events that occurred throughout the incident. They were the airplane impact with damage to the columns, the ensuing fire with loss of steel strength and distortion, and the collapse, which occurred inward without significant tipping. Although the towers were built in the mid-1960s through

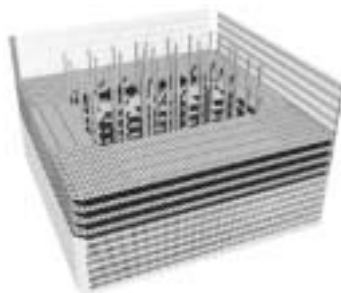


the early 1970s, they represented a new approach to building skyscrapers because they were extremely lightweight and involved modular construction methods that accelerated the



building schedule and reduced the cost. In any event, the buildings were designed to withstand a 225-km/hr hurricane and resist 2-kPa wind load, a lateral load of 5,000 t. So, while the airplane impact destroyed several columns in the WTC towers, the ensuing fire was the principal cause of the collapse. The temperature of the fire caused the WTC's steel columns to lose strength, and it also made the building lose its structural integrity due to the distortion of the steel from the nonuniform temperature in the fire.

Although the authors of the article claim that the towers were not defectively designed, they point out that there will undoubtedly be a number of changes in the building codes as a result of the WTC catastrophe.



MIT Program Works toward Sustainable Development in China

By 2094, scientists predict that housing in China will consume one out of every nine units of energy available to the world. Hoping to lower future energy consumption, MIT is collaborating with groups from Switzerland, China, and Japan to increase Chinese building efficiency.

The MIT program is designing and evaluating prototypes for urban housing sites in Beijing, Shanghai, and Shenzhen. The goal is to use passive and natural means to develop sustainable improvements in Chinese buildings.

For example, natural cooling due to wind and



low nocturnal temperatures can theoretically replace air-conditioning. Similarly, glass-covered terraces can serve as "buffer zones" that trap solar heat during the winter, thus reducing the energy required for mechanical heating.

The researchers use computer simulations of air velocity around the buildings, taking into account open windows, roof slope and edges, building geometry, and vent placement. The results are incorporated into designs that optimize ventilation during the summer and insulation during the winter. The site in Shenzhen, for instance, is designed to promote natural airflow due to pressure differences between the buildings.

In Beijing and Shanghai, the planned buildings will also include skip-stop elevators, which stop only once every three floors and therefore use less energy.

Although the MIT program is focusing on China, the resulting nascent technology should be useful in developing countries all over the world. This ambitious project is therefore poised to significantly decrease global energy consumption.



MilliWave Viscometer Wins R&D Award

Paul Woskov's MilliWave Viscometer wins him his fifth R&D award in seven years. The MIT Plasma Science and Fusion Center principal research engineer developed the instrument to aid in the cleanup of cold war remnants of radioactive waste deposits. The cleanup of such wastes is the largest civil works project in U. S. history with over \$40 billion already spent in its cause.

The MilliWave Viscometer measures the viscosity of molten materials. The new instrument is unique because it is able to function at the high temperatures of molten glass and metals. "Its maximum temperature of operation is more than 1,000 degrees Celsius high than viscometers currently on the market." Woskov's colleagues believe that the invention will reduce the costs of environmental cleanup and the manufacturing of many material products.



Converting Heat to Energy without a Generator

For years, scientists have attempted to convert heat directly to electricity without using the moving parts of a generator. Associate Professor Peter Hagelstein of the MIT Department of Electrical Engineering and Computer Science along with Dr. Yan Kucherov of ENECO, Inc., have announced the first such device, which is virtually silent, vibration-free, and low in maintenance costs.

As they reported during the November 27 poster session of the Materials Research Society, the new device is two times more efficient than the next best converter of heat to electricity, which means that the technology could greatly impact the conversion of heat to electricity in power plants or automobiles. "That such good results were obtained in the first generation of the new device technology," write Hagelstein and Kucherov, "indicates that the general approach has great promise for improved performance in more mature implementations." For instance, the device might be used to convert a car engine's heat exhaust into usable electricity for the air-conditioning system.

Hagelstein and Kucherov based the design of their converter on the basic vacuum tube, in which heat causes electrons to boil off a cathode and absorb onto a cooler anode, converting heat to electricity as electrons travel "uphill" against the electric field gradient. The high manufacturing costs and high operating temperature of vacuum tubes reduced their applicability, but Hagelstein and Kucherov's new technology uses a semiconductor to traverse the gap between the cathode and anode in the tube and make the system more efficient.

"I believe that these new devices represent the first big step in performance of these devices," said Professor Louis Smullin of the Department of Electrical Engineering. "In the '50s there was much hope that direct conversion of heat to electricity would open up a new era, but it was not to be. With these new devices, maybe these dreams will come true."

ENECO will develop the device, and one patent has already been issued.

Transportation Challenging Environmental Sustainability

The growing number of pollutants emitted from transportation vehicles is leading the world into environmental degradation. MIT researchers and Charles River Associates have conducted the "Mobility 2001" project (see <http://lfee.mit.edu> for more information), which is the first stage of a three-year study authorized by the World Business Council for Sustainable Development (WBCSD). This study was designed to find the amount of transportation that the environment could sustain in 2030, as well as methods for attaining this goal.

Drawing on passenger, freight, ground, air, and water transport, the study examined the effect of people's mobile tendencies on economic development, social welfare, and environmental quality. Researchers found that the automobile is the preferred mode of transportation for many people in urban and suburban areas. With a rapidly growing, richer population, the large number of cars and pollutants clog the small number of roads, resulting in environmental damage, high-energy usage, and safety hazards. Other concerns include the construction and usage of roads, bridges, airports, and harbors, as well as the efficiency of consumer transport and airplanes' high-altitude release of carbon compounds. Also, more than 96 percent of the world's trans-

portation depends on petroleum, which yields high-energy fuels, but hugely contaminates the air.

The researchers reasoned that they must solve seven problems in order to maximize the environment's capability to sustain mobility. These problems include ensuring that transport meets people's needs while enhancing quality of life and supporting economic development; modifying vehicles to meet new standards concerning air-pollutant emissions, amount of fuel used, load-carrying capacity, and ownership structure; reconstructing public transportation; creating a more efficient infrastructure for planning, building, and managing mobility; reducing carbon dioxide emissions; fixing problems between passenger and freight transport; and providing options for eradicating congestion.

Combined with technology, political determination, and institutional capability, human beings must help resolve the conflict between their mobility and their environment.



Commodified Light

Like the recent crisis in California, the Northeastern states and electricity corporations may soon face massive energy shortages. New regulations from the Federal Energy Regulatory Committee require the three major energy grids of the Northeast (New York, New England, and "PJM" [a limited-liability-company]) to integrate their services. Despite the intent of such rules, implementation may be difficult.

However, MIT scientist Dr. Marija Ilic of the Department of Electrical Engineering and Computer Science and her colleague, Leonard Hyman of Salomon Smith Barney, suggest an alternative. Their approach would focus on an "Interregional Transmission Organization" (IRTO) as the operator of a network between the grids. This trading system, similar to a pollution credit scheme, would allow companies to buy or sell transmission capacity.

This market solution would maintain flexibility and maximize the decision-making abilities of all companies involved. Ilic and Hyman used computer modeling to show the inexpensive and relative reliable nature of their approach. In contrast to the current solution, which proposes to use the PJM grid as an industry standard, their idea would focus on newly developed software and protocols. This would prevent reliance on old industry standards, helping all parties involved.

Despite the promising outlook for this approach, continued work by scientists, engineers, and economists is necessary for future success and progress toward implementing FERC regulations. Ilic and her research associates are working toward more alternative solutions that might facilitate implementation of a more integrated electricity grid system. ■

World Science News in Review

[Biological Sciences]

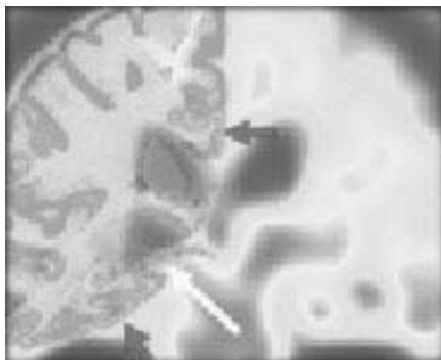
Better Imaging Technique for Alzheimer's Patients

Until now, the brain irregularities of an Alzheimer's patient could be studied only after death. A research team at UCLA reports in the *American Journal of Geriatric Psychiatry* that they have been able to image the plaques and tangles associated with Alzheimer's in a living patient.

These plaques and tangles are "the best marker for disease progression," according to co-author Dr. Gary Small, UCLA professor of psychiatry and biobehavioral sciences. The imaging was accomplished by injecting a protein (FDDNP) containing a radioactive tracer into nine Alzheimer's patients, and subsequently taking Positron Emission Tomography (PET) scans of their brain lesions.

However, scientists have found that these plaques and tangles could also be present in healthy people. This means the new technique is more valuable for future research than as a diagnostic tool. It could help scientists monitor the effects of trial medications on brain pathology. "We're going to need a way to see whether or not the drugs are working rather than wait to see if the patient develops the disease," said Dr. Steven DeKosky, director of the Alzheimer's Disease Research Center at the University of Pittsburgh.

According to DeKosky, the new technology should contribute significantly to Alzheimer's drug development "within the next two to three years."



Cloning Under Fire: Dolly's Got a Problem

Recent reports have shocked active proponents of cloning—Dolly, the 6-year-old cloned sheep, has arthritis in her left hind leg, hip, and knee. Ian Wilmut, one of Dolly's creators, was disappointed with the news, but noted that the problem may be a coincidence rather than a side effect of the cloning.

However, others have raised questions about the arthritis, a problem that generally corresponds to older age. Despite Dolly's successful pregnancy, this health problem has been used to undermine the scientific credibility of cloning. Some scientists

have suggested that the arthritis may be indicative of the unpredictable effects of cloning, and animal rights groups have also used the findings to further their claims.

Despite this momentary setback, research continues. Researchers recently cloned two piglets, genetically modifying them so that their organs would not be rejected if transplanted into humans. This problem with Dolly is unlikely to cascade into a complete abandonment of cloning.

Although Dolly's arthritis is troublesome, she is still healthier than most other cloned animals. Most attempts at cloning large animals have led to deformities, early deaths, or large, unsustainable sizes of organs or of the animal itself. Arthritis is a small concern compared to these larger issues. It is difficult to predict whether any conclusion can really be drawn from the news. What can be learned, however, is that further long-term research and study on cloning issues is necessary.



Biotech Crop Use Increases Globally

Amid great controversy concerning their safety, genetically engineered crops seem to be globally spreading across agricultural fields. Global plantings of the crops have jumped nearly 20 percent since last year, concerning agronomists who say they may cause developing world industries to suffer and could lead to hunger among farmers who cannot compete with the large developed world-based industry that uses the modified crops to produce greater numbers of large fruits and vegetables.

According to a report issued by the International Service for the Acquisition of Agri-Biotech Applications (ISAAA), a group that promotes the technology, farmers grew an estimated 130 million acres of biotech crops in 2001—about 21 million more than the year before.



But behind the increase in numbers is a stark polarity in who has access to the genetically modified crops. The United States and Argentina, who have been pressured by the International Monetary Fund (IMF) to use the crops, account for 90 percent of the sector and most of the growth since last year. But Argentina's farming structure collapsed as a result of IMF recommendations this year, leading many to wonder if the imposition of such technologies on the country's farmers is a desired strategy.

"There was much speculation in 2000 that indeed the global area [of biotech crops] would decrease rather increase" in 2001, said Clive James, a scientist who is chairman of ISAAA. ISAAA defends the safety record of the crops, in spite of recent controversy in the United States and Europe concerning allergies caused by the genetically modified products, but the group did not comment on the potential effects of the new crops on rural economies and global commodity prices that affect developing-world farmers.

The most popular biotech crops contain bacterium genes that make the plants either resistant to bugs or weed killers. Farmers in China who used to spray their cotton crops as many as 15 times a year have started planting an insect-resistant variety known as Bt for its added bacterium gene. The crop doesn't need to be treated more than twice, said James.

But in the process, scientific reports suggest that the toxin used in the plants is killing off important insect life and that similar crops using the "Roundup" formula from Monsanto, Inc., have potentially disastrous human health effects that are not being mentioned by trade representatives trying to advance the spread of these crops in developing countries. As the controversy continues, new research may lead to answers about the safety and efficacy of these new crops, offering insight into whether they may solve large food crises in countries with mass starvation.

Canadian Study Shows Effectiveness of Graphic Cancer Warnings on Cigarette Packages

The Canadian Cancer Society polled 2,000 Canadian adults, 633 of whom were smokers, about the effectiveness of

graphic warnings in causing people to stop smoking. Pictures, including a brain after a stroke, a damaged heart, and a limp cigarette warning of impotence, replaced black-and-white text warnings on cigarette packages. The most effective images were of a diseased mouth and a lung tumor.

In general, 43 percent of the smokers and 40 percent of the nonsmokers grew more concerned with the health hazards of smoking. Fifty-eight percent of the smokers admitted that the full-color picture warnings on the packages provoked more consideration on the effects of cancer. Of the smokers, 44 percent said that the pictures motivated their desire to quit smoking; 21 percent said that the new warnings deterred their desire for a cigarette; and 27 percent declared that they now smoke less within their homes. 35 percent of the smokers and 34 percent of the nonsmokers said that they now know more about the hazards of smoking because of these graphic images.

The Bush administration has failed to address this issue. Now, however, after this study, Representatives James V. Hansen (R-Utah) and Marty Meehan (D-Massachusetts) have declared that they will stimulate legislative action making graphic warnings mandatory on American cigarette products. The World Health Organization (WHO) is considering creating an international treaty calling for mandatory graphic image-based warnings on cigarette packages as a worldwide requirement.

Hopefully, these graphic pictures will thrust the smoky truth of cigarettes into the health concerns of people everywhere, motivating a stop in this disease-instilling practice.

Snakes Eyes Will Change the World

The study of snakes' eyes and infrared sensors by Dr. Michael S. Grace at Florida Institute of Technology could someday lead to major advancements in everything from heat-seeking missiles for the military to tiny devices that might help physicians locate tumors in the human body.

Snakes can use their eyes to create a visual image of the world around them, or they can use their sensitive infrared sensors to create a similar image based on heat emitted by objects in their environment. By understanding how snakes are able to convert infrared radiation into a second source of vision, one could easily design a heat-seeking missile that can secretly invade the heat exhaust valve of an enemy aircraft or a small medical probe that can detect very small temperature changes caused by a tumor in parts of the human body.



[Physical Sciences]

Astronomers Assert Pale-Green Color of Universe

The universe is pale green on the cosmic spectrum, according to astronomer Ivan Baldry and his colleagues at Johns Hopkins University.

After examining data from the Australian 2df Galaxy Redshift Survey of more than 200,000 galaxies to determine the birth rate of stars as the universe aged, Baldry and colleagues created a cosmic spectrum. Each galaxy was assigned a numeric value according to its color. Upon adding them up and taking their average, the universe was declared to be a shade of pale green.

"Because young stars are hot and blue, they dominate the light," Baldry said, "and it's only when the young stars decline that [colors change]." As the universe ages, it begins in the blue period, moves through green, and progresses toward red. "The reason the color's changing is because the rate of stars forming is changing," he said. "We're in a stage of a declining rate of star formation. More stars were forming in the past than at the present time."

Astronomers believe that the pace of star formation has slowed after a stellar baby boom. NASA scientists presented research indicating that the peak star-formation period occurred soon after the Big Bang, which is earlier than previously believed. To see the pale-green color, the human eye would have to see the universe as a whole, not broken up into its component parts. "The only way to see it is if you saw all the universe from the same distance away and it was not moving," Baldry said.

Asteroid Barely Misses Earth

Dubbed "2001 YB5," an asteroid approximately 1,000 feet in diameter and traveling at 68,000 mph crept within 520,000 miles of Earth on Monday, January 7.

"It's a fairly substantial rock. If it had hit us at that sort of speed, you would be taking out a medium-size country, France, I sup-

pose, or Texas, or something of that order," said Director Jay Tate of the Spaceguard Centre in Wales. NASA's Near-Earth Asteroid Tracking program discovered 2001 YB5 on December 26, 2001. Astronomers calculated the asteroid's trajectory and determined that Earth was in no danger of a collision. The asteroid came within twice the distance of the moon.

Dozens of asteroids pass within close proximity of Earth, though few as close as 2001 YB5. As more and more near-Earth asteroids are discovered, astronomers are seeking a standardized means of warning the public.

Mass Spectrometry Aids Drug Research

Mass Spectrometry has been commonly used to measure the decay of carbon atoms to age artifacts like the Shroud of Turin. Ken Turteltaub, a researcher at the Lawrence Livermore National Laboratory, uses it to measure the absorption of medicines and toxins in humans.

The application of the carbon dating technique in medicine reduces the amounts and samples of blood that must be collected from humans or animals for testing. A small quantity of blood and tissue is converted to carbon and labeled with carbon 14. After the sample is accelerated through a magnetic track, the amount that reaches the detector at the end is counted. It "tallies the amount of drug or toxins that reaches the blood, the brain, or other internal organs," said Livermore physicist John Vogel.

After the amount received by the body is counted, other tests are still needed to confirm that those amounts are enough to cause cancer or other diseases. The most immediate use of the technique is to ascertain dosage for new medication. Pharmaceutical companies may use the technology to safely and efficiently test whether or not medications and drugs are appropriate for children. Another potential benefit is easier monitoring of bone-loss drugs on postmenopausal women. Researchers are looking for further applications and are enthusiastic about using mass spectrometry to protect health. ■

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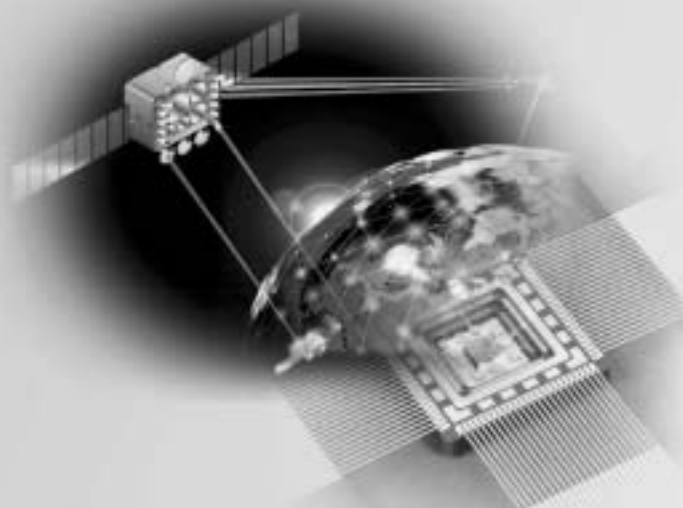
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The Big Bang's Pervasive Plasma: the Quark-Gluon Plasma

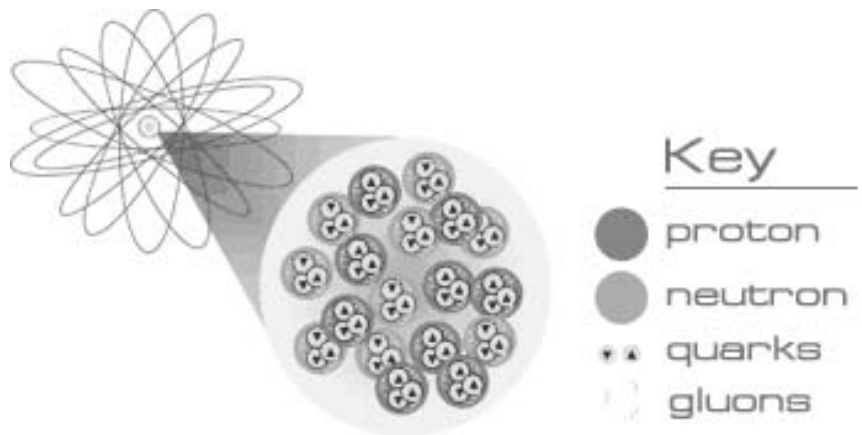
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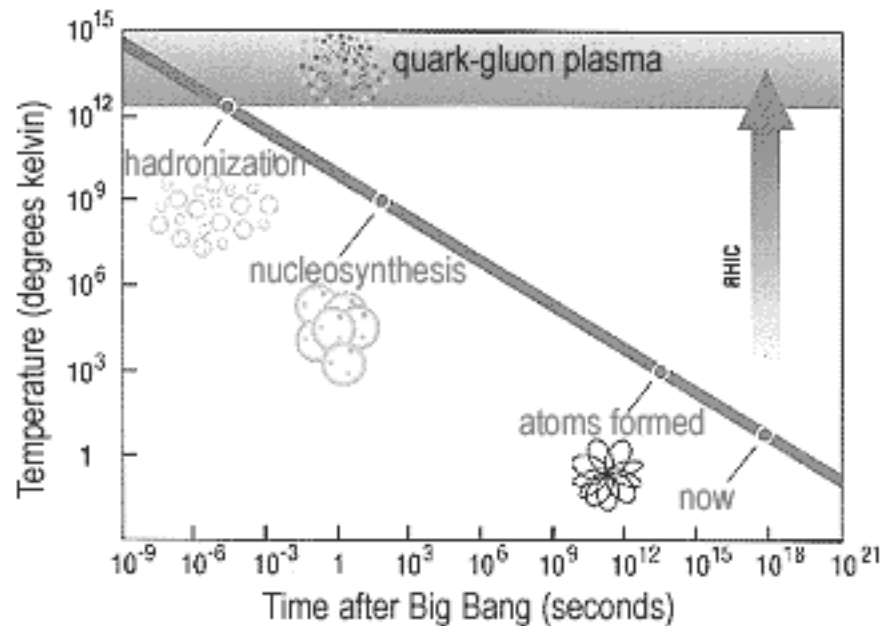
The universe was created twelve to fifteen billion years ago in a massive explosion that physicists term the “Big Bang.”¹ In the first microseconds after the Big Bang, when the temperature and concentration of energy was immensely high, an ancient form of matter pervaded the universe.² This form of matter consisted of all quarks and gluons existing freely in a quark-gluon plasma, which existed throughout the universe until 10^{-5} seconds after the Big Bang when the temperature throughout the universe dropped to 10^{12} Kelvins.³ As the universe expanded and cooled, the quark-gluon plasma underwent hadronization and began to condense and decay into hadrons, strongly interacting particles such as protons, neutrons, and pions.⁴

However, all theories pertaining to matter rest on the assumption that many particles such as protons and neutrons found inside an atom's nucleus are made of quarks. Yet, no one has ever succeeded in isolating a free quark.¹

Quarks are infinitesimal, rattle around inside the proton near the speed of light, and make up just 2 percent of the proton's total mass.⁵ They possess a characteristic that physicists call “color,” which is loosely analogous to electric charge.² Color generates a color field or chromodynamic field. The quantum of this field, the transmitter of the strong force, is the gluon. Gluons carry most of the proton's energy. And like the photon, which transmits the electromagnetic force, a gluon is massless. Yet, unlike a proton which is made of three quarks, a gluon has charge that allows it to generate its own color field, exert its own strong force, and interact with other gluons.⁵ The color field, like the electromagnetic field, can be thought of having two components: color electric and color magnetic.⁵ A fast-moving color charge produced by gluons moving at light speed generates a strong color magnetic field.⁵ Hence, gluons act as little dipole magnets.

The theory of how nuclear particles are composed of quarks and gluons is Quantum



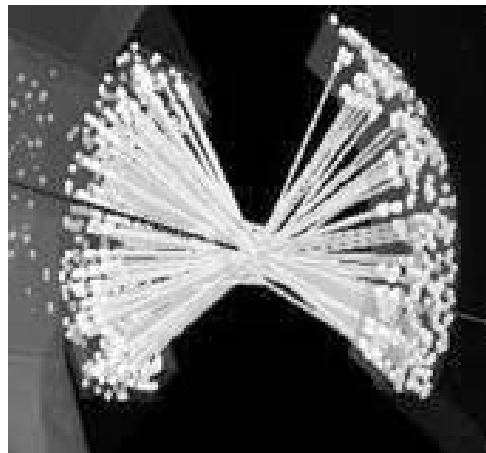


Chromodynamics (QCD), developed in 1973 by MIT Professor Frank Wilczek as a graduate student at Princeton University.⁵ QCD is a quantum field theory, which is founded on three main premises: relativity, where energy can be converted to mass, and vice versa⁵; the vacuum containing numerous energy fields, with energy constantly exhibiting itself as virtual particles that manifest and annihilate in less than 10^{-20} seconds; and the premise that the force two subatomic particles exert on one another is created in part by the subatomic particles.⁵ These subatomic particles are exchanging virtual particles, which comprise the quantum of the quantum field. This exchange of virtual particles is parallel to what occurs when two charged particles such as an electron and a proton interact. Here, the electron and proton exchange a virtual photon, which comprises the quantum of the electromagnetic field.⁵ The theory that describes these interactions is Quantum Electrodynamics (QED), developed by Richard Feynman.

In QED each electron is enveloped by a cloud of photons that exist as virtual particles. Also enveloping each electron are other electrons paired with positrons, the electron's

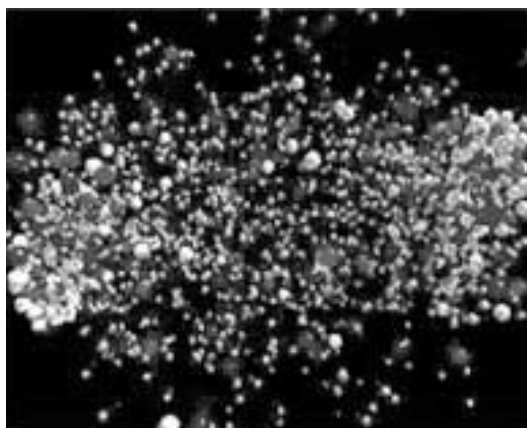
positively charged antimatter twin. This shroud of electron/positron pairs forms a screen that partially cancels the electron's field as seen from the outside of this screen.⁵ Conversely, from the inside of this screen the electron's field seems stronger than expected.⁵ This phenomenon is termed "screening."

QCD is closely modeled after QED. However, the quantum chromodynamic virtual particles, the gluons, produce a type of screening that is opposite to the type of screening produced by the quantum electrodynamics virtual particles, the photons.⁵ The screening that occurs in QCD is termed "antiscreening" because it is opposite to that of QED. In QCD, gluons envelop a quark and align themselves parallel to the color field as would magnets.⁵ Instead of weakening the color field as photons would do to the electromagnetic field, gluons strengthen the color field.⁵



If one quark manages to get inside another gluon cloud, it feels only a feeble attraction.⁵ However, the farther away a quark moves, the more it feels the added pull of the gluons.⁶ These gluons are manifested from gluons emitted by other gluons and by gluons materializing into virtual quark-antiquark pairs, which

exchange more gluons.⁵ The strong force that holds quarks and gluons together inside nuclear particles is analogous to a rubber band connecting two balls. The strong force becomes stronger as quarks stray farther apart and becomes weaker as quarks come together.⁷



QCD demands that a quark-gluon plasma exists at certain energy densities. Since the mid-1980s, researchers have sought to create a quark-gluon plasma, which would be the densest, hottest matter ever observed in a laboratory and possibly the densest, hottest matter in the universe.^{2,8} By using particle colliders to compress nuclei at sufficiently large densities and temperatures, individual protons and neutrons will overlap and dump an enormous amount of energy into a very small volume.^{1,4,8} This collision creates a fireball intense enough to melt protons and neutrons, and allows quarks and gluons to circulate freely as they would deep inside a proton or neutron.^{4,5} However, the quarks and gluons circulate within a much larger volume, forming a quark-gluon plasma.^{4,5}

The heavier the ions, the greater the volume over which energy is released in the collision.¹ The ions of choice are lead and gold.¹ Their atomic weights are 207 atomic mass units and 197 atomic mass units, respectively, and they collide with energies around 3.5 TeV.¹ Large amounts of energy are squeezed into a very small space, resulting in high energy density, which is approximately 3-4 GeV/fm³ at temperatures of 240 MeV.¹ The buzz of colliding nucleons is as dense as 100 nuclei packed into the space of one nucleon.⁷ Its temperature is expected to soar to 100,000 times that of the sun's core.⁷ This should free quarks and gluons into a small bubble of quark-gluon plasma. The result is similar to a hot gas at high pressure. It rapidly explodes, simultaneously expanding and cooling.¹ This problem of the laboratory fireball rapidly expanding and cooling makes the quark-gluon plasma survive only momentarily.⁵ At an energy density of 1 GeV/fm³ and a temperature of 180 MeV, quarks and gluons condense into hadrons through a

process known as hadronization.¹ These hadrons continue to interact with each other as long as the particle density remains high.¹ Yet, these interactions are mediated by the strong force and occur only at a very short range.¹ As further expansion occurs,

these interactions cease at an energy density of 50 MeV/fm³ and a temperature of 100-120 MeV.¹ The particles that are left travel outward toward detectors placed around the reaction zone.

The first research team to approach the creation of a quark-gluon plasma worked at the Super Proton Synchrotron at the European Center for Nuclear Research (CERN) in Geneva, Switzerland. In February 2000, these investigators smashed lead nuclei flying at nearly light speed into other nuclei at fixed targets.² The CERN team received the first glimpse of the quark-gluon plasma. However, there were some flaws in their data: They did not identify convincing signals in their search for direct evidence such as gamma rays that physicists expect the quark-gluon plasma to emit.²

Shortly after the CERN team received its intriguing results, a more powerful particle collider became operational. This Relativistic Heavy Ion Collider (RHIC) at Brookhaven National Laboratory in Upton, New York, collides two beams of gold ions head-on as they travel at nearly the speed of light.⁹ The RHIC smashes nuclei together with 10 times greater energy than the Super Proton Synchrotron at CERN.^{2,8} The results being collected at RHIC are the most reliable results pertaining to the quark-gluon plasma. Recently, researchers have seen the first clear indication of conventional matter dissolving into free-roaming quarks and gluons.¹⁰ Scientist collided pairs of gold nuclei at high energies and observed the particles that sprayed from the impact point. They detected fewer particles from the collisions than the Standard Model of Particle Physics predicts. This suggests that a tiny blob of unbound quarks and gluons may have been created.¹⁰

Understanding the quark-gluon plasma is

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very significant. Verifying its existence would allow physicists to comprehend the structure of nuclear particles and the phase transition that is thought to have occurred when the primordial quark-gluon plasma cooled to form today's nuclear particles.⁵ If the particle colliders necessary for creating the quark-gluon plasma reveal any irregularities in the plasma-to-matter transition, this may shed light on the formation of the first magnetic field, the formation of the first elements, and even a type of undetected dark matter, or "strange matter."⁷ Experiments might yield the first evidence of this proposed strange matter, which is the unseen substance astronomers suspect make up almost 90 percent of the universe. If bubbles in the cooling of the quark-gluon plasma are large enough, and if they chill in just

the right way, some of the plasma might condense into the previously mentioned strange matter because they contain many strange quarks. Lastly, it has been theorized that the quark-gluon plasma may exist in the cores of neutron stars. A neutron star consists of the dark remains of a star that underwent a supernova explosion and collapsed on itself under gravity's influence. Neutron stars pack approximately the mass of the sun inside a sphere 10 kilometers across.¹⁰ A sugar cube-size piece would weigh over a billion tons.¹⁰ Yet, the core of a neutron star is even denser. According to Krishna Rajagopal and Frank Wilczek of MIT, it is in the dense, hot core of a neutron star that subatomic components of protons and neutrons get smashed into a soup called a quark-gluon plasma.¹⁰ ■

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Physiological Markers for Alzheimer's Disease

Martin Kurtev

Alzheimer's disease is the most common cause of intellectual decline associated with aging. This disorder involves the deterioration of mental functions resulting from changes in brain tissue, such as the shrinkage of certain brain structures. There is no known definitive cure for Alzheimer's disease, and treatment is mostly aimed at relief of symptoms. The high emotional and medical costs of caring for a patient with Alzheimer's, along with the prevalence of this disease, make its early detection extremely important. Early detection helps the patient and his/her family adjust to living with the disease and plan for future treatment. Current studies have shown that there are subtle physiological clues that might signal the beginning of Alzheimer's disease. Olfactory deficits and certain defects in the skin cells of Alzheimer's patients are considered two of the strongest indicators of the onset of the disease and may prove to be effective diagnostic tools in the near future.

Diagnosing Alzheimer's disease still poses a serious challenge to the medical profession, and it may take several years of testing before doctors can reach a decision on a patient's condition. A clinical evaluation of Alzheimer's disease must exclude all other neurological, psychiatric, and medical disorders that may be causing the mental decline¹. The current procedure for detecting the onset of Alzheimer's disease begins with a detailed assessment of the patient's and his/her family's medical history. Physical examinations and laboratory tests are performed periodically for several months or even years. Brain scans using new imaging techniques, such as computed tomography (CT) scans and magnetic resonance imaging (MRI), are used to rule out other forms of dementia like tumors and strokes. The patient also undergoes neuropsychological testing in which he/she completes memory, language, arithmetic, and other exercises related to brain functioning. The definitive diagnosis of Alzheimer's disease, however, is only possible during an autopsy when the characteristic neural plaques and fibrillary tangles can be detected. The possible alternative solution to the current diagnostic problems is the presence of a biological marker, like an abnormal protein or tissue, that is external to the brain. These new tests offer hope for not only an early, fast, and easy detection of the disease, but also for finding an actual cure.

A recent study published in the *American Journal of Psychiatry* discussed the possibility of detecting the development of Alzheimer's disease through the use of an olfactory test². The study was based on the observation that patients with Alzheimer's disease have consistently demonstrated olfactory identification deficits in relation to a control group. Dr. D. P. Devanand and colleagues at Columbia University gave a multiple-choice aroma test to 90 patients who were suffering from memory problems and mild cognitive impairments. The patients were asked to identify 40 different smells, such as those of peanuts and menthol. A follow-up study monitored 77 of the patients. Forty-seven of these patients had low olfaction scores, and 19 of them (40%) developed Alzheimer's disease. No patients of the 30 with high olfaction scores developed the disease. The percentage of people who performed poorly on the test and developed Alzheimer's is significantly higher than the occurrence of the ailment in the general population, which is one out of 10 people (10%) over 65 years of age.³

During the follow-up study, one of the challenges Devanand's team faced was conclusively diagnosing participants with Alzheimer's disease. The researchers diagnosed patients for dementia on the basis of DSM-IV criteria. The diagnosis of possible or probable Alzheimer's disease was made on the basis of criteria from the National Institute of Neurological and Communicative Disorders and Stroke (NINDS) and the Alzheimer's Disease and Related Disorders Association. Making a diagnosis based on the established guidelines, however, does not guarantee with certainty that any of the participants will actually develop Alzheimer's disease.

In their attempt to better correlate the olfaction scores with the development of the disease, the researchers divided the patients into two categories—those who were aware of their olfactory deficit and those who were not. They discovered that the participants who were not aware of their olfactory deficiency were more likely to develop Alzheimer's disease than the participants who were aware of their olfactory shortcomings. Of the 47 people with olfactory deficits, 37 were not aware that they had any problems, and 16 of these patients (43%) developed Alzheimer's. More importantly, low olfaction scores accompanied by subjective reports of no problems smelling were present in 16 of the total 19 (84%) patients

who met the criteria for Alzheimer's disease in the follow-up study. These data and statistical analyses showed that low olfaction scores and being unaware of olfaction deficits are strong indicators of the onset of Alzheimer's disease. The researchers also used two other statistical indicators, the Cox proportional hazards model and the Mini-Mental State score, to show that low olfaction plus lack of awareness was a significant predictor of Alzheimer's disease.

The correlation between being unaware of olfactory problems and the development of Alzheimer's disease is important because it identifies a possible area of brain research that may bring us closer to a cure. Even though the sense of smell often declines with age, the loss of normal olfaction may also result from the shrinking of certain brain areas due to Alzheimer's disease. Obviously, a poor sense of smell by itself is not a predictor of the illness, but experiments have shown that it might be related to the disease. Devanand's team proposed that awareness of losing the sense of smell may be localized at the medial-temporal lobe structures, which are known to be affected in early Alzheimer's disease and are associated with olfactory detection deficits. This could explain why low olfaction scores, accompanied by a lack of awareness of the olfactory deficits, strongly predicted Alzheimer's disease.

Skin is another area in which scientists are looking for possible clues that may indicate the onset of Alzheimer's disease. Scientists at NINDS in Bethesda, Maryland, and the Burke Medical Research Institute at Cornell Medical College in White Plains, New York, have discovered physiological differences in the skin cells of those with Alzheimer's disease, a finding that could lead to a standard battery of skin tests for diagnosing the disease.¹ The diagnostic tests are based on the group's discovery that skin cells in Alzheimer's disease patients have defects that upset the cells' ability to properly regulate critical potassium and calcium ions. The presence of these cell defects in the skin suggests that Alzheimer's disease results from physiological changes throughout the body. Dementia may be the first noticeable effect of these changes as the defects affect cells in the brain.

The principal investigator, Daniel L. Alkon, and his colleagues report that, of the 50 people tested, skin cells from 15 patients clinically

diagnosed with Alzheimer's disease were missing a certain type of microscopic tunnel that governs the flow of potassium in and out of the cells. Nearly all of the age-matched members of the control group, and many of the younger ones, had functional potassium channels of this type. When this test and three others were done together, the results were 100 percent accurate in separating those with clinically diagnosed Alzheimer's disease from those without the disease.

The NINDS scientists made their discoveries through a unique line of scientific reasoning. Most scientists who study Alzheimer's disease concentrate on the fibrillary tangles and amyloid plaques prevalent in the brain tissue of those with the disease. Alkon and his colleagues, on the other hand, are memory researchers—they study how the flow of ions and the interactions of neural signals allow the brain to remember. They originally intended only to study memory loss in Alzheimer's disease, but instead found a clinical test for the disease. Since difficulty in forming memories is one of the earliest and most common effects of Alzheimer's disease, they began with the idea that the common denominator for Alzheimer's disease patients might be a defect in the cellular processes of memory. Alkon theorized that such changes in cell physiology might be present throughout the body.

A disruption in the flow of ions across a cell's membrane can have detrimental effects on the cell's overall function, and the adverse condition is likely to affect different physiological processes. The flow of potassium is especially critical in cells responsible for memory formation. The scientists then continued to find two other defects that affect the cells' supply of calcium, a critical ion for the body. The researchers also detected the same cell defects in nerve cells of the olfactory system,

which is an indicator that the abnormalities are also present in other brain cells.

The discovery must be substantiated by further research and a larger experimental group. Also, it is necessary that the results from any physiological test be confirmed later through an autopsy of the patient to prove with certainty the presence of the disease. The study lends support to the already established notion that Alzheimer's disease is present in different parts of the body, such as the olfactory system. Therefore, developing a simple and easy physiological test to detect the disease may soon become a reality. Such a test would be able to detect the disease in its early stages and therefore allow existing methods of patient care to be applied more effectively. By being aware of the presence of the disease before the symptoms take over the patient's body, the patient and his/her family will be better prepared to deal with the emotional hardships that come with the inevitable loss of memory. The studies do not explicitly state how the findings can be used toward the development of a cure for the disease, but the articles have identified two body systems that are more accessible and easier to manipulate than the brain itself.

The studies discussed here offer hope that physicians will ultimately be able to more accurately and easily predict whether a person is at risk for getting Alzheimer's disease, and further studies will hopefully point scientists toward the underlying cause of this disorder. An early diagnosis based on an olfactory or skin test would not only translate into saving millions of dollars in medical costs, but would also allow the patient and his/her family to make a better decision about the course of treatment. Furthermore, as effective drugs for Alzheimer's are discovered, early detection will be of crucial importance to the patient's successful recovery. ■

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The People of Kashmir

Izzat Jarudi

*"Who has not heard of the vale of Cashmere/With its roses the brightest that earth ever gave."
—Thomas Moore*

When the media covers Kashmir, it inevitably focuses on the possibility of war between India and Pakistan. After all, in the half-century of their existence, these two nations have already fought three wars, all involving the disputed territory of Kashmir. Hundreds of thousands have died so far as a result of their clash, and millions more may perish if their fourth war is nuclear. For the Kashmiri people, disaster has already struck in the form of a violent insurgency against the Indian government that has taken the lives of 35,000 Kashmiris in 12 years. A land once considered an unreal paradise has become a very real hell.

Thirteen million Kashmiris, innocents and insurgents alike, have been subjected to nearly every conceivable abuse or hardship since the armed conflict between Muslim militants and Indian security forces erupted in 1989. Their houses have been ransacked and burned. Their men have been imprisoned and tortured. Their women have been harassed and raped. Their tourism-based economy has collapsed. In the words of one Kashmiri poet, even their "culture is dead."¹ Considering the daily traumas these people endure, it is not surprising that the state of Jammu and Kashmir, where the rebellion is raging, has one of the highest rates of suicide in India.²

A Brief History of "the Kashmir Question"

The despair that pervades modern Kashmiri life is difficult to appreciate without some basic understanding of the history of the conflict that goes back to the very birth of the nations of India and Pakistan. The Kashmir dispute began during the partition of British India into India and Pakistan in 1947. Kashmir, then a mainly Muslim state ruled by a Hindu maharajah (Indian king or prince), had not yet acceded to one of the two nations when an uprising of Muslim villagers and an invasion by Pakistani raiders in the west finally convinced the maharajah to join India in return for military aid. The first of three wars between India and Pakistan over Kashmir ensued, ending in 1949 with the negotiation of a cease-fire by the United Nations. Pakistan kept one-third of the territory, the



northern and western portions that it had originally invaded, today called Azad (“Free”) Kashmir and the Northern Areas. India kept the rest, the southern and southeastern portions that it organized as the modern state of Jammu and Kashmir.

Two wars and 50 years later, not much has changed geographically. The cease-fire line, which the two sides agreed in 1949 would temporarily divide the administration of the two regions of the province until the conflict was resolved, is still there. This de facto border was confirmed in the negotiations after their last war in 1971, but is now known as the Line of Control (LoC). Technically, India and Pakistan are at peace. Since 1989, however, the Indian government has maintained a strong military presence in Jammu and Kashmir. Half a million security personnel, including members of the army, federal paramilitary forces, and state police, are stationed there to suppress armed movements for Kashmiri independence or Pakistani accession. On the other hand, Pakistan has lent moral and political, if not military and financial support to the Muslim militants that include Kashmiri, Pakistani, and foreign guerrillas from countries like Afghanistan.³

Clearly, if these 50 years of conflict and bloodshed have proved anything to the world, it is that neither India nor Pakistan is willing to give up its claim to Kashmir. Their mutual interest in the province is not for something tangible like natural resources (of which Kashmir has few except beauty), but for something symbolic like an affirmation of the principles upon which each was founded in 1947. To India, the loss of Jammu and Kashmir, its only Muslim-majority state, to Pakistan would undermine the Indian identity as a secular nation.¹ To Pakistan, accession would validate existence as a necessary, separate home for the Muslim minority of India.³

Human Rights Abuses

The geopolitics of the region aside, Kashmir is more than a pawn in the struggle for hegemony in the Indian subcontinent. It is the home of 13 million Kashmiris, who for the last decade have been caught in the cross fire between India and Pakistan, between Indian security forces and Muslim militants. As one Kashmiri put it, “Here we’re a sandwich between two guns.”¹

Indian Security Forces

In an attempt to quash the violent insurgency in Jammu and Kashmir, some Indian security personnel have resorted to brutal tactics against the Kashmiri population, innocents included.



Portions of the capital Srinagar and the northern town of Sopore have been burned to the ground.¹ Muslim neighborhoods that security forces suspected to be sympathetic to the separatist cause have been subjected to a collective punishment that includes indiscriminate shootings, beatings, and rape.⁴ In 1991, *The New York Times* reporter Barbara Crossette witnessed one such “crackdown” in Batamaloo, a town in the Kashmir Valley:

For three days in March, the people of Batamaloo, a middle-class neighborhood here, were victims of India’s war against an independence movement it can no longer contain except by force. They call it “the crackdown,” and it can happen, without warning, anywhere in the Kashmir Valley. An area is surrounded, shops are closed, people are confined to their houses or made to stand for hours, other houses are ransacked, women abused, graveyards dug up, mosques violated. The purpose is to ferret out militants and break the morale of their supporters. At the end of the siege, boys as young as 12 or 14 are taken away for interrogation. In Batamaloo, where more than 100 young men were rounded up on March 27, mothers came out the next day to wail in panic and rage. “Hindustanis!” some cried, giving their words for Indians the venom of a curse. When they began to march, they were driven back with tear gas and blows from rattan poles. By midmorning, one woman was dead and 20 hospitalized.⁵

Since then, the focus of Indian efforts has shifted geographically from the central Kashmir Valley to border districts where militants are now concentrated. Nevertheless, the abuses continue. In those areas today, even carrying a pager is enough to warrant interrogation.⁶ Friends and family seeking information about the “disappearances” of loved ones who have been arbitrarily arrested without charge have received little help from the courts, because special laws in the state allow Indian security forces to simply ignore their authority.¹

Detained without trial, the “disappeared” and

others suspected of militant activism often face torture, summary execution, or perhaps a new “countermilitant” assignment to assassinate other alleged insurgents and intimidate local residents. Human Rights Watch has documented some of the brutal methods of torture used on these prisoners and their appalling effects:

Severe beatings with truncheons, rolling a heavy log on the legs, hanging the detainee upside down, use of electric shocks, immersion in water while being suspended upside down, and the insertion of an iron rod on which chili paste has been applied into the rectum. Extensive beatings and use of the roller frequently lead to renal damage or failure; being suspended for prolonged periods upside down can lead to nerve damage and paralysis of the limbs.⁴

Muslim Militants

Human Rights Watch also reports that abuses are not limited to one side; Muslim militants are also guilty of civilian massacres, summary executions, rape, and torture.⁴ With equally questionable standards for suspicion, they have kidnapped and assassinated government officials, civil servants, and suspected informers. In fact, the event that led the Indian government to send security forces to Jammu and Kashmir in 1989 was a kidnapping by militants of the home minister’s daughter.

Muslim militants have also targeted Hindu families, harassing, torturing, murdering, and threatening them in an attempt to drive them out of the valley.⁷ Foreign guerrillas in Kashmir fighting a “holy war” are responsible for some of the more brutal attacks on members of the Hindu minority.

In recent years, after being driven out of the Kashmir Valley, armed insurgents have limited their strategy from genuine military engagements to hit-and-run grenade or sniper attacks in cities.⁴ Failing to distinguish between military

and civilian targets, they have killed innocents, including women, children, and journalists, in their attacks.

For Tahir Mohiddin, a Kashmiri newspaper editor, the pattern of civilian abuse by both sides is clear:

First come the terrorist blasts, grenade attacks. Then comes the crackdown by Indian forces. The militants use coercion to seek refuge in villages. After they leave security forces arrive and then come the beatings to find out information.⁶

The Lack of Transparency

Although the pattern is clear, it is difficult to gauge the scope of civilian abuse by security forces and militants over the last 12 years. Security force members conduct their own investigations of human rights violations, but do not make their findings public, paralyzing government organizations like the State Human Rights Commission that are charged with confirming reports of abuses in Jammu and Kashmir.⁴ The work of international human rights organizations like Amnesty International has also been frustrated by an Indian policy that denies them access to Jammu and Kashmir.⁷

Human rights activists and lawyers are often threatened and sometimes killed. At the same time, those Kashmiris who dare to document and report abuses risk suffering a similar fate soon after. Fear of retaliation has kept many civilians silent about the crimes they have witnessed. Doctors who treated torture victims, for example, did not share that information with Human Rights Watch until they were promised strict confidentiality.⁴

Although these obstacles to the truth limit the accuracy of such estimates, Kashmiri and Indian human rights groups quantify the abuses over the last twelve years in terms of hundreds of “disappearances,” thousands of summary executions, and tens of thousands of deaths. As a result, there are now 16,000 to 20,000 orphans and widows in the Kashmir Valley alone.⁸

The Disappearance of Tourism

Twelve years of violence has cost countless Kashmiris their lives, but even more have lost their livelihoods. The insurgency has virtually eliminated tourism to Jammu and Kashmir, an industry that once supported 100,000 people and produced more than three-quarters of the state’s revenue.⁹ In 1989, 750,000 tourists visited the “Switzerland of the East” to enjoy the beauty of its lakes and the Himalayan mountains.¹⁰ The following year, the number dropped to virtually zero.¹¹ Since then, the number of tourists per year



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has fluctuated wildly with the level of violence, but has never come close to its former levels. Everything from the threat of land mines along mountain hikes to kidnapping and murder by Muslim militants has convinced many tourists (and investors) to avoid what was once the most popular destination in the subcontinent.

Without the business from tourists, hotels are empty of everyone but journalists and soldiers, and restaurant and houseboat owners, cabmen, and shopkeepers are also struggling to survive. Many more mobile merchants have had to take Kashmir's trademark carpets, papier mâché and other handicrafts out of Srinagar to New Delhi where they have customers.¹²

Societal Trauma

Beyond inducing economic collapse, the insurgency has also threatened the general health of the population. There are not enough hospitals to treat the victims of cross fire, abuse, and trauma all over Jammu and Kashmir; as a result, conditions are unhygienic and doctors are over-worked. Other health services like child immunization programs have also suffered.¹³

Perhaps the most disturbing trend is the dramatic increase in the number of patients who need psycho-social care. Medecins San Frontieres (MSF), one of only two foreign aid agencies in Srinagar, is focused on managing this overwhelming problem. According to MSF representative Paul van Haperen, "There is barely a family that has not been affected. There's been a tenfold rise in the past decade in the number of cases of trauma."¹⁴ The unfortunate result of this mental health crisis is that more than 2,000 Kashmiris have committed suicide over the last 10 years.² The vast majority of those suicide victims were between 16 and 25 years old.

A Hopeless Youth

Since 1989, Kashmiri youth have had little to look forward to: Economic depression has left few jobs for the young. There are 200,000 unemployed graduates in the Kashmir Valley alone. At the same time, the quality of education has plummeted. Most could not get a proper education

even if they wanted to. Militants have set fire to schools that they believed were working against their cause.¹⁵ On the other hand, security forces have occupied many schools and universities, particularly in rural areas. The remaining schools in Jammu and Kashmir are often closed due to outbreaks of violence.

With such a low standard of education and little opportunity for employment, most young Kashmiris no longer see the point of further schooling.¹⁵ Those with a good education have left Kashmir to find better opportunities in the rest of the subcontinent and world, causing a "brain drain."¹⁴ Others have joined the militants; some of these young fighters choose this out of vanity so that they can show off their guns and use them to settle personal disputes.¹³ As one Kashmiri explains, however, most join out of despair:

Thousands of local boys turned to militant training across the border. The basic cause is not ideological or the jihad factor. Most went because they have nothing here. No future. No job. No hope. If they had hope, they would not go.⁶

Exodus

Other despairing civilians who had the means to leave Jammu and Kashmir fled the political violence and economic depression in the state, particularly to Pakistan or other parts of India. By 1990, 100,000 Hindus had already left the Kashmir Valley, where they were being persecuted by Muslim militants.⁴

On the other hand, since 1989, 18,000 Muslims have found refuge in Azad Kashmir either with relatives or in camps. The Pakistani government has set up 15 camps for them, giving each person \$12 a month with free housing, electricity, and medical care; however, sanitation is poor, infectious diseases like dysentery are common, and depression is pervasive. Moreover, many feel like second-class citizens because they are not allowed to move to other parts of Pakistan where they could find jobs and be safer, away from the volatile LoC.¹⁶

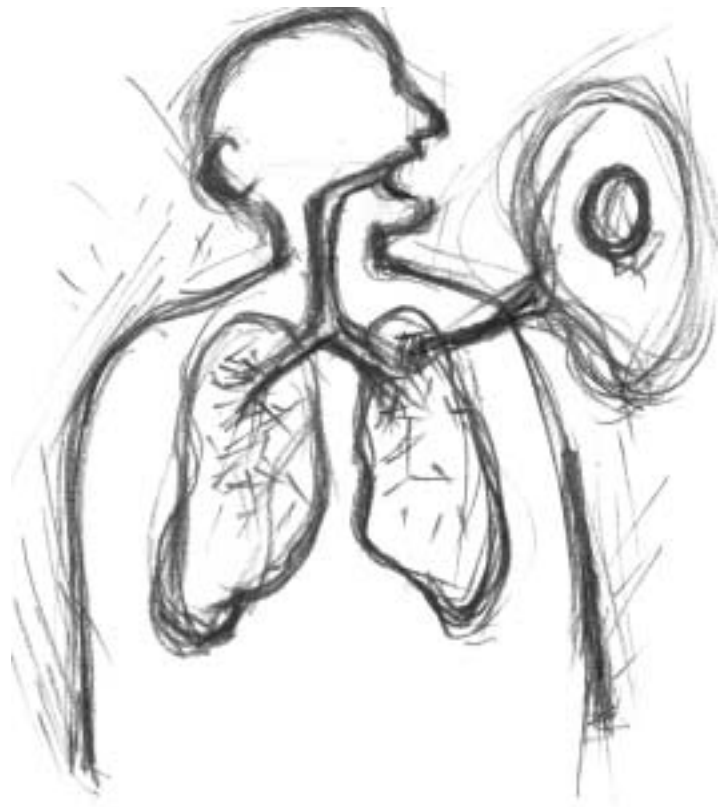
In spite of all they have suffered at the hands of Indian security forces and Muslim militants, however, a few Kashmiris still have hope that the 12-year struggle will end soon so that they can return home. Imtiaz Ahmed Lone, now a student studying for a science degree at a local college, is optimistic about a peaceful resolution to the conflict in the place where he grew up: "I think there will come a day when we can return. There is a lot of change in this world so it can happen."¹⁶ ■

Tuberculosis: An Overlooked Global Threat

Shefali Oza

“**W**e live in an age when unnecessary things are our only necessities,” wrote Oscar Wilde in *The Picture of Dorian Gray*. A more accurate statement for today would be that we live in a place where unnecessary things are our only necessities. While Wilde’s words correctly describe most residents in developed nations, the situation in developing nations is quite different. The tuberculosis crisis is a prime example of this dissimilarity. Tuberculosis has nearly been forgotten in the developed world, but it remains a household problem in poor countries. Although a cure for tuberculosis is readily available, the international community has been slow to respond. This indifference has allowed the disease to take shape into something that threatens even the nations that ignore its existence.

A common misconception in the First World is that diseases such as tuberculosis, polio, and malaria have nearly or completely vanished from the planet. Unfortunately, this is not the case. The primary difference between disease control in developed and developing nations is the lack of funding for prevention and treatment of diseases in Third World countries. Tuberculosis, an airborne infectious disease, is the number one cause of death among adults in the world.¹ The irony of the situation is that it is one of the few diseases that has a cure, and yet one of the most widespread and worsening crises of the time. Many public health officials have even argued that this lack of medical care in poor nations is a human rights issue that must be addressed at once.



Unfortunately, although excellent solutions, such as direct-observed treatment, short-course (DOTS) exist, the overall lack of international effort and interest has led to severe complications that now threaten not only developing nations but the entire world. Multidrug-resistant tuberculosis (MDR-TB) is the most dangerous and complex of these cases. These evolved strains of tuberculosis are making simple first-line drug treatment ineffective in many areas. In the words of Dr. Paul Farmer, a leading infectious disease physician and expert in the field of tuberculosis treatment, "The rapid rise of multidrug-resistant tuberculosis is a public health catastrophe of the first order."²

Multidrug-resistant tuberculosis has made the situation more difficult, but by no means impossible to fight. New strategies to combat MDR-TB, such as DOTS-plus, have been demonstrated to be effective in model programs. The Global Fund to Fight AIDS, Tuberculosis, and Malaria (Global ATM) is an innovative idea to bring aid to poor countries. The Global Tuberculosis Drug Facility allows better access to antituberculosis drugs in countries currently hard-hit by the disease.³ Yet this is not enough to fight such a crisis. As long as the international interest in tuberculosis remains weak, there is no hope in finding an end to the crisis before the disease spreads beyond control.

Tuberculosis Basics

Dr. Farmer wrote, "Looking toward the next millennium it is difficult to be optimistic," in regards to the growing tuberculosis crisis.⁴ And he is right: The World Health Organization (WHO) estimates that 8.4 million people were newly infected with tuberculosis in 1999.⁵ Even more startling is the estimate that one-third of the world's population is currently infected with the disease.⁶ Of course, this one-third is not uniformly distributed among the populations of the world. Tuberculosis is considered a disease of the poor, most prominent in overcrowded resource-poor settings. One report cites that 90 percent of all tuberculosis infection cases are in the developing world.⁷

The cold shoulder given to this disease by most industrialized nations is not surprising. The reaction of these countries to the tuberculosis

pandemic is parallel to their reactions in similar situations. The HIV/AIDS pandemic in Africa, severe malnutrition, and the lack of treatment for other curable infectious diseases are all examples of chronic emergencies in the Third World that are essentially overlooked by developed nations. Resource-poor countries clearly do not have the resources to fight such problems on their own. The global tuberculosis epidemic is not of concern to nations that have, in essence, already dealt with their own national tuberculosis crises. This way of thinking prevails in developed nations even though the WHO declared tuberculosis a global health emergency in 1993.⁸ This negligence has been criticized by many. Farmer wrote, "The appalling global burden of tuberculosis at the turn of the millennium, despite the availability of effective control measures, is a blot on the conscience of mankind."⁹

Tuberculosis drugs, although having slightly improved over time, are very difficult to consume because of their harsh side effects. Short-course chemotherapy was a new form of treatment developed in the late 1960s as an alternative to the initial antituberculosis drugs on the market,¹⁰ but it still has very unpleasant side effects. To avoid these side effects, patients sometimes take the drug course until their health seems to improve, and then stop. But in resource-poor countries, ease is not as much an issue as price.¹¹ Unfortunately, not only does the victim remain infected if treatment is stopped before completion, but he is also very likely to acquire a strain of tuberculosis that is resistant to that drug and can be passed along to others. Dr. Farmer described a situation in Peru where a mother, unable to afford full treatment after becoming infected, developed multidrug-resistant tuberculosis and passed it on to her son. Farmer wrote, "Corina was unable to complete her treatment. As her husband recalls it, they could afford to buy only two of the four drugs prescribed."¹² Both Corina and her son died without receiving a full, correct treatment regimen.

Even in the developed world, treatment was hampered by the lack of patient compliance in taking the necessary medications. To prevent this massive problem of drug resistance, direct-observed treatment (DOT) was standardized by

the WHO in 1991.¹³

According to the WHO, "DOTS is [the most effective strategy] available for controlling the TB epidemic today."⁶ As the name suggests, DOTS is a treatment program in which every tuberculosis patient is observed daily by a health worker to guarantee that medication is taken at the proper times. This greatly reduces the development of drug resistance. The health workers are usually locals and do not need to be trained in medicine, thereby lowering the cost of the program. In areas where DOTS is in effect, tuberculosis cure rates are as high as 95 percent.¹¹ The overall average cure rate from DOTS in 1997 was estimated to be 80 percent, an extremely high success rate.¹⁴ The DOTS protocol requires the following five components:

- Government commitment
- Case detection (by sputum smear microscopy)
- Standardized treatment for six to eight months, DOT for at least the first two months
- Constant supply of all antituberculosis drugs
- Standardized recording and reporting system¹⁴

Through these tenets, DOTS allows resource-poor settings to have nearly the same tuberculosis treatment benefits as countries of the developed world. In fact, treatment is the main reason for the basic disappearance of tuberculosis from the developed world. The DOTS approach to tuberculosis treatment tries to provide DOTS patients with the same opportunities for consistent treatment.

Unfortunately, even with the extremely powerful DOTS strategy, the tuberculosis crisis has continued to worsen over time. Two very important reasons for this have been discussed in numerous publications. The first is that DOTS has not been implemented throughout the world. According to WHO statistics, in principle, 45 percent of the world's population had access to DOTS in 1999.⁵ This number includes developed nations where DOTS is available but not needed because of low tuberculosis rates. A more informative statistic from the WHO is that, in 1999, DOTS treated only 23 percent of infected tuberculosis patients.⁷ The lackluster implementation of the successful DOTS program is a very unfortunate consequence of the inaction of

countries that can afford to help but, at best, choose to act in a very limited capacity. This failure of effective action has now come back to haunt the entire world. The second reason the crisis is worsening is that drug-resistant forms of tuberculosis are now spreading. Where DOTS has not been implemented, there is no standard to guarantee tuberculosis patients are taking the full course of treatment. In resource-poor countries where patients buy only as many drugs as they can afford, acquired drug-resistance has skyrocketed. These strains of drug-resistance can then be passed to others in close contact with the infected person. The same problem occurs in places with little DOTS implementation as a result of mismanagement, such as not having a constant drug supply, doctors prescribing incorrect drugs, and patients not being observed to ensure they take their doses.

Multidrug-resistant tuberculosis is defined as a strain that is resistant to at least isoniazid and rifampicin, the most powerful antituberculosis drugs available (DOTS-plus page, others).¹⁵ MDR-TB is a completely man-made problem resulting from ineffective control of tuberculosis treatment.⁹ In 1997, the WHO published a survey in coordination with the International Union Against Tuberculosis and Lung Disease (IUATLD) on MDR-TB that was an eye-opening report for the world. It detailed the presence of drug-resistant tuberculosis in all 35 countries it surveyed.⁹ The most recent and disturbing survey from 2000 showed the presence of MDR-TB in all 100 countries surveyed.¹⁶ Not only is MDR-TB more expensive to treat because second-line drugs are needed, but in its most extreme case, it threatens resistance to all antituberculosis drugs that have been developed. The world's carelessness in eradicating the disease may have placed tuberculosis parallel to an era before antibiotics. MDR-TB has now become a significant cause of global concern. According to the WHO, "Given the increasing trend toward globalization, transnational migration, and tourism, all countries are potential targets for outbreaks of MDR-TB."¹⁵

The Global Impact of Drug-Resistant Tuberculosis, a report commissioned by the Open Society Institute and Harvard Medical School, says that MDR-TB is a manifestation of the global neglect

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for tuberculosis control.¹⁷ Even more direct are the human rights arguments that suggest fighting tuberculosis is a global responsibility. A report about tuberculosis and human rights, published by the WHO, says, "Vulnerable and marginalized populations bear an undue proportion of health problems. Overt or implicit discrimination violates one of the fundamental principles of human rights."¹⁸ The report argues that all people have the right to certain fundamentals, including basic health care. Access to tuberculosis drugs is essential, especially since these drugs are readily available. Therefore, tuberculosis treatment has become as much a human rights issue as government crimes against a population, for instance.

Possible Solutions

Whether through naivete, carelessness, or blatant disregard, tuberculosis has not received the public attention a disease of its magnitude would have if it were a disease of the developed world. MDR-TB is a major problem that caught much of the international community unawares. Even though MDR-TB has not been able to bring tuberculosis directly into the public eye, the panic it has caused has started to mobilize an international community of concern that was previously deemed unnecessary. New strategies have been developed, drug prices are being questioned and lowered, and funding is being made available. While this is an improvement, the international community still lacks the passion needed to eradicate this disease.

The most promising solution to MDR-TB is based on the already effective DOTS program. The new treatment program, called DOTS-plus, includes the five tenets of DOTS. In addition, DOTS-plus takes into account the need for individual treatment regimens using second-line drugs depending on each patient's particular strain of drug-resistant tuberculosis. The necessity for a new strategy became evident when cure rates in high-MDR-TB regions were analyzed. Low-prevalence-MDR-TB areas have had DOTS success rates up to 95 percent, as previously mentioned. Areas with high-MDR-TB prevalence, on the other hand, have a range of 6 percent to 59 percent for cure rates through DOTS, showing a tremendous 40 to 60 percent drop.¹⁹ Another

study showed that 93 percent of people who failed the DOTS treatment had some form of drug-resistant tuberculosis¹³ (new white plague). The amplifier effect is an additional problem facing many MDR-TB patients being treated only with DOTS. As first-line drugs are continued, the patients may develop resistance to other agents as well as those of their original MDR-TB strain.¹⁰

Leading tuberculosis experts have been quick to emphasize, however, that DOTS is still the main program of treatment. In areas of strong DOTS programs for regular tuberculosis, MDR-TB should not be able to develop. Therefore, a dual program is needed. DOTS-plus must be implemented where MDR-TB is present. At the same time, DOTS programs must be expanded and reinforced to reach all areas of the globe. Another emphasis is that DOTS-plus must be implemented only where DOTS is already a strong program to prevent further drug resistance resulting from inadequate infrastructure.¹⁵ Otherwise, strains of tuberculosis resistant to second- and third-line drugs may develop as freely as MDR-TB has over the last several years. The world will face a calamity in which a curable disease has been transformed into an incurable disease simply due to disorganization.

DOTS and DOTS-plus have established international standards for tuberculosis treatment. Standards alone, however, will not solve the tuberculosis problem. Massive amounts of resources must be mobilized to make the treatment programs successful. A joint international effort has led to the development of several initiatives that will hopefully provide the necessary resources to lessen this crisis. The Global TB Drug Facility (GDF), run through the Stop TB Partnership, is a mechanism intended to bring a constant supply of high-quality but inexpensive first-line tuberculosis drugs to developing nations.³ The GDF also plans rapid DOTS expansion into areas that currently lack the treatment program. Governments and nongovernment organizations (NGOs) apply to the GDF for inexpensive first-line drugs. Approval from the GDF for these drugs means the country has a strong infrastructure present for tuberculosis drug delivery. Thus, the GDF is a way for DOTS programs to successfully maintain a constant supply

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of drugs at a lower price.³

To address the problem of MDR-TB, a Working Group on DOTS-plus for MDR-TB (The Working Group) was established. The Working Group assesses the global MDR-TB crisis and has established the Green Light Committee to ensure proper use of drugs at a lower cost. The Green Light Committee, which includes members of the WHO, Medecins Sans Frontieres (MSF), Harvard Medical School, and the Centers for Disease Control (CDC), among others, will give the “green light” after assessing a certain area’s situation and whether or not it has the infrastructure necessary for proper drug delivery.²⁰ Thus, it has established pilot programs that can serve as models for the future if shown to be successful. Under the organization of the United Nations, the Global Fund to Fight AIDS, Tuberculosis, and Malaria (Global ATM), hopes to aid programs that fight the three diseases that are its focus through contributions from governments and organizations. Unfortunately, the Global ATM has so far had a lukewarm response from governments, including the United States. The Global Fund, asking for approximately \$10 billion per year, has only received a fraction of that amount thus far. Once again, this evidences the lack of international commitment.

Fortunately, the work of the WHO, MSF, and Harvard Medical School in lowering drug prices has paid off. Their persistence in negotiations with pharmaceutical companies created a milestone in tuberculosis treatment history in July 2001.²⁰ Through an MSF proposal of bulk purchasing, the tuberculosis drug prices have been dropped by 48 percent to 97 percent for five second-line drugs. This will allow MSF to purchase a full-treatment course for nearly \$3,000, which

normally costs \$15,000. Some countries may see as large as a 94 percent cut in drug prices.²⁰

On the other hand, a question often asked is why no current tuberculosis research is being conducted in pharmaceutical companies, especially considering the disease is the number one infectious killer of adults in the world. A WHO study analyzed the pharmaceutical response to tuberculosis research and found some startling results. The main reason stated in the report was lack of commercial return.¹¹ For such a high investment, tuberculosis drugs do not offer pharmaceutical companies the profit they desire in return. One interviewee in the survey said, “Tuberculosis is life threatening, but it has no commercial lure.”¹¹ No significant drug development has taken place in 25 years.¹¹ However, many public health officials argue that drug development is essential, especially given the current situation. If MDR-TB continues to spread, it is very likely a strain will develop that is resistant to all current tuberculosis drugs. Without continuing drug research, there will be no potential cure against such an evolved disease.

In conclusion, to say the tuberculosis pandemic is an unfortunate crisis right now is a great understatement. The disease has been allowed to evolve into something more dangerous and deadly. Unless the international community responds quickly to this threat, tuberculosis is bound to become a beast beyond all reckoning. Although strategies and solutions have been found, much more must be done to implement them to their full capacity. A partial implementation may do more damage than good. Essential to the success of tuberculosis eradication is massive funding and drug research. Without these, the world will be devastated by the disease. ■

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Water Shortage: Conservation Mechanisms in Oak Seedlings

Frederick Tan

Seasonal drought is a major problem for vegetation in California. As a result of high temperatures and variable amounts of precipitation, the availability of water itself is a form of stress. Finding sources of water is absolutely critical for survival and growth, and it often determines whether or not a plant will survive until the next growing season. In the case of newly established oak seedlings, this is especially true.

Within California's Mediterranean regions, conditions have placed a great deal of stress on two species of oak. *Quercus lobata* (valley oak) and *Quercus agrifolia* (coastal live oak) are in jeopardy because new seedlings are not surviving beyond the first or second year after germination. This in turn suggests that few seedlings reach adulthood and that a younger generation of oaks has not yet replenished older oaks in the population. The most common oaks visible along California's coasts and valleys are those that are more than one hundred years old. Without the further establishment of seedlings and the development of a younger generation of oaks, there is a clear natural regeneration problem.

Of course, many variables have to be considered when determining potential factors that affect natural oak regeneration. Herbivory by small and large native animals, ranching, aquifer use, and summer drought are all possible stress factors that prevent the establishment of seedlings. The specific factor addressed in this study, however, is the lack of available groundwater in conjunction with California's predominantly Mediterranean climate. In particular, the study was designed to analyze the various mechanisms *Q. lobata* and *Q. agrifolia* used to cope with drought.

Water Stress: Drought

Drought is a factor that many oaks face in the wilderness. For example, in the event that water is scarce, oaks respond to the lack of water in a variety of ways. It is known that some oaks close their stomata to prevent further water loss (water savers), while others leave theirs open and utilize

all available water resources to compensate for excessive transpiration rates (water spenders).¹ An oak experiencing water stress might also use a mechanism like the xanthophyll cycle to down-regulate its photosystems and dissipate excess amounts of absorbed radiation.^{2,3} Whether or not oak seedlings can respond to drought effectively is still not clear. What is clear, however, is the high seedling mortality rate in California and the possibility that lack of water is the cause.

The number of valley oak communities has rapidly decreased over the past century. In 1910, it was reported that 400 square miles of valley oak woodland covered the eastern San Joaquin Valley. Current values show that only 18.75 square miles of riparian valley oak woodland (12,000 acres) are left intact. In total, valley oaks currently occupy about 275,000 acres scattered throughout California, and even this value is still highly debated. Of this remaining acreage, approximately 10 percent is located on reserves. The remaining 90 percent is found on privately owned property. Even worse, it is estimated that there is one sapling for every 10 mature trees.⁴ As a result, the long-term reproductive success of the valley oak is at risk.

Coastal live oak communities, in contrast, have a one-to-three sapling-mature tree ratio and cover much more acreage.⁵ However, even though the coastal live oak is less at risk when compared to the valley oak, the reproductive success of this species has also been very low.

Additional Stress Factors

Underground water levels tend to vary significantly throughout California. This variance is due largely in part to differences in annual amounts of precipitation, rain that actually penetrates deeper layers of soil, surrounding environmental conditions, and the amount of water used by both plants and animals in the region. Due to California's Mediterranean climate, coastal areas receive on average between 20 and 80 inches of annual precipitation in the form of rain and fog. Inland areas receive between 6 and 30 inches.⁴

Human intervention also adversely affects water supplies in given regions. The act of build-

ing roads and cities on drainage basins decreases the recharge area for the local aquifer, thereby preventing desperately needed precipitation from seeping into the ground. Humans also use the aquifer for their own special purposes. Activities such as irrigation, gardening, farming, and ranching inevitably lead to the lowering of the water table and decreases in the total amount of underground water. Ranching and farming, in particular, lead to greater compaction of the soil, thereby changing the soil characteristics of a particular region and decreasing the likelihood of water penetration. In dry conditions, such human activities provide additional stress factors for saplings to overcome.

With every passing year, humanity's influence on water supplies grows stronger. In recent decades, California's population growth has been unprecedented. In the past 10 years alone there has been an increase of 13.8 percent in California's population (around 4,100,000 people). California's current population estimates cite almost 34 million inhabitants and rising.⁶ It is not surprising that the extent of urbanization and agricultural development goes hand in hand with population growth. Residential, industrial, commercial, and agricultural development projects have necessarily picked up the pace to appease the demands of a growing population. Most regions being developed, however, are some of the most ecologically diverse areas in the state. The effect of such population growth on California's fragile ecosystem has been of great concern.

Also, the herbivory of oak saplings is a very important factor preventing greater rates of seedling establishment. Small animals such as gophers and squirrels living near valley oak and coastal live oak communities have hindered the establishment of seedlings by consuming them at an early age. Studies conducted in the Santa Barbara region have shown greater survival rates among *Q. lobata* and *Q. agrifolia* seedlings when protected from rodents.⁷

The Study

To test how well seedlings cope in the event of

a drought, seedlings of *Q. lobata* and *Q. agrifolia*, deciduous and evergreen species, respectively, were grown at the University of California at Santa Barbara (UCSB) from acorns gathered at Sedgwick Ranch located in the Santa Ynez Valley, California. To limit genetic variation within both test populations, acorns from each species were gathered from a single parent tree.

Seeds were first germinated in plastic tubes (height 21cm, diameter 4cm) to let roots grow lengthwise. Two weeks later, seedlings were transferred from the tubes to 3-gallon-deep pots. Pots were rectangular in shape and had thin pieces of fabric mesh placed on their bases to allow drainage but prevent oak roots from growing out. Regular UC soil (1 vermiculite; 1 perlite; 1 sand; 1 peat moss; 1 oak leaf mold; 1 common soil) was used and was pounded uniformly in the pot with a wooden block so that each layer of soil would be dense and compact, simulating soil characteristics at Sedgwick Ranch. After soil compaction, every pot was watered to field capacity (about 640 ml of water per kilogram of soil). And lastly, each pot had 250 ml of pebbles (diameter 4 mm) spread over the surface of the soil to prevent excessive evaporation. Such precautions were taken so that the majority of measured water loss would be a result of stomatal opening and closure.

A total of 60 seedlings were used for the study at UCSB. Since it was decided that a representative sample would be used from each species, 30 of the 60 were *Q. lobata* and 30 *Q. agrifolia*. Each group of 30 was subdivided into two groups of 15 for water stressed and control (well-watered)

treatments. Control plants received a 500 ml refill of water every two days, while water-stressed plants received none.

The additional reason for using a representative sample of both *Q. agrifolia* and *Q. lobata* in the study was to observe the response of deciduous oaks to drought as compared to evergreen responses. In addition, it allowed for an investigation into the importance of sclerophylly, defined as the characteristic of having more leaf mass per unit area.

The role of sclerophylly as a water-conserving adaptation is still unclear. It was once thought that sclerophylly increased a plant's resistance to drought. Armed with thicker cuticles and a greater leaf thickness, it was believed that a plant with sclerophyllous leaves would fare better under water-deprived conditions and would prevent the loss of vital amounts of water through its leaves.¹ The experimental design of the study facilitates a comparison between sclerophyllous and nonsclerophyllous oaks.

To assess overall plant health and productivity, several measurements were taken over the course of the study. Measurements of overall photosynthetic rate were extrapolated from carbon dioxide uptake values. Stomatal conductance, the rates at which leaf stomata open and close during the day, was extrapolated from the amount of water transpired. Both measurements were taken with the aid of an Infrared Gas Analyzer (Li-Corr 6400, Li-Corr Corporation, Nebraska). In addition, predawn leaf water potentials were taken on the morning of each test day using a pressure bomb (PMS Instruments

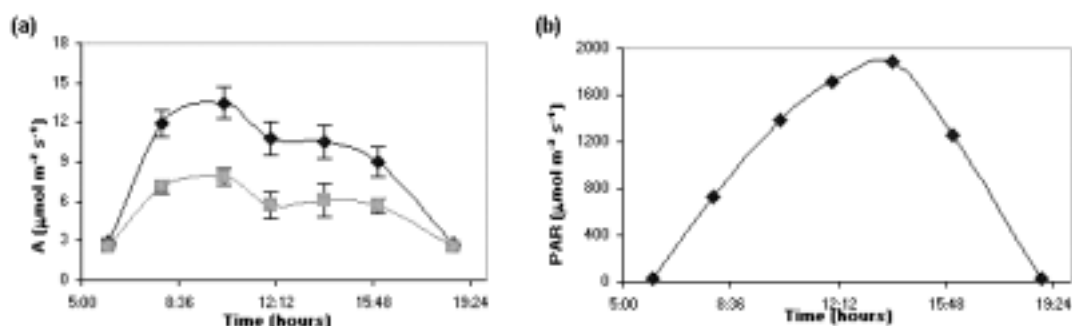


Figure 1. Photosynthetic rates (A) and corresponding light intensities (PAR). (a) photosynthetic rates (A) of *Q. lobata* (diamonds) and *Q. agrifolia* (squares) under 100% field capacity

(n=15 for both *Q. lobata* and *Q. agrifolia*). (b) light intensities present for photosynthetic rates graphed in (a).

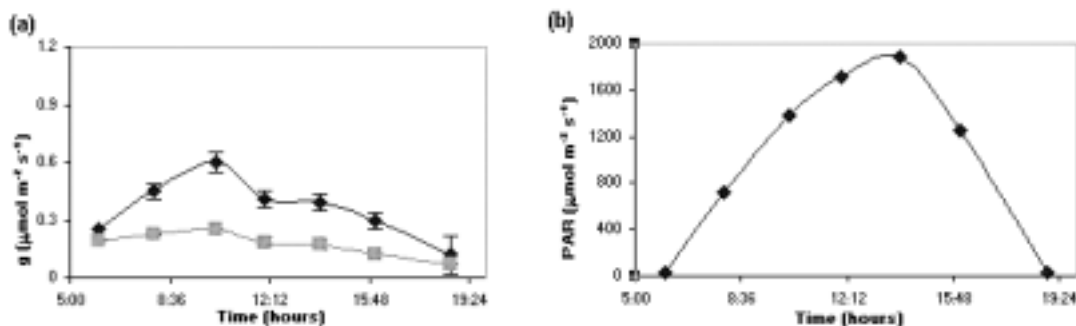


Figure 2. Stomatal conductance (g) and corresponding light intensities (PAR). (a) stomatal conductance of *Q. lobata* (diamonds) and *Q. agrifolia* (squares) under 100% field capacity (n=15

for both *Q. lobata* and *Q. agrifolia*). (b) light intensities present for conductance rates graphed in (a).

Company, Corvallis, Oregon) and fluorescence measurements were taken using a Hansatech Fluorometer (Hansatech Instruments Ltd., Norfolk, England) to assess plant photosystem health.

Daylight temperatures near the university greenhouses ranged between 21°C and 27°C, while solar radiation intensities usually reached around 2000 $\mu\text{mol m}^{-2} \text{s}^{-1}$ by midday.

Results and Implications

The plants grown at UCSB did not exhibit signs of water stress because of the large amounts of water still present inside the pots. The last measurements showed that soil was at 70 percent of field capacity for both species and that soil moisture was still very high. Signs of water stress in oaks generally appear when soils exhibit water levels between 20 percent and 30 percent of field capacity.⁸ Unfortunately that was not the case at this point in the experiment. Oaks are generally more water stressed during the months of August and September. Therefore, it was too early to make a full analysis of how oaks respond to water stress.

Photosynthetic Rate Patterns

Under nonwater-stressed conditions, both species of oak experienced photosynthetic rates characterized by morning peaks, midday depressions, constant photosynthetic levels for about one hour thereafter, and small photosynthetic bursts in late afternoon (Figure 1a). The rise in photosynthetic rate during early morning hours is a result of the presence of optimal photosyn-

thetic conditions. Seedlings took advantage of the moderate morning temperatures and light intensities. As midday approached, rapid increases in both temperature and light intensities resulted in decreased photosynthetic rates (Figure 1b). Late afternoon bursts of photosynthesis are a result of optimal photosynthetic conditions, as during the early morning hours of the day.

This type of photosynthetic pattern is characteristic of some Mediterranean evergreen oak species.⁸ Surprisingly *Q. lobata*, a deciduous oak, exhibited similar photosynthetic patterns.

Changes in Stomatal Conductance

The opening and closing of leaf stomata necessary for CO₂ uptake is absolutely the greatest water investment a plant makes during the day. Almost all of the water a plant loses is a result of transpiration, which in turn is a direct result of stomatal conductance. Therefore, to see how seedlings react to a lack of water, stomatal conductance observations would be of great value.

Measurements taken on experimental seedlings (oaks at 100% to 70% of field capacity) revealed that average stomatal conductance rates were characterized by rises during early morning hours, decreases during midday, fairly constant levels for about an hour, and declines during late afternoon (Figure 2a). It should be noted that conductance patterns were somewhat parallel to photosynthetic rates.

Sclerophylly

Additionally, there is no significant difference between the responses of deciduous oaks and

Recommended Reading

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evergreen oaks. The data suggested that sclerophylls made no significant contribution to *Q. agrifolia*'s resistance to drought. However, since the study did not run to completion, it is too early to draw a definite conclusion on this matter.

Interdependence

The close relationship between stomatal conductance and photosynthetic rate is no surprise. Photosynthetic productivity is largely determined by the amount of carbon dioxide present in the leaf. And in turn, levels of carbon dioxide depend almost entirely on how often leaf stomata open and close over the course of the day.

Since stomatal conductance is influenced by a lack of water, one would expect that photosynthetic rate, by default, would be adversely affected as well. Unfortunately, the experimental oaks were last measured under normal conditions (70% of field capacity). The amount of measured water loss from the soil per day for both species of oak averaged 30 ml. Such a slow rate of drying led to the failure of the experiment. Due to the onset of winter and a worsening climate, the experimental oak saplings at UCSB were not allowed to reach greater degrees of water stress, and the

experiment had to be abandoned. Further study is needed to assess the full effect that drought has on *Q. lobata* and *Q. agrifolia* saplings.

Previous Research

Studies involving the evergreen oak *Quercus suber* and the deciduous oak *Quercus faginea* addressed the same question. Of interest was whether or not the dominance of *Q. suber* over *Q. faginea* in southwestern Portugal was a result of drought. The results showed that the evergreen oak species *Q. suber* was more capable of adapting to drought over the deciduous *Q. faginea* because of certain mechanisms that allowed it to conserve vital amounts of water. For example, stomatal conductance for *Q. suber* declined during midday, even when not water-stressed, thereby preventing excess transpiration of water. Also, the amount of water *Q. suber* stored in its leaves was significantly less.⁸

Such differences were not apparent in the study conducted at UCSB, but it does provide grounds for further research.

Acknowledgments

Special thanks to Catarina Mata. 🇵🇹

On the Refugee Problem in Eritrea

Selam Daniel

Introduction

By the end of 2000, at least 34.5 million people—refugees and internally displaced—had fled their homes because of war, persecution, and human rights abuses.¹ Combined, the number of people that have been uprooted roughly equals the sum of the populations of Austria, Belgium, Switzerland, and Greece.²

Of these, an estimated 25 million people are internally displaced in at least 40 countries.³ These people live in Kosovo, Sierra Leone, the Sudan, Afghanistan, Colombia, and many other countries. Afghanistan hosts the second largest community of internally-displaced persons (IDPs), after Eritrea.⁴

The United States Committee on Refugees estimates that there are over 14 million refugees worldwide⁵—an increase of 4 percent from last year, with Afghanistan, Burundi, Iraq, Sudan, Bosnia-Herzegovina, Somalia, Angola, Sierra Leone, Eritrea, and Vietnam as the top 10 countries.⁶

The following analyzes the refugee crisis of Eritrea as a case study to better understand the plight of refugees and the internally displaced worldwide, and to identify ways that the international community can help.

Eritrea: A Brief History

At the end of the nineteenth century, Italians colonized Eritrea, joining together loosely related people from nine ethnic groups. The original ratio of 50 percent Orthodox Christians and 50 percent Sunni Muslims still exists today. Their forced colonization disrupted already existing economic, social, and legal systems in these communities. The Italians developed Eritrea as a settler colony, setting up roads, plantations, seaports, and an army of 65,000 Eritreans who would fight in Italy's other colonies, Libya and Somalia.

In 1952, the UN combined Eritrea with neighboring Ethiopia under a federation, giving Eritrea two official languages and its own flag, constitution, and parliament. The United States, interested



IDP camp in Gash Barka, Eritrea.



Top: Eritrean woman in Senafe IDP camp. Bottom: Festivities in Gherset celebrating the fourth day of a baby's life.

in the strategic Red Sea access from Eritrea, backed this pact, gaining several military and communication bases in Eritrea as a pay-back for the arrangement. No poll was ever taken asking the Eritrean people to vote on the matter.

Immediately after this federation was formed, the emperor of Ethiopia, Haile Selassie, completely stripped Eritreans of all rights and autonomy, as had been agreed upon in the pact, and banned all forms of public protest. Eritreans were met with silence when they petitioned the UN to at least uphold the terms of the federation pact. Further, Emperor Haile Selassie disbanded the Eritrean national assembly and annexed the territory, triggering a 30-year liberation war by Eritreans. It is widely believed among Eritreans and non-Eritreans alike that these events and the failure

of the international community to act justly without underlying interests are the sources of the current suffering in Eritrea.

The next 30 years of the liberation war were critical in defining the Eritrean government's growing distrust with international agencies. Although Eritrea and Ethiopia share roughly the same geography and demographics, Eritrea was left to fend for itself in gaining its freedom and keeping its population from starving to death. Meanwhile, many of the world's great powers looked upon Ethiopia with mainly political motivation and contributed billions and billions of dollars in food and military aid. In fact, from 1952–1976 more than half of all U.S. aid to Africa's 54 countries went to Ethiopia.⁷

In the 1950s, in the midst of a war fought by civilians in rubber sandals with rifles, the United States introduced the first jet fighters to appear on the African continent. Their mission was to fight for Ethiopia to conquer Eritrea in return for prime land on the Red Sea's coast for communication and spy bases to monitor Europe and Asia. The jet fighters raised the level of military sophistication with U.S.-supplied F-86 Sabre Jets and counterinsurgency tactics borrowed from the

Vietnam War. Israel also sent military advisers and arms. When the reinforced Ethiopian army invaded Keren, a market center in the heart of the country, the first flow of Eritreans fled to Sudan.

When a military junta overthrew Emperor Haile Selassie in 1974, the Soviet Union became aligned with Ethiopia. The war escalated quickly when \$11 billion in new arms from Moscow were sent to Ethiopia's capital, Addis Ababa. The second wave of refugees fled to Sudan. Fighting had reached the heart of the Eritrean capital, Asmara, which changed the demographics of the refugees to also include urban as well as rural dwellers.

In 1978, fighting almost entirely with captured weapons, the Eritreans were able to secure the Sahil Mountains of Eritrea, occupying this area as a base for the next 10 years.

A massive famine in 1984 posed an even larger problem. Tens of thousands of Eritreans were forced to cross the border into Sudan in search of food and safety. It is estimated that the number of Eritrean refugees in Sudan had peaked at about 500,000.⁸

For the next 13 years, thousands of Eritreans and Ethiopians died as the war continued. In May 1991 Eritrea overthrew Ethiopia's Mengistu Haile Mariam, finally obtaining its freedom.

Current Refugee Situation

Over the last 30 years, more than one million Eritrean refugees languished in exile abroad, more than half of them in urban slums and rural refugee camps in Sudan.⁹ Although several hundred thousand people have returned to Eritrea, there are still an estimated 142,000 Eritreans in Kassala and Gedaref in Sudan.¹⁰ The U.N. High Commission for Refugees (UNHCR) has worked in collaboration with UNMEE (UN Mission in Eritrea and Ethiopia) to repatriate a total of 36,500 Eritrean refugees from Sudan.¹¹ An overwhelming majority of these refugees originally come from Gash-Barka, the western region of Eritrea.

Within Eritrea, another 50,000 are currently internally displaced.¹² These IDPs have fled three times in the last 10 years, each time because of renewed military conflict. They lived in relatives' homes when lucky enough, but mostly they fled to the mountains, where they attempted to do what Eritreans do best: survive. Right now there is no Ethiopian occupation in Eritrea, but land mines prevent the IDPs from finally going home.

Eritreans that lived in Ethiopia were also expelled in 1998 when full-scale fighting broke out again. In 2000, when Ethiopia captured about one third of Eritrea's sands (the Gash Barka Zone), one million Eritreans fled, including tens

of thousands of new refugees to Sudan. Tens of thousands of Eritreans had been permanently disabled, hundreds of thousands dead. A third of the population was displaced, a third of those people being children. It is estimated that every Eritrean family lost two or three members to the war. It is this deepest sacrifice of flesh and blood that makes the reality of the current emergency situation even more painful for Eritreans worldwide. The male population has been decreased dramatically, affecting the most fundamental socioeconomic systems in the country. Among the refugee population, an overwhelming majority of families are female-headed, severely affecting agricultural production. For IDPs in particular, 80 percent of households are female-headed.¹³

Field Research

The meaning of the title of Dan Connell's *Getting Home Is Only Half the Challenge* really hit home in my recent trip to Eritrea. Over the course of three weeks I attempted to experience and photograph the refugee experience of the IDPs and repatriates of Eritrea. It was one thing to read reports and statistics, it was an entirely different thing to see the crisis through their eyes.

Education

One woman told me that she had chosen to settle in Gherset because it offered better schools for her children than the other resettlement camps in Gash Barka. Her three children attended school at the UNESCO funded facilities. (See photo.) In most areas, school is available until the 5th grade in both Tigrinia, the national language, and Arabic, a language spoken by most Eritrean Muslims, especially those returning from camps in Sudan. When possible, the schools are integrated to facilitate the full inclusion of refugees into society. The teacher of the school pictured estimated about 80 students per class. School is held six days a week, from 7 a.m. to noon. At the beginning of each school year, each pupil receives five exercise books to write in. The schools lack other educational supplies to enhance the lessons, such as maps and charts. In other resettlement villages, especially in areas where IDPs have fled, school is being held in abandoned buildings, and under trees.

Health

I visited Gherset on a very special day. It was the fourth day of a child's life, and the celebrations had just begun. She was born to a 27-year-old woman who had lived in a refugee camp in Sudan since the age of 3. She had grown up, married, and given birth to her three other children in a refugee camp. She had lived in Gherset for

seven months with her mother, aunt, husband, and children. The birth was her fourth. Each time her mother had been the midwife; the floor of the tent had been their maternity ward. I asked what would have happened if there had been complications with the birth. The aunt stared at me blankly. The mother looked at the ground. The grandmother looked at her hands in her lap. I shifted uncomfortably. Outside, the translator/guide told me that there was absolutely no transportation to or from the camp. Since there was also no on-site health clinic, refugees could not take advantage of the free health care that their refugee I.D. cards granted them at any health clinic in the region. I asked the local guide when he had last seen a doctor. He said it had been a few years—since the day he had left Sudan.

Every repatriate undergoes a basic health screening for sicknesses that would allow him or her to sit in a bus rather than stand in a truck. There are not enough medical supplies to afford a follow-up visit for the thousands of war-injured refugees. Malaria and polio are the most common sicknesses reported in the clinics.

That afternoon, my host family prepared a very special dinner—*ghat*, a meal made from flour roasted on an open fire and mixed with boiling water and salt. As the women stirred the flour, they made loud, high-pitched jubulations, signaling the great miracle for the entire neighborhood to hear. Another child had been born in Gherset.

Food Aid

Food is distributed once a month in Senafe to the 11,000 IDPs who reside in the area. Representatives from each family make the trip to the distribution site, sometimes walking for more than a day. Each person receives wheat, oil, salt, and kerosene.

For repatriates, a two-month ration is given upon entry to Eritrea as well as a metal and canvas family shelter kit. The UNHCR also distributes hand tools for farming, or a cash equivalent for those who wish to resettle in the cities. No training is provided, however, as part of the aid package. In some areas, distribution of two



Top: Gherset school and teacher.
Bottom: Festivities in Gherset celebrating the fourth day of a baby's life.

hectares of farmland per refugee family has begun. After their first two months, they receive monthly food rations for one year. After that, they are expected to have found means to survive.

For both groups, high-calorie biscuits are given, when available, to malnourished children and pregnant or lactating mothers, but recent shortages have made this difficult.

Shelter

Each family receives a *rhonda* structure (a domelike metal frame of about 10 feet by 6 feet) and the mats needed to cover it—straw mats for summer, plastic mats for the rainy season. The locals say that even in the rainy season, it is often too hot to use the plastic mats, so they do their best to improvise with mud and straw, bending and shaping the *rhonda* structure to better suit their needs. (See photo.) In the early 1990s corrugated metal was often donated by international agencies, but has since been abandoned as the heat makes the metal an unsuitable roof. Occasionally, fire breaks out in one hut, and several homes can quickly burn to the ground at once.

Currently, there is a shortage of *rhonda* structures all over the country, leaving families to live in plastic tents held up by branches and ropes. Often, a tent of about 200 square feet, partitioned by a cloth to make separate rooms, houses a family of seven. If the family keeps livestock such as feed chickens, they must also share the space, as there are no permanent materials with which to make sturdy fences. UN volunteers say it won't be long until the tents run out.

Water

Drought has affected water supplies for both agriculture and drinking for the last 17 years. At the camps, water is either available by pump or delivered by trucks once a month. Diseases are rampant, especially in those camps where water is kept in large storage tanks for extended periods of time. Widespread chlorination will not be possible until an organized water system is developed for the entire country. Even in the capital city, residents are being forced to turn to bottled water as the Italian-built pipes are beginning to rust, releasing dangerous chemicals into the water supply. For the poorer residents, there is no way to avoid the risk of drinking these poisons. Sanitation is a concern, as these refugees have inhabited temporary housing for years. Long-term human waste systems have not been developed. In some camps, makeshift latrines have been set up on the outskirts of town, but many people simply head to the mountains. For the stalls, there are sanitation workers who empty the

large tanks of human waste when they are completely filled. Combine this lack of proper latrines with a poor water supply and poor handling at the household level, and you have the potential for severe diarrhea outbreaks, especially among children.¹⁴

Land Mines

Four teenage boys were killed and three others seriously injured in a mine accident outside Senafe during my last week in Eritrea. According to the UN Mine Action Coordination Center (UNMACC), inhabitants of that area had been educated about land mine safety procedures, and the demarcations had been made.¹⁵ In the last few years, over 70 people have died in mine accidents, and over 150 more have been injured. Clearly, deactivation of land mines is a key factor in determining when many of the IDPs can return home safely.

Solutions

While there is no definitive answer for the refugee problem in Eritrea, or any other part of the world, there are a number of potential solutions worth investigating. The key to any sustainable solution is that it is designed especially for these refugees given their exact circumstances; a cookie-cutter approach certainly will not work. The problems are multitiered. There is the immediate concern for the basic human needs such as food and shelter, but there is also the need for organization of health care and water systems and a long-term strategy for reintegrating these refugees into society. Among the many needs in Eritrea:

- Training for repatriates on making an income.
- Supplies for elementary and secondary schools in camps.
- Medical supplies including land mine kits, malaria, and polio vaccinations.
- Improved structures built to better suit Eritrea's geography and climate. Also, a material alternative to the traditional wood and thatch, which is used to build homes but is currently in short supply.
- Water sanitation systems suitable for either individual homes or entire camps, but also separate systems for agriculture and livestock.
- Land mine clearance teams to mark dangerous zones, and deactivation of the more than 2 million mines¹⁶ that exist in Eritrea.
- Family reunification programs to address the separation of families in the aftermath of the Ethiopian-Eritrean conflict. ■

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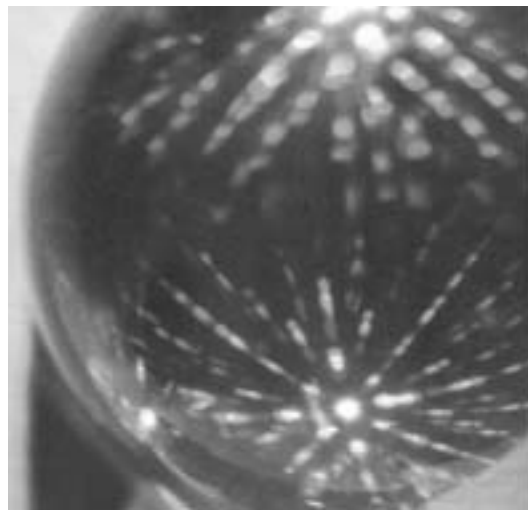
Palladium Coatings of Targets for Inertial Fusion Energy

Elizabeth Stephens

Whether arguing about geocentric orbits or creating stories of rebellious gods cast into the heavens for their deeds, humans have needed to understand and rationalize the heavens. The ancient Mayans revered the stars and, in some sense, conquered them by forming incredibly accurate models of the heavens. In the field of nuclear fusion today, scientists have a new dream for star conquest: to harness the energy of the stars to fuel our human world. General Atomics is working to produce a viable fusion energy plant within the next 20 to 40 years. The specific goal may be simply stated. Work in the form of electromagnetic energy is put in to get energy out, and the net must be maximized. The energy utilized is what binds the very nuclei.

Fusion promises to offer a clean (minimal radioactive by-products), inexpensive, and abundant (obtained from water) source of energy for the future. Inertial Fusion Energy (IFE),^{1,2,3} which involves compression of a small (~ 2 to 4 mm in diameter) deuterium-tritium-filled (DT-filled) shell, the “target,” by a driver such as a high-power laser, is an alternative to the more conventional magnetic fusion scheme. In order for this to be profitable, the process must occur six times per second and cost less than 30 cents. The shells also need to have shell walls on the order of tens of microns and uniformity within 10 percent. These are very challenging constraints.

Fabrication of the target for IFE experiments is a crucial step in making this scheme viable. The most promising current designs for IFE include a so-called “radiation preheat direct drive target” (Fig. 1). The shell can be thought of as an inner portion of fuel (payload) surrounded by an ablator with hi-Z rich exterior. Laser beams are used to vaporize the ablator and reaction forces from the ejected gases compress its contents. But as the laser vaporizes the hi-Z coating, the hot



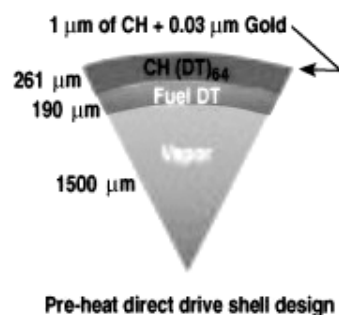


Figure 1

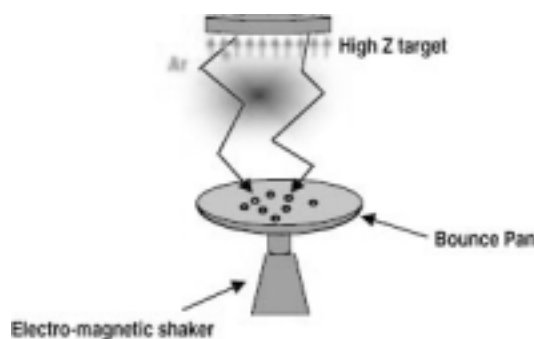


Figure 2

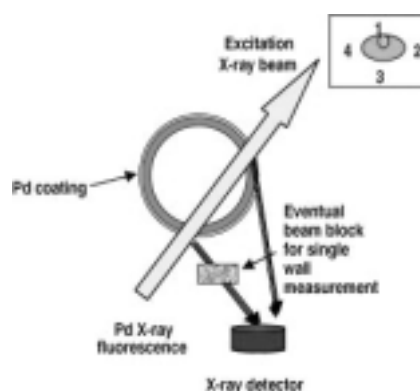


Figure 3

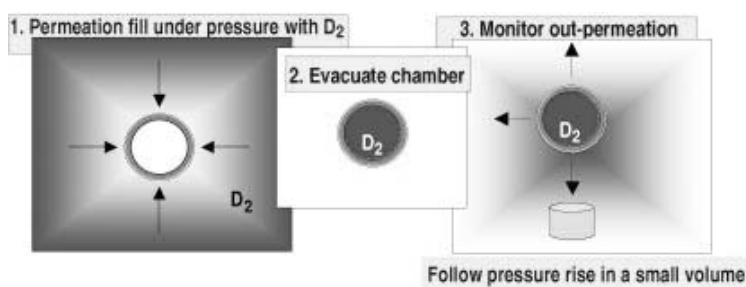


Figure 4

plasma emits a short burst of x-rays that penetrates beneath the vaporization front and, by heating the ablator, stabilizes it against instabilities. But the target first must get to the center of the hot reaction chamber without the fuel layer melting. By concentrating the hi-Z material into a surface coating and choosing a reflective metal for the element, this component could also protect the frozen fuel from exposure to blackbody radiation of the chamber. The chamber must be hot in order to maximize thermal efficiency of the power plant, as governed by Carnot cycles. High reflectivity of such a coating is required in order to tolerate the blackbody radiation from such a chamber. Therefore, coatings with high reflectivities are desired. Secondly, the coating of the shell must enable a quick fill time. Because of the hazards of tritium, its degradation into He3 creating bubbles, and the practical functioning of a power plant needing to shoot six shells per second, the fill time must be short and the tritium inventory kept low. Knowing that the fill time is directly proportional to shell permeability,⁵ ideally the shell must be quite permeable.

Previous work involved the use of gold as the overcoating for its excellent reflectivity in the optical wavelength region of interest (~ 0.5 to $25 \mu\text{m}$). Au coatings, however, had proven to be not permeable enough for a practical power plant. We chose to investigate Pd because of its known high permeability to hydrogen and its isotopes.^{6,7} This particular metal had also proved promising in the computer simulations. Pd reflectivity is known to be lower than Au, but there were significant discrepancies in previous works on Pd reflectivity.⁸ Our work addressed that question as well.

The work reported in this paper describes deposition and characterization of palladium as the hi-Z material. We have deposited Pd on shells while they were agitated to obtain uniform reproducible coatings. We have used an x-ray fluorescence technique to accurately measure thicknesses and uniformities of the deposited layers on shells. We have demonstrated that these palladium-coated shells are substantially more permeable than gold, the previous hi-Z material used. While Pd coatings on flats deformed and cracked, Pd coatings on shells remained stable upon extended and repeated exposure to the surrogate fusion fuel, D2. The main disadvantage of Pd coatings compared to Au is their lower reflectivity, which leads to a lower working temperature of the proposed fusion reactor.

II. Experimental Techniques

A. Deposition Pd coatings were sputtered onto targets.^{9,10} We used both flat targets, such as glass slides and Si wafers, and shells. In the future this coating will actually go onto a foam shell. Since foam shells are not yet available, we used full-density PAMS (poly-alpha methyl styrene) shells. In order to uniformly coat shells we used an electromagnetic shaker that rapidly bounced the shells. A number of different variables could be controlled in the deposition process. These included the sputter gunpower, gun-substrate distance, deposition pressure, and shell agitation. The pressure and gun-substrate distance are particularly important, because the longer the path or the more particles in the path, the more likely it is that the sputtered Pd atoms will scatter and lose kinetic energy before arrival on the substrate, resulting in less dense and reflective coatings. Therefore, both higher pressure and longer gun-substrate distance result in more scattering and less dense coatings. There was a minimum gun-shell distance, since the PAMS shells cannot be brought too close or they will melt. We used the deposition condition on flats and shells for consistency.

B. Thickness Measurement by X-Ray Fluorescence (XRF) (Fig. 2) Since the thickness of Pd needs to be a narrow range (~ 300 to 1000 \AA), it is crucial to measure the coating thickness accurately. In addition, we needed to ascertain any Pd thickness nonuniformity around the shells. Coatings are traditionally measured using profilometry, which simply traces the profile of the film where a portion has been scratched off. It is practically a step measurement. Profilometry, while possible on flats, is impractical to use on shells. A witness plate can be used for each coating run alongside the shells.¹¹ However, there are a number of problems with that technique. The amount of metal deposited onto a flat such as the witness plate is not equal to that deposited onto a shell. If there were no scattering, one would expect an area on a witness plate to have four times the amount of coating than that of an area of shell. This is determined through simple geometry: A shell's area is four times that of a flat; because these shells are bouncing randomly, the entire shell surface is coated. But the scattering of sputtered material on the way to the shells can alter this factor from the theoretical value of four. Furthermore, it is difficult to position the witness plate correctly, because it can be placed only at the edge of the pan. When the witness plate is placed at the same height as the shells, it is inaccurate due to shadowing of the edge of the pan.

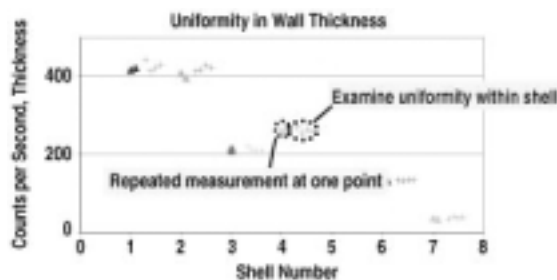


Figure 5a

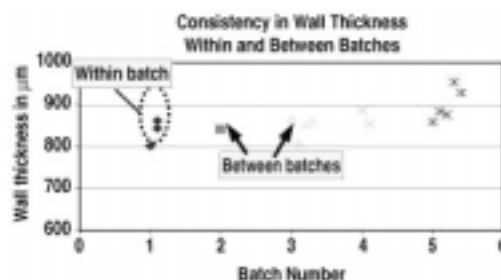


Figure 5b

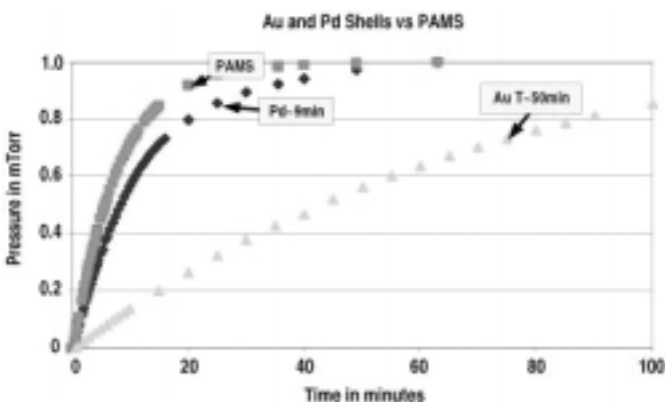


Figure 6

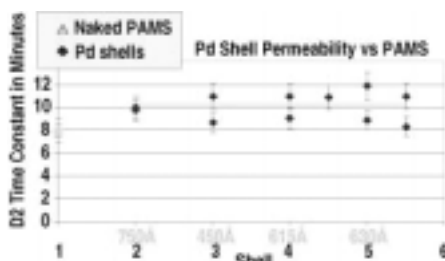


Figure 7

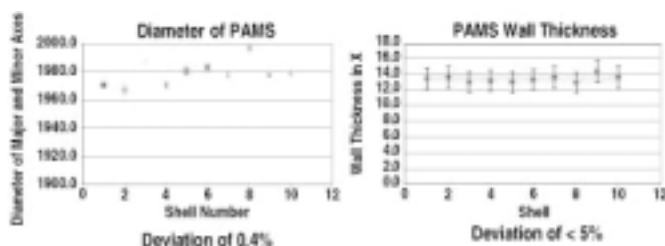


Figure 8

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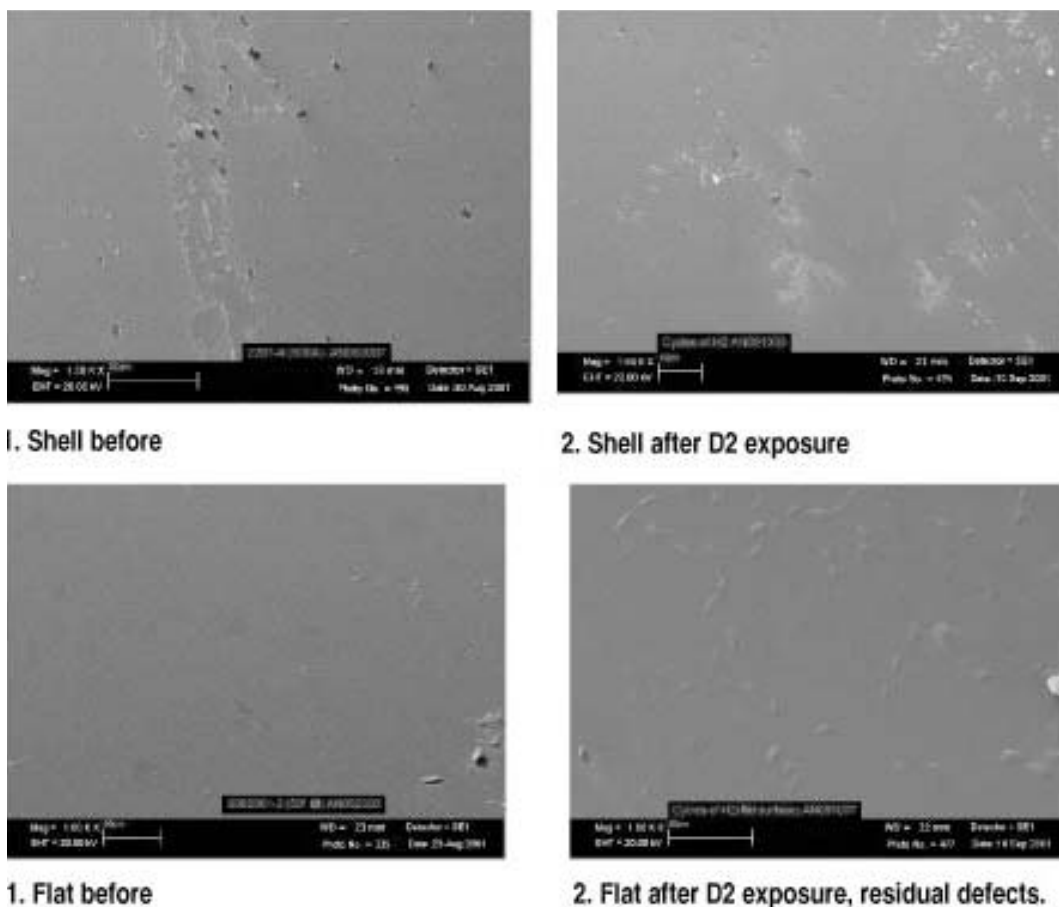


Figure 9

On the other hand, if it is placed such that there is no shadowing, it is significantly higher than the shells. In any case, the witness plate is not in the same condition as the shells. In addition, no thickness uniformity information on the shells can be obtained when using a witness plate.

XRF provides a relatively simple, non-destructive method to determine the amount of metal deposited. In this method the sample is hit with an x-ray beam. As a result, the metal is excited and emits x-rays characteristic of the elements present in the sample. A detector captures a portion of these x-rays and the resulting peaks correspond to the amount of element present in the sample.¹² In measuring shells, the beam hits two spots on the shells (Fig. 3). The shell is aligned so that one beam hits the south pole and the other hits a spot on the outer circumference. The resulting signal includes the metal from both spots. By rotating the shell around the z-axis (keeping the south pole spot stationary) we could vary one of the spots measured instead of two. Therefore, wall thickness of individual spots on the shell can be measured providing the much-needed uniformity data. To make this method more accurate we plan on blocking the beam emitted by the spot at the south pole so that only one spot will be

measured. In this process the beams also traverse the PAMS, but we found that there was no attenuation from the PAMS.¹³

C. Permeability Measurements (Fig. 4) In order to measure the permeability of our shells, we placed the shell in a small-volume chamber with a pressure gauge. After filling the chamber for several half-lives, such that the shell was almost completely filled with gas, the chamber was evacuated. Then the pressure rise in the chamber resulting from the outgassing of the shell was monitored. This rise in pressure was then fitted to an exponential function to determine a permeation half-life. Background outgassing from gas absorbed in the chamber walls was taken into account when appropriate.^{14,15}

III. Results and Discussion

Palladium

As mentioned previously, in an effort to improve permeability characteristics of the composite target, we turned to palladium to replace gold. Palladium has the unique quality of being highly permeable to hydrogen and thus is frequently used as a catalyst and in purifying hydrogen. However, Pd films are also known to greatly

deform and crack under exposure to hydrogen due to a large expansion of their crystal structure.^{16, 17, 18, 19, 20}

We successfully coated PAMS shells with palladium. We then analyzed the shells for uniformity and consistency, permeability, reflectivity, and cracking in the Pd layer upon exposure to deuterium. Uniformity measurements were performed using the XRF technique. By rotating the shell along the z-axis and keeping one spot fixed we could measure wall thickness at different points. The data from these measurements showed that the variations of wall thickness on an individual shell were within the measurement error (Fig. 5a). We proceeded to check the shell-against-shell uniformity within a given batch (Fig. 5b). These measurements showed that the shells within a batch were uniform within the measurement error of about 10 percent. We then wanted to verify that shells of different batches were consistent. In analyzing shells of different batches we also found consistency of about 10 percent. So the shells produced were uniform and reproducible.

We used palladium for its permeability to hydrogen and its isotopes, which our experiments confirmed. Due to radioactivity issues with DT, we used deuterium (D₂) gas as a surrogate for the permeability measurements. Figure 6 shows that outgassing data for deuterium through a bare PAMS shell and an ~ 1100Å Pd-coated PAMS shell are very similar. In general, Pd-coated shells have a permeation time constant of about 10 ± 1 minute, only slightly less permeable than the bare PAMS ($\sim 8 \pm 1$ min). Therefore, Pd coatings are indeed very permeable when compared to gold coatings, which had time constants of ~ 1 hour for $\sim 250\text{\AA}$ coatings, as previously measured. Interestingly, we found that the permeability of Pd shells did not depend on the coating thickness. Shells of considerably different thickness exhibited the same time constant (Fig. 7). This implies that there may be a limiting step such as disassociation of the D₂ into Pd and then the gas would quickly pass through to the center. The variation of permeability between shells was within measurement errors, but any variation of the mandrels underneath the Pd would contribute to our measured variations in permeability of palladium shells. In order to determine how much of the variation was caused by the mandrels, we measured the variation in diameter and wall thickness of the mandrels. These two factors directly determine the time constant. From this analysis we found that variation in diameter contributed a 0.5 percent error, while variation in wall thickness contributed a 5

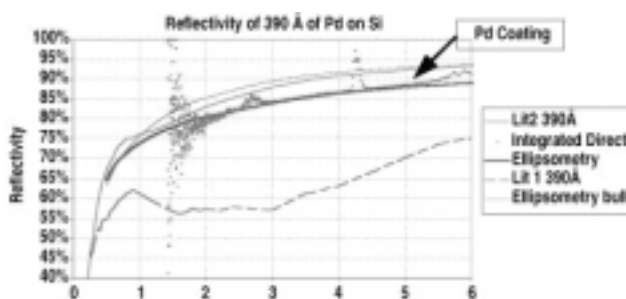


Figure 10

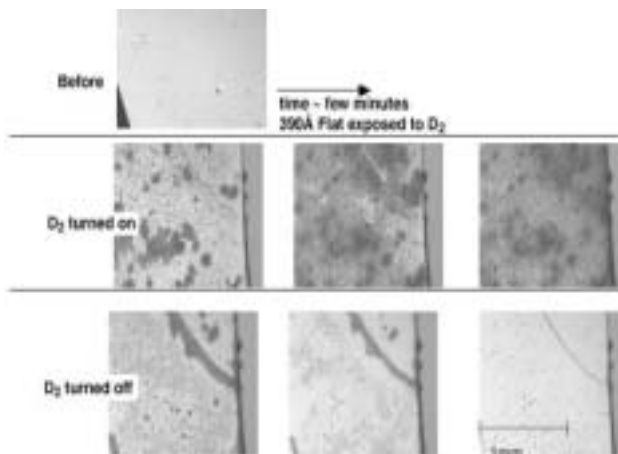


Figure 11

percent error (Fig. 8). These errors, therefore, contribute to the 10 percent error we saw in Pd-coated shells, but it seems that some of the variation is due to the palladium coating itself.

In order to test for deformation, we coated a glass plate with palladium and exposed it to D₂ for a period of several minutes. Immediately, the coating exhibited gross deformities that grew worse over time. When the D₂ exposure stopped, the coating began to lose its deformities, but the coating on the plate never returned to its original state (Fig. 9). In performing the same experiment with palladium-coated shells, we found no visual deformations. SEM examination of the shells and flats confirmed these results. While the shells displayed the same amount of nonuniformity before and after exposure, the flats showed residual defects from D₂ exposure (Fig. 10). Furthermore, we saw no deformation in the shells that were repeatedly exposed to D₂ for longer periods of time in permeation measurements. From these results, we inferred that filling with DT should be rapid and cause no damage to the Pd coating layer.

We expected the reflectivity of the palladium coatings to be lower, and this was confirmed. Although our palladium coatings had reflectivities that were close to the highest literature values

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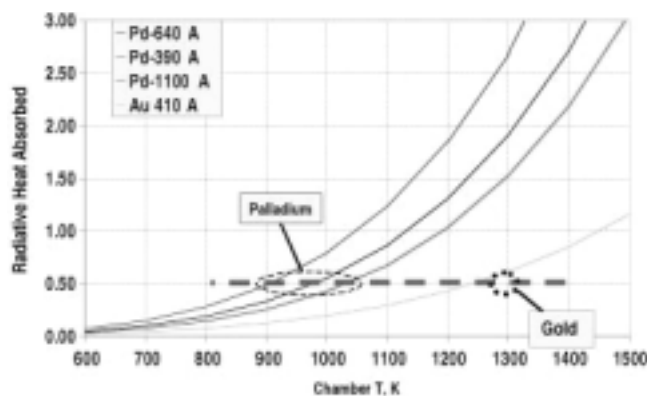


Figure 12

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for palladium, they were still below that of gold (Fig. 11). An important feature to notice is the large spread in the literature values. This demonstrates the effects of different deposition conditions and working methods on reflectivity measurements.²¹ The measurements were done on flats using two independent methods, ellipsometry and integrated direct measurement. In ellipsometry, the material's optical constants, n and k values, are found and can then be used to determine reflectivity at arbitrary angles of incidence using the Fresnel reflection equations.^{22, 23} The second is simply a direct measurement of the light reflected over all angles for a specific angle of incidence. It should be noted that reflectivities obtained by direct measurements were taken at discrete angles and were used for rapid feedback for process control, and thus they are adequate for comparisons only. Ellipsometry results provide reflectivities at all angles, which are needed for calculation of the heat load on the target because it experiences the omnidirectional radiant heat as it traverses the hot reactor chamber before it gets shot by the driver beams.

We convolved the data with a blackbody spectrum to determine the total heat absorbed at various chamber temperatures. Then, by using the maximum heat absorption value for target survival determined by the detailed thermal calculations and simulations,^{24, 25} we found the maximum chamber temperature for which shells coated by various thicknesses of Pd would survive the

chamber heat (Fig. 12). The calculated values for gold-coated ($\sim 300\text{\AA}$) shells are also shown. While the gold shells could survive at a maximum temperature of 1,300K, the optically opaque palladium shells could survive at a maximum of 1,100K. Although this is a disadvantage of the Pd coatings, we hope that by using mixtures of Pd and Au we can form coatings that have high permeabilities, due to Pd presence, and high reflectivities, due to Au presence. In fact, initial results on this work are encouraging and will be reported in a future publication.


IV. Conclusion

We deposited Pd on shells while they were agitated to obtain uniform reproducible coatings; we used the XRF technique to accurately measure thickness and uniformity of the deposited layers on shells; and we demonstrated that these palladium-coated shells are indeed substantially more permeable than gold. While Pd coatings on flats deformed and cracked, Pd coatings on shells remained stable upon extended and repeated exposure to D2. The main disadvantage of Pd coatings compared to gold is their lower reflectivity. We hope that adding gold to the Pd coating will increase reflectivity while maintaining high permeability. Initial results on this work have been encouraging.

Over the long term, we need to measure reflectivity of actual shells instead of flats, measure reflectivity in cryogenic conditions, examine coating actual foam shells to be used in IFE, and adjust permeation temperature in order to find optimal permeation conditions.

Acknowledgments:

Special thanks go to Abbas Nikroo for his contributions to this work. Without his direction none of this could be accomplished. Thanks also to General Atomics for its generous support of student research.

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Regulation of ADAR2 Activity by RNA Editing

Jay Shrestha

Introduction

RNA editing is a posttranscriptional modification of gene-encoded sequence, which allows organisms to produce functionally distinct proteins from a single gene. It can involve single- or multiple-base deletion, insertion, and/or substitution in the pre-mRNA (mRNA prior to splicing). This is a widespread phenomenon in eukaryotes.

Modification by deletion and/or insertion is found mainly in mitochondria of primitive eukaryotes.¹ Editing in mammals is comprised mostly of cytidine-to-uracil (catalyzed by RNA-dependent cytidine deaminase) and adenosine-to-inosine (catalyzed by RNA-dependant adenosine deaminase) conversions. These conversions are a result of hydrolytic deamination reactions catalyzed by the respective enzymes. These base conversions may give rise to changes in codons and thus in the amino acid sequence of the gene, which in turn can affect the function of the encoded protein. As editing occurs prior to splicing of the pre-mRNA, these conversions can also result in alternative splicing. The increase in variation of protein sequence encoded by a single gene can be better understood by looking more closely at such edited proteins. Glutamate receptor protein subunit GluR-6 in the central nervous system has three potential exonic editing sites in its pre-mRNA: isoleucine/valine, tyrosine/cysteine, and glutamine/arginine. Editing can give rise to a mixture of eight alternative sequence configurations.^{2,3} In transcripts of *cacophony*, which encodes the voltage-gated calcium channel in *Drosophila*, the presence of 10 different editing sites gives the potential to generate more than 1,000 different protein isoforms by RNA editing. This number can increase if we take alternative splicing into consideration.^{4,5}

Three different RNA-dependent adenosine deaminases (ADAR) have been determined: namely ADAR1, ADAR2, and ADAR3 (RED2) (Figure 1). These enzymes contain a deaminase domain near the C terminus and two or three double-stranded RNA binding domains 5' to the deaminase domain. They also contain nuclear localization sequences (NLS) that bind to different nuclear transport proteins. ADARs have homology to DNA methyltransferases, which methylate DNA by a base flipping mechanism. It has been suggested that ADARs also follow this "flip out" mechanism for editing dsRNA.⁶

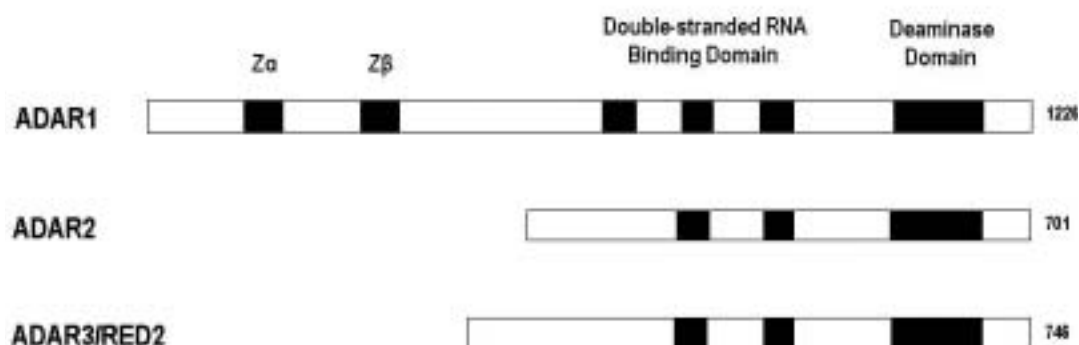


Figure 1

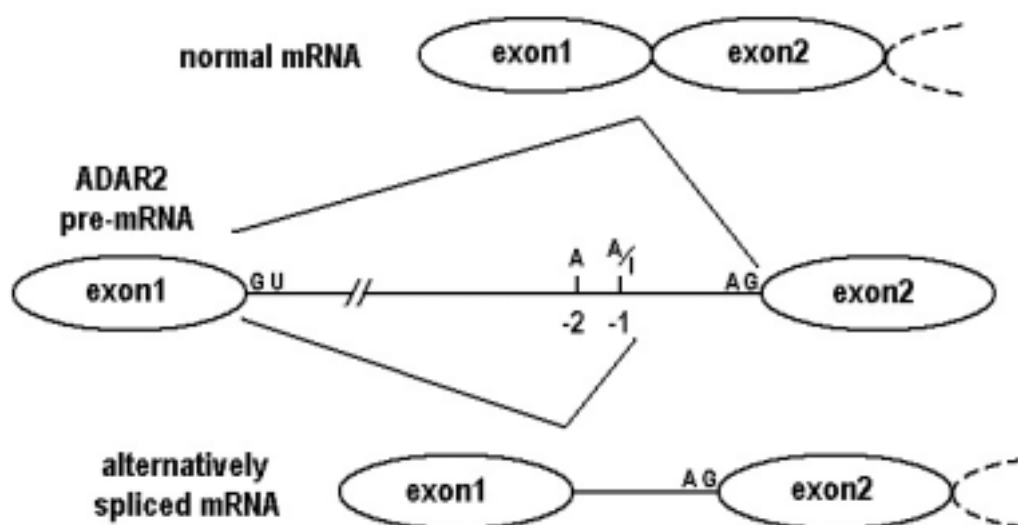


Figure 2

ADAR1 also contains two Z-DNA binding domains called Z α and Z β near its N terminus. The presence of the Z-DNA binding domains in ADAR1 has led to an interesting deduction of mechanism by which ADAR1 may carry out its function. Z-DNA forms transiently due to the torsional strain generated on the DNA as RNA Polymerase travels down during transcription. It has been proposed that ADAR1 binds to this trail of transiently formed Z-DNA. This brings ADAR1 in close proximity to its substrate, which is the pre-mRNA being transcribed by the RNA Polymerase.⁷

ADAR1 and ADAR2 are almost ubiquitously expressed (Wagner et al). ADAR3 (RED2) is expressed exclusively in the brain, but it cannot

catalyze deamination of adenosine in dsRNA nor can it edit any known pre-mRNAs.^{8,9}

There is degeneracy seen in the substrates that are edited by ADAR1 and ADAR2. A number of editing sites can be edited by both of these enzymes with varying efficiencies. There are also some editing sites that are specific to any one of the enzymes. One of the most important substrates for adenosine deamination by ADAR2 is transcript of glutamate receptor (GluR) channel subunit B10 found in the brain. In the pre-mRNA of this subunit, GluR-B, RNA editing changes the glutamine (Q) codon CAG to a CIG (I is recognized as U during translation), which specifies arginine (R). This single editing position (the Q/R-site) controls the Ca²⁺ permeability of

the glutamate receptor.¹¹ Almost 99.9 percent of the transcripts of GluR-B are edited at this site.¹² The glutamate receptor is characterized by a low Ca²⁺ permeability.¹³ Presence of glutamine at this site causes influx of Ca²⁺ ions through the channel. In addition to its function in cell-to-cell signaling, it is known that influx of Ca²⁺ ions upon activation of Glu-R modulates gene state-ment and cell proliferation in the neurons and glial cells.¹⁴ It has been shown that in tissues from malignant human brain tumors GluR-B is sub-stantially underedited, with 12 to 31 percent present in the GluR-B(Q) form.¹²

The importance of the Q/R editing site in GluR-B became evident when mutant mouse line, heterozygous for GluR-B(Q), was generated. These mice displayed a severe epileptic pheno-type and died within three weeks of birth as a result of the increased Ca²⁺ permeability of the glutamine receptors.¹⁵ Epileptic seizures are prevalent in patients with gliomas, which could at least partly be a result of change in Q/R-site edit-ing.¹²

Mice heterozygous at the ADAR2 locus were normal and showed editing in 99 percent of the GluR-B pre-mRNA.¹² ADAR2 knockout mice showed a normal embryonic growth but died during infancy (Higuchi et al). These mice were prone to epileptic seizures, and only 40 percent of GluR-B pre-mRNA molecules were edited at the Q/R site. When alleles encoding the edited ver-sion of GluR-B, GluR-B(R) in which arginine was genetically encoded were expressed in the ADAR2 knockout mice, the knockout phenotype was rescued.¹⁶ This experiment showed that the GluR-B Q/R site is physiologically the most important editing site for ADAR2.¹⁶

Interestingly, an editing site is present in the first intron of ADAR2 RNA transcript (position -1 in Figure 2), which is specifically edited by the ADAR2 protein in vivo. The -1 position is the splice acceptor site in the ADAR2 pre-mRNA transcript. The A-to-I conversion in the -1 position and the presence of an A at the -2 position give rise to a new splice acceptor junction at this site (I is recognized as G, and AG is a conserved consensus sequence for a splice acceptor junc-tion). Edited pre-mRNAs are spliced at this site to produce mRNAs that have a 47 nucleotide

intronic sequence present in between exons 1 and 2 (Figure 2). This splice vari-ant of ADAR2, when trans-lated, produces a nonfunc-tional protein due to a frame shift caused by the alterna-tive splicing event.

Materials and Methods

Stably transfected human cell lines¹² with ectopic state-ment of different levels of ADAR1 and ADAR2 were used for this study. Due to its low endogenous ADAR activity, Human embryonic kidney (HEK293) cells were used as the parental cell line.

Cell lines N5, N8, and N6 showed increasing lev-els of ADAR1 statement (with the same level of ADAR2 statement). Cell lines R10, R14, and R13 showed increasing levels of ADAR2 statement (with the same level of ADAR1 statement).

Total RNA from N6 and R13 cell lines were extracted with TRIzol Reagent (GIBCO) and digested with RNase-free DNase I. These digests were tested for presence of any residual DNA. Successfully purified total RNAs were reverse transcribed to produce cDNA using random hexamer primers and SuperScript II reverse transcriptase. The cDNAs were amplified by PCR. For analysis of intronic editing (at the -1 position) primers A2UI1D 5'-GGAATTCTATTAGTCAC TAAGCAAAGTGTGTCAG-3' (sense, intron1) and A2E2U 5'-GCGGTACCCAGGTGTGCTGCCAT CCTTGG-3' (antisense, exon 2) were used. This set of primers amplifies the ADAR2 cDNA derived from the pre-mRNA. The PCR products were then digested with Kpn1 and EcoRI restric-tion endonucleases and ligated to BlueScript plasmid. The plasmids were transformed into *E.coli*. The DNA preps isolated from the success-ful transformants were used for gel-sequencing reaction.

For analysis of alternative splicing, primers A2D 5'-GTATTTTGCCATGGATATAGAAGA TG-3' (sense, exon1) and A2U 5'-GTACTGG

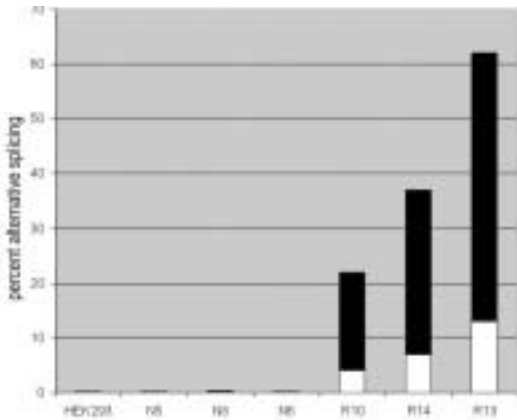


Figure 3

Cell Line	Editing Position						
	-27	-24	-2	-1	+18	+23	+24
HEK293	12	82	0	0	88	8	8
N5	10	89	0	102	10	10	10
N8	103	88	0	0	8	8	8
N6	37	77	0	0	8	8	8
R10	1	8	0	4	8	8	8
R14	2	8	0	7	8	103	8
R13	2	8	0	12	8	11	8

Table 1

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GATCCAGGCTTGATCTCATTGAGCTG-3' (antisense, exon 2) were used. This set of primers amplifies both splice variants from the cDNA.

Results

The gel sequence of the first intron in the ADAR2 pre-mRNA transcript revealed editing at the –1 position in R13 cell lines (Figure 2). Four out of 49 (about 8 percent) primary mRNA transcripts sequenced showed an A-to-I editing at this position. None of the 20 primary mRNA transcripts of N6 sequenced showed editing at this position. There was no editing seen at the –2 site for both the cell lines. Editing at the –2 site would make any editing at the –1 site irrelevant (as a splice acceptor site would not be formed because of an A-to-I conversion at the –1 position). None of the pre-mRNA transcripts showed any editing at the –24 position, which also lies in the intron. Additional data of editing at these two sites in different cell lines from studies conducted in our lab is listed in Table 1. The data clearly shows a direct relationship between level of ADAR2 statement and editing at the –1 site.

The semiquantitative RT-PCR of HEK293, N6, R13, and other cell lines suggested a direct relationship between ADAR2 statement and alternative splicing (Figure 3). The existence of alternative splice variant was confirmed by sequence analysis of the PCR products of ADAR2 pre-mRNA. The data also suggests that the ADAR2 pre-mRNAs that are edited in cell lines overexpressing the gene may also splice the edited pre-mRNAs preferentially. The R13 cell lines show a 13 percent increase in occurrence of pre-mRNAs edited at the –1 position (Table 1).

But the occurrence of alternatively spliced variant in increased to 53 percent in this cell line (Figure 3).

Discussion

Evidence of self-editing of ADAR2 to produce nonfunctional splice variants was first discovered in mice.¹⁷ This self-editing has also been observed in human cell lines. It has been suggested that this self-editing of ADAR2 gives rise to an autoregulatory feedback mechanism in cells. This could be an important mode of regulating ADAR2 activity.

The most important known function of ADAR2 protein is the editing of the GluR-B subunit of glutamate receptors at the Q/R site. It has been suggested that the abnormal cell proliferation seen in brain tumors and the epileptic seizures prevalent in such patients could partly be induced by the change in ADAR2 activity, which leads to an underediting of the GluR-B subunit causing Ca²⁺ influx into the cells.¹² In the future, drugs could be designed to enhance RNA editing in tumor cells.¹² We still need to isolate additional targets of ADAR2 in order to find out if this underediting is seen in other cancer tissues. Although the autoregulatory feedback model of ADAR2 regulation is quite promising, other modes of protein regulation, particularly post-translational modification and controlled subcellular localization of ADAR2, have to be investigated to better understand the mechanism of ADAR2 regulation.

Acknowledgments

Special thanks to Dr. Stefan Maas. 

The Potential of Stem Cells

Ngan Tina Huang

In the past several years, human stem cell research has been placed at the forefront of public attention. Embryonic stem (ES) cells have tremendous flexibility in developing into specialized cells, so they offer hope to patients suffering from debilitating illnesses such as Parkinson's and Huntington's disease. In light of the moral issues that ES cells raise, some scientists turn to adult stem cells as a less controversial alternative. Already, some types of stem cells have found their way into tissue engineering applications, and with time, we expect to realize additional stem cell technology. Let us elucidate the unique potential of embryonic and adult stem cells by examining their history, biological basis, and applications.

Historical Overview

ES cells have already been characterized in the animal model. The development of ES cells can be traced from early studies with mouse teratocarcinomas, tumors in the gonads. It was found that teratocarcinomas produced differentiated embryonic carcinoma (EC) cells that contain a variety of cell types, including muscle, bone, and cartilage. From these observations, scientists began to realize the potential of EC cells in producing stem cells that were pluripotent—capable of giving rise to many cell types. However, since EC cells were often accompanied by genetic mutations, a novel idea was to derive pluripotent cells directly from blastocysts. This was successfully carried out in 1981 by Gail Martin and Martin Evans, independently.^{1,2} Later, in 1995, James Thomson and colleagues derived ES cells from the rhesus monkey primate.³ These studies provided the paradigm for later experiments.

Besides previous work in animal models, the interest in the human model was influenced by two significant events. The first breakthrough was the cloning of the sheep Dolly by Ian Wilmut and colleagues.⁴ This event confirmed that cells can be genetically reprogrammed to produce a viable organism.⁵ The second breakthrough was the derivation of human ES (hES) cells by Thomson and colleagues because it initiated a supply of hES cells for research.⁶ These two events ushered the fantasy of human genetic reprogramming into reality.

Biological Basis

The basic biological aspects of embryonic stem cells are well known. In mammals, the fertilized oocyte and blastomeres of 2-4 and 8-cell-stage embryos are totipotent, capable of giving rise to all

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cell types. At the blastocyst stage, the inner cell mass (ICM) gives rise to ES cells that are pluripotent (Figure 1).⁷ When grown in vitro, these ES cells have the unique ability to remain undifferentiated with unlimited self-renewal capacity and to spontaneously differentiate into somatic cells.⁸ They can also aggregate into balls of differentiated cells known as embryonic bodies (EBs) (Figure 2). As cells within the EBs develop, they organize into three distinct layers—the ectoderm, mesoderm, and endoderm—from which various somatic cell types are derived.

ES Cell Applications

Several medical applications using mammalian ES cells have proved successful. One area is in Parkinson's disease, a degenerative disorder characterized by the loss of midbrain dopamine neurons. Björklund et al. (2002) showed that injections of mouse ES into the rat striatum produced dopamine-producing neurons in rat brains, leading to partial recovery of the disease.^{9,10} Another area is the treatment of damaged spinal cords. Derived from mouse ES cells, immature nerve cells that were injected into paralyzed rats showed improved mobility.¹¹ As scientists unravel the mysteries of hES differentiation, practical applications for humans will hopefully be in the near future.

One of the major goals of ES cell research is to understand how these cells can be directed toward specific lineages of differentiation. In mice, soluble factors are known to direct differentiation toward certain cell types. For example, interleukin-1 (IL-1) directs cells to become macrophages or neutrophils; retinoic acid induces neuron formation, and transforming growth factor beta (TGF- β) induces myogenesis.^{12,13} The effects of soluble factors on hES are only beginning to be studied. Schuldiner et al. (2000) studied the effects of eight growth factors on the hES differentiation and found that each growth factor directed the cells to a unique set of differentiated cells.¹⁴ They categorized the effects into three general types: (1) Activin-A- and TGF- β 1-induced mesodermal cells; (2) retinoic acid, epidermal growth factor (EGF), bone morphogenic protein-4 (BMP-4), and basic fibroblast growth factor (bFGF) activated ectodermal and

mesodermal cells; and (3) β nerve growth factor (bNGF) and hepatocyte growth factor (HGF) directed all three embryonic germ layers. None of the growth factors could exclusively produce one single cell type.

Currently, researchers at the MIT Langer labs are studying hES cell differentiation. Supervised by Dr. Robert Langer and Dr. Shulamit Levenberg in the Department of Chemical Engineering, I am conducting research on the mechanism of hES differentiation toward endothelial cells. These blood vessel-forming cells generated from hES cells could be used for generating new blood vessels in ischemic regions of the brain, heart, and other tissues.

In January 2002, the publication of the first human therapeutic clone marks a new frontier for stem cell research and a step closer to practical therapeutic applications. Therapeutic cloning uses a patient's own genetic material to generate cells to treat debilitating diseases. Jose B. Cibelli's team at Advanced Cell Technology (Worcester, MA) successfully created a cloned human embryo to harvest hES cells for medical treatment.¹⁵ This was carried out by replacing the genetic material in the donor egg with that of the patient and then coaxing the egg to divide. Once a blastocyst formed, the ICM was removed and grown in culture for stem cells. Cibelli hopes to derive nerve cells for healing damaged spinal cords and treating brain disorders.

Adult Stem Cells

In addition to embryonic stem cells, other types of stem cells are derived from adults, known as somatic stem cells. Somatic stem cells are characterized by their ability of self-renewal as well as their multipotency, the capability to give rise to many types of differentiated cells. Although once thought to be more rigid than ES cells, some adult stem cells have a plastic nature. For example, bone marrow cells can be induced to form muscle cells and neural cells.^{16,17}

Among adult stem cells, epithelial stem cells have achieved success in tissue engineering applications. In normal skin, epithelial stem cells are located in the basal keratinocyte layer, and they ensure the renewal of skin by giving rise to daughter cells that differentiate and migrate

toward the suprabasal layers. Already, epithelial stem cells are used in the production of synthetic skin grafts for the treatment of burns and some skin diseases. Synthetic skin grafts are made by culturing keratinocytes onto a dermislike substrate, and the success of the graft depends on the ability of epithelial stem cells to replenish the cell supply. Several companies like Advanced Tissues Sciences, Inc. (La Jolla, CA) and Organogenesis, Inc. (Canton, MA) manufacture a commercially available skin substitute (Figure 3).

Outlook for Stem Cells

Stem cells have come a long way, but before they can be incorporated in clinical settings, several obstacles must be overcome. First, it is important to be able to direct the differentiation of pure cell populations in large quantities.¹⁸ The availability of homogeneous cells would make stem cell treatment a feasible option for patients.

Second, safety concerns must be met. The ES-derived cells should not cause teratomas or teratocarcinomas when transplanted in vivo, nor should they be immunologically rejected by the patient.⁸ Therapeutic cloning seems a viable solution to immunologic incompatibility, but further studies are necessary to verify this. Finally, ES cells must be available for research purposes. Due to the ethical and moral aspects of this topic, hES research is currently still very limited, and the progress in this field is slow.

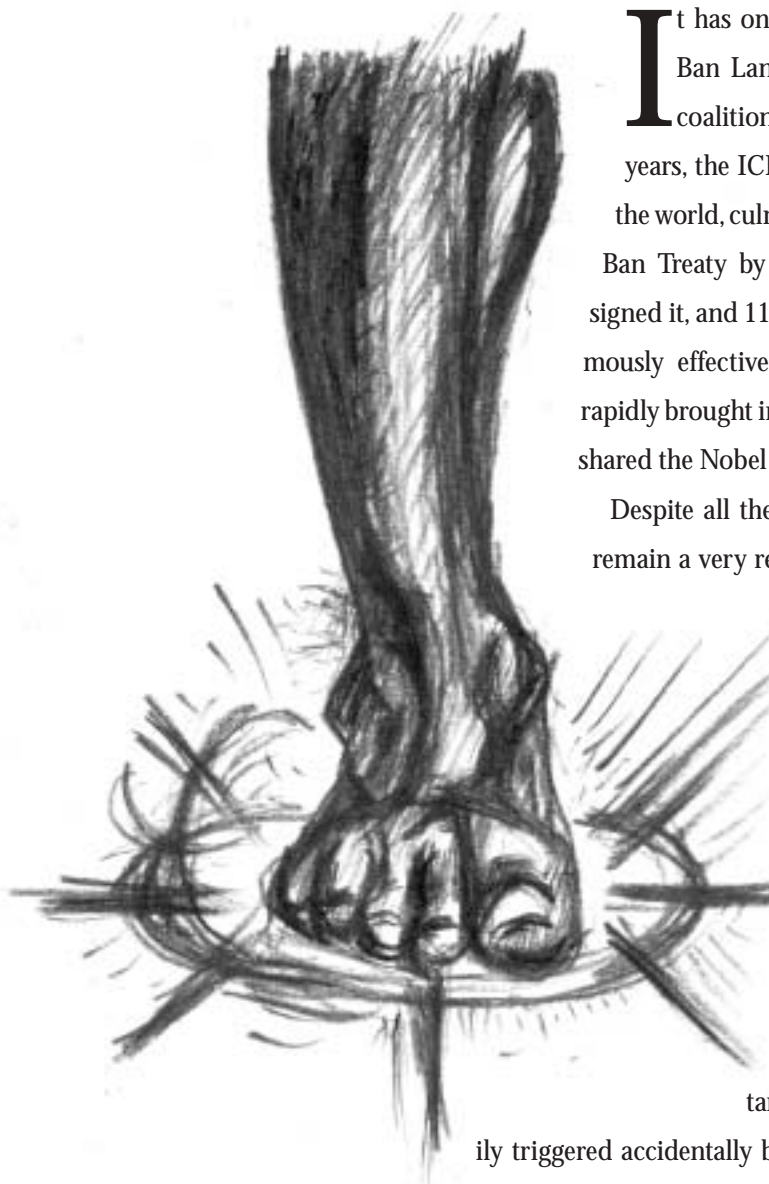
Although many questions still remain unanswered, it is clear that stem cells have a unique potential to treat many diseases. In both the embryonic and adult stem cell settings, we have tasted the promise for success in various breakthroughs. As research continues, we will gain more insight about the mechanism of stem cell differentiation and learn how to reprogram its course. ■

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Land Mines:

A Humanitarian Crisis, and the International Campaign to Ban Them

Julia de Kadt



It has only been a decade since the International Campaign to Ban Land Mines (ICBL) was launched in October 1992 by a coalition of nongovernmental organizations. In its first five years, the ICBL won the support of numerous governments around the world, culminating in December 1997 with the signing of the Mine Ban Treaty by 122 countries.^{1,2} Since then, 19 more countries have signed it, and 119 of the total have ratified it.³ The treaty has been enormously effective in the strength of its provisions, which have been rapidly brought into force. In 1997, the ICBL and organizer Jody Williams shared the Nobel Peace Prize for their efforts.⁴

Despite all the progress that has been made since 1992, land mines remain a very real problem. There are still an estimated 80 to 110 million land mines in the ground around the world that continue to be used by nonparties to the treaty, and in some cases, signatories.^{3,5} At the same time, several major powers including the United States, Russia, and China refuse to sign the treaty.

The Nature and Effects of Land Mines

Land mines are a particularly devastating weapon for several reasons. Perhaps most destructive is their indiscriminate nature. They cannot be targeted at specific individuals or vehicles and can be easily triggered accidentally by civilians. Even during a military campaign, they are not very effective weapons.⁶ During the Vietnam War, one-third of injuries sustained by

American soldiers were caused by land mines. A large majority of those were American land mines, exploded when soldiers needed to backtrack through previously mined land.⁷ Using land mines in a modern war in which there is a lot of movement is dangerous to one's own soldiers and not particularly effective against enemy soldiers because targeting is impossible.

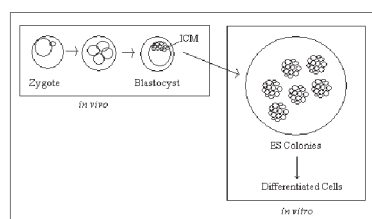


Figure 1



Figure 2

However, it is the impact they have on civilian populations once war has ended that causes the greatest concern. The immediate economic costs of land mines are enormous. While they are cheap to purchase (as little as \$3) and easy to deploy, the cost of removing a single mine averages between \$300 and \$1,000.^{6,8} Providing prosthetics and surgery to adult victims typically costs around \$3,000.⁶

Children make up a considerable proportion of land mine victims and die more often than adults from their injuries. They are more vulnerable to land mines because they tend to pick up objects found lying about and often wander off well-known, safe paths. Additionally, their shorter height usually causes more severe injuries from the blast of a land mine because it occurs closer to their vital organs and head.^{9,10} Caring for children who have lost limbs is particularly expensive, requiring new prosthetics every six months due to growth. Many child victims of land mines in the developing world receive virtually no medical attention at all.¹⁰

Although the immediate costs of de-mining and caring for survivors are intractable for the developing world, the indirect and long-term costs, both economic and social, of land mines are far higher.⁵ Most importantly, the presence of mines, or even simply the belief that they may be present, inhibits reconstruction and development subsequent to a war. Much arable land may

no longer be safe to use, resulting in impeded economic growth. Mined routes make movement difficult and hinder the return of refugees and soldiers to their homes, the delivery of governmental services such as health care and education, and even the holding of legitimate elections.⁵

The return of refugees, already challenging to a government immediately after a war, is only exacerbated by

land mines. People who return home to find their fields mined may have great difficulty in finding ways to earn income.⁵ Additionally, newly returned refugees are unaware of the locations of minefields and thus are likely to become victims. Land mines also lead to continuing militarization, because those most impacted by them often turn to militias for assistance. These groups may further impede the delivery of government services and make de-mining less likely to occur.⁵

Moreover, land mines cause ongoing medical problems, beyond those related to caring for the injured.⁵ Their presence impedes delivery of basic health services, such as immunization and prenatal care, resulting in even higher disability and mortality rates. Malnutrition also becomes a greater threat with the presence of mines because much land becomes too dangerous to farm and many families lose breadwinners to disability. Paths to clean water are often mined, forcing people to drink contaminated water, which increases the likelihood of outbreaks of diseases such as cholera. Many mines contain heavy metals or toxic chemicals that can affect water and land, resulting in associated health problems.¹¹ Mines also result in the overuse of land known to be safe, which then renders that land unproductive.

Developing countries depend mostly on agricultural production by rural farmers.⁵ As this is the group most severely affected by mines, the economy as a whole suffers greatly. Additionally,

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resources that could be well used in many other areas must continue to be directed to de-mining activities. This also increases dependence on foreign aid. Industries dependent on the presence of trans-

portation networks suffer, and the presence of mines makes tourism less likely. Mines also seriously impact infrastructure, resulting in under-used or inaccessible facilities and great waste of resources. Clearly, mines make it far more difficult for a country to recover from a war, and their impact on civilians is devastating.

Reasons for ICBL's Success

The ICBL initially consisted of six NGOs—Handicap International, Human Rights Watch, Medico International, Mines Advisory Group, Physicians for Human Rights, and Vietnam Veterans of America Foundation—but grew rapidly to represent well over 1,000 groups from across the world.¹ These groups came together because the work of various NGOs, ranging from environmental to children's rights issues, was being made significantly more difficult by the presence of land mines. The huge numbers of land mines buried throughout the world came to be seen as a humanitarian crisis, not just for the immediate human suffering they caused when exploding, but also for the extent to which they impeded reconstruction and development after the cessation of conflict.

Beyond the strength of the coalition of NGOs, a number of factors contributed to the unique success of the ICBL.¹² Members of the campaign had good cause to believe that the use of land mines was already outlawed by international law, as the weapons do not distinguish between soldiers and civilians. Under the Protocol of 1997 attached to the Geneva Convention, "indiscriminate attacks," defined as those that "are of a nature

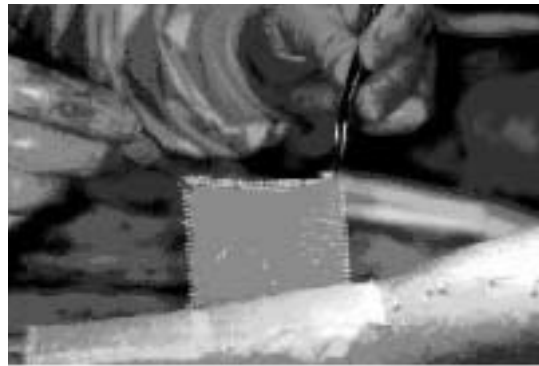


Figure 3

to strike military objectives or civilian objectives without distinction," are illegal.¹³

In addition to this legal advantage over opponents to their campaign, the fact that the cold war was over helped

the ICBL to also focus the world's attention on issues of conventional warfare, rather than on just nuclear warfare and disarmament. Without the overriding fear of nuclear war, people were ready to evaluate the types of weapons that had actually been in widespread use, and it became clear that land mines had caused great devastation to civilian populations.


Unlike many grassroots campaigns, the ICBL worked with, not against, the governments they were trying to convince.¹² As a result, governments quickly aligned themselves with the campaign, facilitating the development of a treaty. The dedication of certain politicians, in particular Lloyd Axworthy, was also particularly valuable.

A foundation of strong personal relationships also played an important role, and not just within the ICBL itself. Good personal relationships with government and military representatives helped to build political will for change. The loose nature of the organization was also valuable in providing the flexibility for the campaign to work throughout the world and at many different levels.

The clear-cut nature of the issue was also critical: This was a campaign behind which even members of the military could stand without any compromise of their priorities. While a few countries, most notably the United States, continue to claim that the use of land mines is strategically important, most other countries feel that they are militarily ineffective and that the postwar damage they cause make their continued use inexcusable.

Obstacles to Complete Success

Despite the overall success of the campaign so far, it has fallen short in certain important respects. Most notable was the failure of the U.S., along with several other major powers, to sign onto the Mine Ban Treaty. The U.S. refused to sign the treaty claiming that it needed to use mines in the demilitarized zone in Korea. It is more likely that its reluctance stems not from the genuine belief that land mines are vital or even useful weapons, but rather from a fear that giving

in on one weapon would pave the way for further, more substantial demands like the banning of cluster bombs that pose threats similar to land mines.¹⁶ The U.S. did indicate that it would sign the treaty in 2006, once it had developed a replacement weapon. However, extensive research has failed to yield any alternatives deemed satisfactory so it appears unlikely that the U.S. will sign onto the treaty by its proposed target date of 2006.^{14,15} 

15. *Wall Street Journal*. Land mines treaty is latest global pact to draw White House skepticism. August 3, 2001.
16. Cluster Bombs: The military effectiveness and impact on civilians of cluster munitions. <http://www.landmineaction.org/assets/downloads/Cluster%20bombs%20report%20summary.pdf>

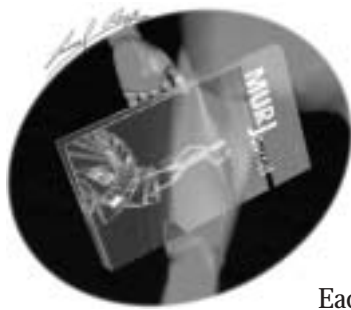
Abstractions

Uncharted Potentials

Faisal Reza

Is all that we see or seem...

What is the next big find going to be? Will it be the culmination of meticulous calculations and expectations? Or will it confound the senses, an almost inexplicable wonder? The long-held tenets of science revere methodology, proof and reproducibility. These scientific principles are reaffirmed through mathematics and vindicated by engineering. Noteworthy achievements necessarily build upon precedents and, in doing so, lend credibility to themselves. Respecting left-brain sensibilities, science uses its inherent ordered means to establish organization from a chaotic universe. In stark contrast, the foundations of art continually shift with unpredictable, fresh innovation and enthusiastic pioneering. The contemporary artistic predispositions and vogues are supplanted by stylistic originality and creative radicalism. Following right-brain passions, the arts irreverently celebrate the complexity of the world within us. Yet, imagine the possibilities if such sensibilities and passions mingled.



The arts and the sciences have more in common than we might first imagine. Each novel scientific discovery or artistic masterpiece engenders its successor, either as an affirmation or a repudiation of the status quo. In doing so, it asks each of us to question commonly held beliefs and prejudices. Is an idea in accordance with observations and critiques? Or does a technique bring forth a new expressive form or paradigm? But most importantly, notice that neither of these questions is exclusive to the arts or to the sciences. Sharing similar challenges and motivations, they are our pursuit of uncharted potentials.

What does this continuum of art and science seem like to you? Look around. What do you see? While engaging each potential on this continuum, a new quanta of information is sought, suitable for human consumption. Recognize that this new find, and the body of knowledge to which it adds, can be both aesthetically appealing and logically elegant. Should it be any surprise that our explorations be marked with any less combination of calculation and creativity? Upon closer inspection, one notes that the big finds have, and will continue to affirm, a simple, powerful truth:

Art is the science of our souls as much as science is the art of our minds.

...but a dream within a dream?

– Edgar Allan Poe (1827)

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