Technology Transfer Stories: 25 Innovations That Changed the World

The Better World Report

2006 Edition

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AUTM

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THE BETTER WORLD REPORT

2006 Edition

Part of The Better World Project

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The Better World Project

The Association of University Technology Managers launched the Better World Project in 2005 to promote public understanding of how academic research and technology transfer have changed our way of life and made the world a better place. The project draws from more than a decade's worth of case studies and news from AUTM members — the professionals who make academic technology transfer happen.

The first edition of the project focuses on products derived from U.S. and Canadian academic research. Future reports will include stories and perspectives from around the globe that convey the benefits of academic research in human terms.

Materials and Support

The Better World Project includes:

- *The Better World Report*: In-depth articles about 25 innovations derived from academic research that have changed the world
- *Reports From the Field*: 100 technology transfer success stories, from research to realization
- Better World Project Online: A searchable database to help you find stories of interest to you and your community

The Better World Project materials are available in print and electronic forms. Visit The Better World Project Web site or contact AUTM headquarters for details.

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The Association of University Technology Managers

AUTM is a nonprofit professional association with membership of more than 3,500 intellectual property managers and business executives from nearly 50 countries. The association's mission is to advance the field of technology transfer, and enhance the ability to bring academic and nonprofit research to people around the world. AUTM members represent more than 350 universities, research institutions, teaching hospitals and government agencies as well as hundreds of companies involved with managing and licensing innovations derived from academic and nonprofit research.

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The Better World Report wouldn't exist if not for the directors of institutions' technology transfer offices and their staffs, who diligently gathered and submitted these stories and others. AUTM recognizes this dedication — which is never part of technology transfer professionals' job descriptions, but represents a considerable extra effort and labor of love — and expresses gratitude for their considerable contributions.

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Forward

Welcome to a Better World

We have a story we want to tell. In fact, we have hundreds of them.

The stories are about people whose lives have changed for the better. They are stories about the world around us, and how it is becoming a healthier and safer place.

The Association of University Technology Managers has been in the business of building a better world for a long time. AUTM members manage the transfer of discoveries resulting from academic research to companies that transform these intricate technologies into viable products for the world far beyond the boundaries of the campus.

Many of these products have become household names: Honeycrisp apples, Google, the television V-chip, nicotine patches and Taxol, for example. Others with names such as Exosurf, the PSA test, Altropane, Rheo Knee and SpeechEasy may not be as well-known but have affected society profoundly — saving lives, improving well-being and contributing to a stronger economy.

Too often, the stories behind these innovations have been forgotten or lost in the passage of years, or simply never told. No one ever sat down and explained how these products for a better world came to be in the context of the human experience. Yet the stories are immensely human, from the first spark of wonder and discovery to the final product that, for some people, can change everything. Without the tireless work and commitment of academic researchers on campuses across the globe, there would be no products and no stories to tell.

This inaugural edition of *The Better World Report* contains 25 good stories from the United States and Canada, but they're just the beginning. There are many more to tell. In the coming years, The Better World Project — an overarching program that includes *The Better World Report, Reports From the Field* and Better World Project Online — will continue to capture and tell the stories of products that have improved the health, safety and welfare of people worldwide.

The* Better World Report *is about academic research … It's about people who are passionate about their research and helping others, even if it takes years of sustained effort.

In fact, AUTM already is planning the next edition, which will feature more stories from the United States and Canada as well as other countries where AUTM members are sharing news about products that originated in their research institutions and now are available to the public. *The Better World Report* is about academic research — no matter where it occurs on the face of the Earth. It's about people who are passionate about their research and helping others, even if it takes years of sustained effort.

Forward

The U.S. Congress' passage of the Bayh-Dole Act in 1980 was a watershed in the growth and development of technology transfer in the United States — empowering academic institutions to become an important driver in today's knowledge-based economy. Now, numerous countries have academic technology transfer policies and processes to connect academic discoveries with citizens' needs as well as evolving national, and global, economies.

Given the Bayh-Dole Act's role in advancing the practice of technology transfer, it's no surprise that for this first edition AUTM turned to one of its authors, former U.S. Sen. Birch Bayh, to share his thoughts about the legislation he co-authored more than 25 years ago with Sen. Robert Dole. His introductory essay to *The Better World Report* is a reasoned call to action for everyone engaged in U.S. academic technology transfer.

Future editions of *The Better World Report* will include stories and perspectives from many countries. The goal of every publication, however, will remain constant: to illustrate how academic research and technology transfer have changed our way of life and made a better world.

Preface

A Time to Speak Up

By Sen. Birch Bayh

Sen. Birch Bayh served in the U.S. Senate for 18 years, and was a co-author of the Bayh-Dole Act. He is currently a partner in the Legislative Practice Group at Venable LLP in Washington, D.C.

In 1978, Senator Bob Dole and I introduced legislation which later became the Bayh-Dole Act at a press conference where several universities spoke movingly about potentially promising therapies that would never benefit the American public which sponsored the research. The reason? It was very difficult for universities and small businesses to obtain clear ownership rights needed for moving their concepts to the marketplace.

> ***Knowing is not enough; we must apply. Being willing is not enough; we must do.***
>
> **— Leonardo da Vinci**

Prior to passage of the Act, promising discoveries withered away because previous policies required that results of federally funded R&D should be made available to the public without regard to the commercial consequences. The result was that thousands of government funded patents quietly gathered dust on the shelves of federal agencies.

The steady erosion in the 1970s of American competitiveness was an unintended consequence of this policy as we fell further behind our high technology competitors. Pressure increased to show a greater return for the billions invested by our hardworking men and women in our public sector research institutions.

Congress overwhelmingly felt we needed a new policy which enabled our universities and small businesses to gain ownership to the patents for ideas developed from their research.

In turn, these patents could be licensed to businesses who then had the incentive to invest the resources necessary to develop the idea and make it available to the consumers. Often the investment required tens, if not hundreds, of millions of dollars before the product reached the market. Without ownership rights, there would be no incentive to invest. The result was the passage of the Bayh-Dole Act of 1980.

The past 25 years of Bayh-Dole illustrate that unleashing our unparalleled universities and nonprofit institutions was a significant factor in the rebirth of the U.S. economy. U.S. high technology businesses and manufacturers have again become world leaders.

Bayh-Dole's success would not have surprised a famous independent inventor. Here's what patent owner Abraham Lincoln said in his Second Lecture on Discoveries and Inventions:

> Next came the Patent laws… Before then, any man might instantly use what another had invented; so that the inventor had no special advantage from his own invention. The patent system changed this; secured to the inventor, for a limited time, the exclusive use of his invention; and thereby added the fuel of interest to the fire of genius, in the discovery and production of new and useful things.

It is exactly this fuel of interest that was missing in the previous patent policy. Based upon a misguided, even arrogant, belief that taking inventions away from their creators would better serve the public, federal agencies took inventions from universities and gave them away freely through non-exclusive licenses. Predictably, this system failed miserably.

Ironically, this appears to be where our critics want to return. From their perspective, innovation looks simple. They believe that companies easily find hidden treasures in our nonprofit sector, negotiate exclusive licenses and bottle up science while they make killings in the market.

The reality is quite different. First, university research is a long way from a commercial product. Because the vast majority of nonprofit R&D is basic research, any resulting patent is much more an idea than a product. The companies most likely to develop such inventions are small businesses, which must have strong intellectual property protection to justify their investments.

The modern day detractors of Bayh-Dole, who suggest that this legislation creates an incentive for researchers to get rich, which is more important to them than honest research, have no understanding of what motivates those who devote their lives to science. There may be a few greedy researchers, however, the odds are stacked heavily against a scientist living on easy street. The great motivating factor in their lives is expanding the field of human knowledge, coupled with a passion that their research finds a practical application.

I well remember the testimony of Dr. Leland Clark, with the Children's Hospital Research Foundation. Dr. Clark's obsession was finding practical solutions to improve the lives of the children and adults facing cancer and serious burns. Here's what he told the Senate Judiciary Committee in strongly endorsing the Bayh-Dole bill:

> The point is, as part of the mental process which leads to an invention, the inventor often envisions possibilities for application which are not immediately evident to others. The inventor's personal persistence and confidence is often the deciding factor which carries the idea forward and prevents the invention from being set aside or ignored.

There is ample evidence from AUTM and others that universities are integral parts of the U.S. economy. Less frequently mentioned is that the Bayh-Dole Act has strengthened science as well.

A few years ago, the National Science Foundation in its *Science and Engineering Indicators* lauded the growth in jointly authored university/industry research papers as a significant step forward for American science. Before Bayh-Dole, companies were rightly leery of having their best and brightest perform research with their public sector counterparts for fear of losing patent rights to the federal government. Bayh-Dole removed this unhealthy barrier.

The 2004 edition of *Science and Engineering Indicators* shows that U.S. patents frequently cite academic articles particularly in the life sciences, physics, engineering and technology arenas. "This growth in citations of S&E (note: science and engineering) literature, referenced by scientific field, technology class of the patent, and nationality of the inventor and cited literature, provide an indicator of the link between research

and practical application."

We are blessed to be so wealthy that we can afford the luxury of having world-class centers of learning. We are blessed that many of the brightest minds in America study at and devote their lives to working in our research institutions. It is also fortunate that many young people from other countries join in this endeavor.

Taxpayers who fund the public sector institutions through their tax dollars support the advancement of science, but even more, they want a better life for themselves and their children through continued economic growth. Bayh-Dole is making this dream possible. We should be rightly proud of our achievements of the past 25 years. We should also be willing to honestly examine the activities of our universities, researchers and businesses to ensure that we are true to the mission set before us by Bayh-Dole — to increase knowledge while bringing practical solutions to the world community.

It is a privilege to have played a small role in this effort. The illustrations that the Association of University Technology Managers included in this booklet aptly show that we have come a long way. Yet, I must close with a warning to those who are tempted to follow the logic of those critics who seem determined to destroy Bayh-Dole rather than to perfect it.

It is unfortunate that today's critics of Bayh-Dole spread the belief that all problems which may exist in those instances where they allege wrongdoing can be remedied by making the product of university research available to the public generally. This principle sounds good in a vacuum, but it has failed dismally in our free enterprise system. This was the status before Bayh-Dole, when more than $30 billion of taxpayer money had been spent on research, only to produce thousands of patents gathering dust in the Patent and Trademark Office. When I opened the hearings on this legislation 25 years ago, I said:

> The United States has built its prosperity on innovation. That tradition of unsurpassed innovation remains our heritage, but without continued effort it is not necessarily our destiny. There is no engraving in stone from on high that we shall remain No. 1 in international economic competition. In a number of industries we are no longer even No. 2. New incentives and polices are needed to reverse this trend.

It is no accident the rest of the world is copying the Bayh-Dole model. The European Union, Japan, China, India and many others hope to tap their own cutting edge university research to win the future economic race. We in the United States cannot afford to rest on our laurels.

The Bayh-Dole Act more than fulfilled our hopes and dreams. It, as well as all other laws, should be monitored continuously and revised when necessary. Many, many lives are the better for the success our universities, small businesses and nonprofit organizations have had as a result of this law. It simply works. We should never forget this lesson.

Many years ago, the great philosopher and cultural critic Santayana warned us that "Those who do not learn from history are doomed to repeat its mistakes." Otherwise, as another great philosopher, Yogi Berra, once said, it will be *deja vu* all over again.

Chapter 1

V-Chip Keeps Television Violence From Reaching Children

Unchecked television violence prompts a Simon Fraser University professor to create the V-chip, a device that allows parents to block programs with explicit content.

President Bill Clinton holds a V-chip while discussing the Telecommunications Act of 1996. Photo courtesy of Tri-Vision International Ltd.

Simon Fraser University

Tim Collings was an engineering professor at Simon Fraser University in Vancouver, British Columbia, Canada, when a man shot and killed 14 female students at Montréal's École Polytechnique on Dec. 6, 1989, before turning the gun on himself.

That tragedy, which rocked relatively peaceful Canada, set him down a path that led to the invention of the internationally hailed V-chip. Parents across North America now use V-chip to control the amount of violence, sex and foul language their children are exposed to through television.

"I don't come from a social science background," says Collings, who notes that he was already aware of violence on television before the Montreal murders. "But I did follow the studies that showed that the killer was affected by violent media material that he had seen," he says. "It has an impact, no doubt about that."

Tim Collings with Vice President Al Gore. Photo courtesy of Tri-Vision International Ltd.

"I became interested in wanting to do something," he says. "I wanted to help break the cycle of violence that seemed to be growing in our society."

Applying Engineering Skills to Help Parents

Collings says he did not favor censorship or controlling the content on televisions at the source. Instead, he set about using his engineering skills to — at a minimum — allow parents to control the amount of violence their children watched on television.

He was in luck because at about the same time, closed captioning systems were being introduced to North American television. And in 1990 the U.S. Congress began requiring television receivers to contain circuitry designed to decode and display closed captioning. Collings was able to figure out a way use the same data packet systems that delivered the closed captioning text to carry program ratings information.

He designed the V-chip so parents can click on a menu that presents a rating system. If they want to limit the programs that their children see to those rated PG, they can block the others that have ratings for violence, sex or profanity.

"When I started working on this, there was no V-chip technology that would read codes and respond to the preferences of viewers and their parents," says Collings, who now has three children ages 10, 12 and 14. Ironically, Collings says he didn't have a television in his home until 2000. He believes the V-chip is an especially important tool for parents whose children are 12 or younger.

When Collings developed his prototype, he took it to the Canadian Radio and Telecommunications Commission, the equivalent of the U.S. Federal Communications Commission. There, he found an ally and sponsor in chairman Keith Spicer. "It was a watershed moment," Collings says. "Spicer really pushed this and it became one of his main legacies."

Written Into the Telecommunications Act of 1996

Spicer introduced Collings to then FCC Chairman Reed Hundt. "I demonstrated it to him and congressmen and senators," he says. "Eventually, and to my surprise, it made its way into the Telecommunications Act of 1996 that required the device in every television built after 1999 with a screen size of 13 inches or larger."

In 1997, Collings and SFU awarded the international rights to his invention to Tri-Vision International Ltd., a public company that trades on the Toronto Stock Exchange. Tri-Vision trademarked the technology as V.gis™ and has worked with Collings to ensure all electronics manufacturers in Canada and the United States are properly licensed to use his invention.

Collings continues as a director of Tri-Vision and chairs its research committee. He also owns a portion of the company.

Murray Eldon, a spokesman for Tri-Vision, says the company has earned between $16 and $18 million in royalties from the technology and that revenues could go up significantly in coming years because the FCC now requires all digital receivers to have digital V-Chips as of March 16, 2006. In the United States alone, annual television sales range between $25 million and $32 million. In Canada, the figure is about $1.8 million a year.

Praise for a Great Idea

Joanne Cantor, a professor emeritus in communications studies at the University of Wisconsin-Madison is a noted researcher on the psychological effects of media violence on children. She praises Collings as a "real pioneer whose work has had some very positive effects … He's the one who really got this going," Cantor says.

"No one ever imagined that Congress would pass a law that would require the networks to do anything. Just the requirement of ratings is a concept that is enormously new," she says. "It is a great idea. Unfortunately, research shows that the V-chip has as yet not been widely adopted by parents.

"In my opinion, it is hard to program and understand," she says. "Companies may be required to put them in all televisions, but they are not required to make them easy to use."

Eldon, of Tri-Vision, agreed that television manufacturers have not made the V-chip simple to program. "It could be a lot more user friendly," he says. "The FCC has noted that the current tools have not worked as well as envisioned."

"I wanted to help break the cycle of violence that seemed to be growing in our society."

— Tim Collings, V-chip inventor

Simon Fraser University

Making the V-Chip Easier to Use

Eldon says that many advocates of parental television control hope that the ratings system will be revised to be more accurate and that V-chips will become easier to use and understand.

Cantor does not fault Collings. "It's not Tim's fault," she says. "His impact has been significant and influenced other devices that will block what kind of programs get into our homes."

Collings acknowledges that the number of people using V-chips may be relatively small at this point. "I've spoken to people who use it, but it is a somewhat new technology," he says. "And those inclined to use it are parents with young children."

"I don't know if my work has saved lives," Collings says. "I'm not going to go that far. But the effects of violence on television have been studied *ad nauseam*. The three main (effects) are desensitization to violence, creating the fear that society is really like that — especially in little kids — and the creation of copy cats," he says. "I would like to think, though, that my work has made society safer for people."

— By Brian E. Clark

Chapter 2

Saving Water Resources *and* Money

Municipalities and industrial plants are under pressure to meet increasingly stringent clean-water regulations, which often are costly to implement. But they may get some assistance from a cutting-edge firm that has commercialized an innovative water treatment process developed at the University of Idaho.

Interior of the new wastewater research facility in Hayden, Idaho.
Photo courtesy of Blue Water Technologies Inc.

University of Idaho

Municipalities and industrial plants across the United States are finding themselves between a rock and hard place.

On the one hand, they'll need to spend millions of dollars to improve their water treatment systems to comply with new clean water regulations. On the other hand, the existing technology to upgrade water treatment systems is not highly effective.

Much of their dilemma revolves around regulations to reduce nutrients such as phosphorus in discharged water by as much as 95 percent. Phosphorus, a vital nutrient in all living things, can be harmful when excessive amounts are in lakes and streams. Too much phosphorus causes rampant algae growth, which further diminishes the quality of water and can kill fish and other organisms vital to aquatic ecosystems.

Conventional water treatment systems may be capable of reducing phosphorous levels to as low as 500 parts per billion. But in certain parts of the country, such as the Spokane River in the northwest United States, new phosphorous reduction regulations allow for only 50 parts per billion — far below the water cleaning capabilities of conventional systems.

Luckily, a new water treatment technology has entered the marketplace — and not a moment too soon.

It's called BluePRO™, a low-cost, low-maintenance solution that is highly effective in removing phosphorus and other contaminants from water.

Image courtesy of Blue Water Technologies Inc.

Scrubbing Wastewater With Coated Sand

The BluePRO filtration system is based on the pioneering research of Professor Greg Möller, Ph.D., and Remy Newcombe, Ph.D. The two conducted initial work on the technology at the University of Idaho in Moscow, under the sponsorship of the U.S. Environmental Protection Agency and other U.S. government agencies. In 2003, Blue Water Technologies Inc., based in Hayden, Idaho, was founded to commercialize the technology; it also obtained the license to the technology underlying BluePRO.

Similar to existing water filtration systems, BluePRO uses sand as a key filtering agent. But it's not just ordinary sand that you might find at the beach.

Instead, it's coated with iron oxide, a rust-like property that is particularly absorbent. The specially coated sand scrubs phosphorus and other undesirable

properties in wastewater that flows through large tanks. As the sand sinks from the top of the tank to the bottom, the iron oxide detaches and absorbs the phosphorus. Next, the water, sand and iron oxide are separated from each other by density. The clean water is pumped out, the sand is separated and removed for reuse and the waste solid containing iron oxide/phosphorous particles is removed for disposal.

"The sand filter is the core of our product," explains Tom Daugherty, president of Blue Water Technologies Inc. "These filters have no moving parts, so they're easy to maintain. And only up to 10 percent of the sand must be replaced annually over the 20-year life cycle of the filters. These are a few of the reasons why BluePRO is so cost-effective."

Depending on the size of the community involved, use of the BluePRO system can cost as little as $12 per household annually for about 20 years.

In cases like the Spokane River where conventional systems are incapable of reducing phosphorus to lower levels required by the EPA, other exotic systems involving reverse osmosis and membrane filtration could conceivably do the job, Daugherty says. "But their cost would be many times more than that of the BluePRO system," he says. And cost efficiency definitely is a critical issue when considering the scale of phosphorous reduction needed in the United States.

As much as half of the country's waters do not adequately support life because of excessive phosphorus and other nutrients, according to the EPA. To meet the EPA's lower phosphorous levels in these bodies of water, an effective, relatively inexpensive solution like BluePRO would help thousands of cash-strapped municipalities responsible for water treatment.

Putting BluePRO to the Test

In view of increasing regulatory requirements for cleaner water, it's no surprise that numerous potential customers have shown an interest in purchasing the BluePRO filtration system, especially given its affordability and ease of use. In fact, Blue Water Technologies Inc. created a portable trailer-mounted water treatment system to demonstrate the value of BluePRO filtration systems at various locations throughout the Northwest.

However, a number of companies and communities have been reluctant to invest millions to upgrade their wastewater treatment systems with BluePRO, noting that it has been demonstrated only on a small scale — not in large-scale applications.

Undaunted, Blue Water Technologies Inc. teamed up with the town of Hayden, Idaho, to create a 1,200-square foot, $1 million dollar test facility connected to Hayden's wastewater treatment plant, capable of treating 1.5 million gallons of contaminated wastewater every day. Launched in May 2005, the Hayden Wastewater Research Facility showcases BluePRO technology in a real-life setting.

"The Hayden facility gives researchers at the University of Idaho and other institutions a full-sized environment in which trials and demonstrations of other experimental water treatment processes can be conducted," says Gene Merrell, interim director of the Idaho Research Foundation at the University of Idaho, and

The BluePRO system can lower phosphorous levels from 3,000 parts per billion to 10 parts per billion — a 99.7 percent reduction.

University of Idaho

assistant vice president and chief technology transfer officer at the University of Idaho's University Research Office.

The main focus of the Hayden Wastewater Research Facility is phosphorous removal, given the EPA's regulatory push to reduce phosphorous levels in water.

"When it comes to phosphorus, natural water should have less than 40 parts per billion, and 20 parts per billion is even better," notes Möller.

In late 2005 the Hayden facility dramatically surpassed clean water requirements, showing that the BluePRO system can lower phosphorous levels from 3,000 parts per billion to 10 parts per billion — a 99.7 percent reduction.

Researchers at the Hayden facility are setting out to prove that a modified BluePRO process can remove other harmful substances besides phosphorus. These include arsenic, heavy metals and endocrine disrupters commonly found in detergents, birth control pills and other personal care and pharmaceutical products that are flushed down toilets or put down the drain. Endocrine disrupters are particularly worrisome, as they can cause cancer and birth defects, and can adversely affect immune and reproductive systems in humans and animals.

Improving the environment while saving money in the process may seem like a dream to most taxpayers and business executives. Yet this dream is quickly becoming a reality, thanks to the University of Idaho's groundbreaking scientific discoveries that are being perfected, commercialized and marketed by Blue Water Technologies Inc.

— By Bill Shepard

Chapter 3

Groundwater Treatment Technologies Offer Increased Efficiency and Reduced Expense

Permeable reactive barriers developed at the University of Waterloo are two to five times less expensive than traditional pump-and-treat methods and in field tests are proving to be more effective in removing groundwater contaminants.

An installation of a permeable reactive barrier for the treatment of contaminated groundwater. Photo courtesy of professor David Blowes

University of Waterloo

Contaminated drinking water is a worldwide problem, causing disease and death in developed and undeveloped countries alike. Especially troubling to remediation specialists are areas where the aquifer has become contaminated with heavy metals. These pollutants — which include mercury, arsenic, chromium and lead — are known to be toxic and difficult to extract from groundwater.

Throughout the western U.S. states, where gold and silver mines once provided abundant wealth, abandoned mine shafts have left an unexpected legacy: ground water contaminated by mine tailings.

Clean-up efforts in these areas have been notoriously expensive and frequently unsuccessful. A new class of remediation technologies, collectively known as permeable reactive barriers, or PRBs, are helping to undo the damage done by more than a century of mining and other activities in the United States and throughout the world. These technologies, developed at the University of Waterloo in Ontario, Canada, are likely to revolutionize the way contaminated groundwater is treated in the future.

A Relatively Simple System

The PRB system is relatively simple, says Scott Inwood, technology transfer manager at the University of Waterloo. A typical installation involves selecting and placing a chemically reactive material into an excavated trench or chamber and positioning it to intercept the path of the contaminated groundwater plume. The PRB acts as an effective filter that removes contaminants as the groundwater flows through it. Scientists select reactive materials depending on the target contaminants that need to be treated, making the PRBs useful in a variety of applications.

The PRB technologies provide a more economical, efficient means of treating groundwater than traditional pump-and-treat methods. These conventional methods involve pumping contaminated water to the surface and treating it using filters, chemicals, electricity and manpower. The pump-and-treat approach can waste clean water and often produces contaminated byproducts. In some cases, this can cause the direction of the contaminated plume to change, increasing the risk of contaminating adjacent properties.

The mechanical pump-and-treat approach is two to five times more expensive than using the passive, unmanned, electricity-free PRB technologies, according to a 2001 report by the U.S. Environmental Protection Agency. Aside from providing the lowest-cost alternative method, PRBs have proven to be more effective in meeting stringent regulatory criteria. And, because they are buried underground, PRBs do not create eyesores or huge surface equipment scars that may reduce property values.

Governments, Corporations Support PRBs

The University of Waterloo, Canadian and U.S. governments, and several multinational corporations have invested significantly in the research and development of passive remediation technologies at the University of Waterloo, resulting in the creation of more than 20 technologies and more than 100 patents and patent applications.

One targets common inorganic industrial contaminants, or metals, such as chromium, uranium, copper, zinc, arsenic and mercury.

David Blowes, a professor of Earth sciences and a Canada research chair, and Carol Ptacek, an adjunct professor and research scientist with Environment Canada, invented the metals-specific PRB. While researching, they found that PRBs that use zero-valent iron or organic carbon-reactive materials could be used to treat groundwater. The two were studying dissolved metals at a mining site in New Brunswick when they realized that contaminants were being removed in some places, but not in others. That's when they began searching for practical ways of promoting chemical reactions in the aquifer that would remediate the site.

The metals-specific PRB is now used at several Superfund cleanup sites across the United States, as well as similar sites in Canada, Europe, South America and Australia.

"Our system is efficient as possible and less expensive," Ptacek says. "Over the last decade, we've seen a gradual transition, from doing groundwater remediation by pumping to remediation by manipulating the aquifer."

The Path to Licensing Has Been Difficult

In spite of the many significant benefits this technology offers, the path to successful licensing of the technologies has been arduous. "Regulatory agencies and engineering consultants don't want to use a technology that's not proven," Inwood says. "We initiated a number of small-scale demonstration projects over an eight-year period to generate enough data that would provide the credibility to secure the first commercial license of the technology."

The metals-specific PRB technology is now being field-tested at five sites in Canada and the United States, where the two governments have garnered licenses for field demonstrations. So far, 12 commercial entities have licensed the technology, including several in Canada, five in the United States and several in the European Union.

Inwood believes the technology will be widely used and accepted by the time the patent expires in 2012.

— By Jill D. Ladwig

The metals-specific PRB is now used at several Superfund cleanup sites across the United States, as well as similar sites in Canada, Europe, South America and Australia.

Chapter 4

The Honeycrisp: a Sweet, Tart Jump-Start for a Sagging Limb of the Apple Industry

The Honeycrisp apple has brought much-needed revenue to small family-run orchards in the upper Midwest and New York state. Developed by professor James Luby and research scientist David Bedford at the Minnesota Agricultural Experiment Station, the apple was introduced to the public in 1991 and sells at a premium price because of a sweet-tart flavor and firm texture that appeals to a wide range of consumers.

Photo courtesy of the New York Apple Association

University of Minnesota

Things looked pretty grim in the 1980s and 1990s for upper Midwest apple growers. Paralleling the plight of many family farms, century-old orchards were going from tidy tree-lined rows to gnarled, ramshackle woodlots.

Cheap overseas fruit forced sections at an alarming rate. Big Washington state orchards dominated retail store sales. In fact, it got so bad that small orchards that already had to deal with challenges like a short growing season and muscle-straining labor were sometimes selling apples for less than they cost to produce. But help was on the way. And its source wasn't a government program or market upswing, but an apple with almost magical properties.

Matchmaking in the New Millennium

What are the properties of this magic fruit and where does it come from? It marries sweetness sought by some and tartness touted by others, and it thrives in the hard climate of northern-tier states. Though the original apple hails from Kazakhstan's Heaven's Gate Mountains, the Honeycrisp hails from Minnesota, Land of Ten Thousand Lakes.

Professor Jim Luby and research scientist David Bedford, who work at the Minnesota Agricultural Experiment Station at the University of Minnesota, introduced the Honeycrisp to the public in 1991. They are part of a program that has developed 23 apple varieties since 1908; each new variety takes about 25 years to develop. Despite being scientists, Luby and Bedford practice a technique for developing apples that looks a lot like old-fashioned match making. They take one apple variety that, on its own, might be lacking and combine with another, possessing strengths that the first lacks, with hopes of a fruitful union.

Photo courtesy of the New York Apple Association

As in human conception, the egg cell in the flower needs to be fertilized to develop into the embryonic tree contained in the apple seed. Flowers are hand-pollinated in the field, with the pollen of one apple applied to the blossom of another.

Pollinating is conducted in batches of several hundred flowers; the large number of fertilized seeds created helps give a sense of the genetic range produced by this union. These seeds mature

into trees and bear fruit in five to seven years. What develops, to follow the analogy, are children who may or may not resemble the parents. Bedford and Luby select the best offspring.

At any given time, the Minnesota Agricultural Experiment Station has hundreds of apple varieties, or cultivars, growing. It's part of Luby and Bedford's job to taste them all, sometimes as many as 500 in a day. They're in search of fruit that brings together a troika of characteristics: appearance, flavor and texture. And when they find an apple, like the Honeycrisp, that has all these, it becomes a candidate for cloning.

Though the word "cloning" sounds high-tech, the practice of grafting a cutting of the desired variety to a rootstock dates back to Roman times. "Cloning is the easy part," says Luby. "Sorting through all the varieties — that's the hard part."

To date, the University of Minnesota has sold more than 3 million Honeycrisp trees, and a portion of revenues go back into the fruit breeding program to develop new varieties.

Upsetting the Apple Cart

In the early 1990s, Luby and Bedford, and a handful of aficionados at the artisan end of the fruit business, knew they had something special. "The Honeycrisp had outstanding texture, crispness, and juiciness," says Luby. "It stood out among thousands of varieties." But there remained the job of bringing the product to the public. And somehow convincing them — if this apple was to work economic as well as gustatory magic — that it was a great fruit worth paying a premium for.

"If the customer looked down at the paperwork during a sales call, I knew he wouldn't buy. But if he looked up at the ceiling, I knew I had a chance," says Dennis Courtier, owner of Pepin Heights Orchard Inc. in Minnesota's bluff country along the Mississippi River. Courtier is a longtime grower-shipper-packer who handles about a quarter of the Honeycrisps grown in the U.S and helped blaze a trail for this new kid on the apple block.

Small-Scale Goes Big-Time

The Honeycrisp's road was slow and, at first, uphill. Consumers were used to generic varieties available at grocery chains selling for less than a dollar a pound. But somewhere in the mid-nineties, as Courtier and others were hand-selling Honeycrisps to specialty markets, consumer tastes were changing. Suddenly, there were organics, slow foods and micro brews. Small-scale was big time. And big stores, though by no means going away, seemed to compete for a different consumer.

By the late 1990s, a pound of Honeycrisps retailed for $2.50. And they were selling. Stores couldn't keep them on the shelves. That was good news to growers who took a chance on planting this experimental variety in the mid- and late '90s.

A third of Courtier's growers went out of business in the hard times between 1990 and 2000. But those who switched to Honeycrisps are doing well. "They're sending their kids to

"Eighty percent of my customers will buy nothing but Honeycrisp. I don't think we'd be growing apples if we didn't grow Honeycrisp."

— Doug Shefelbine, Shefelbine Orchards

University of Minnesota

college — and not necessarily on a scholarship," Courtier says. "At the end of the day," he says, "consumers are willing to pay a higher price for a better product."

Doug Shefelbine of Shefelbine Orchards in Holmen, Wis., is a case in point. "Eighty percent of my customers will buy nothing but Honeycrisp. I don't think we'd be growing apples if we didn't grow Honeycrisp," he says.

Specialty varieties like the Honeycrisp are important, says Shannon Shaffer, membership and communications manager for the U.S. Apple Association . "They keep consumer excitement going. They're vital to the industry."

A Way of Life Goes On

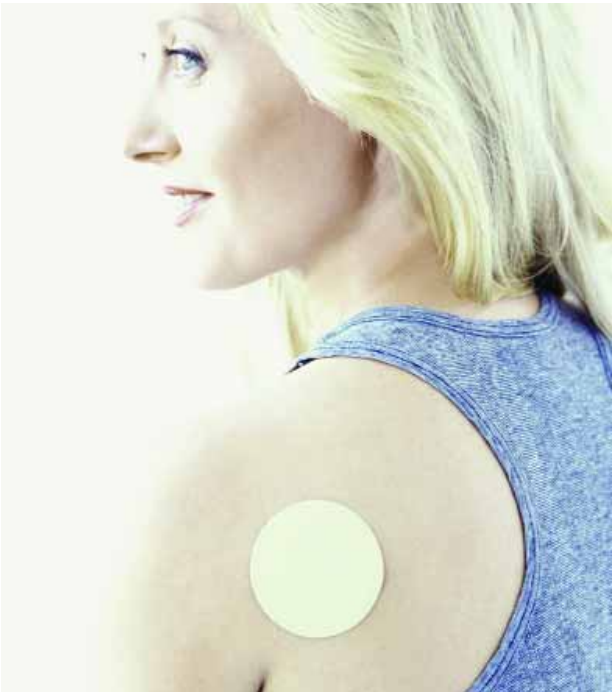
The Honeycrisp has helped smaller growers in Minnesota, Wisconsin, upper Michigan and northern New England whose profit margins per apple need to be higher. Honeycrisps are not without their challenges — trees sometimes produce only biannual crops, need frequent calcium spraying and require picking in small batches — but orchard owners have never been known for liking things easy. And now, the metal cider presses, gray wood crates, John Deere tractors, and orchards themselves that have served so many North Country generations can go on. And a very traditional form of business, and living, can continue.

— By John Motoviloff

Chapter 5

Turning Quitters Into Winners: the Nicotine Patch Success Story

A casual conversation between two brothers in the early 1980s leads to the research and development of the Habitrol nicotine patch, which has helped thousands kick the smoking habit each year.



University of California, Los Angeles

When Jed Rose, Ph.D., gave his brother a ride to their family reunion back in 1981, the topic of work came up in their conversation. Little did Jed know that their discussion would lead to a major medical discovery that would save thousands of lives.

At the time, Jed Rose was a faculty member of the University of California, Los Angeles School of Medicine and founder of UCLA's Nicotine Research Program, and his brother Dr. Daniel Rose was a physician with a successful private practice in Healdsburg, Calif.

"I remember talking to Dan about my research on separating nicotine from sensory factors like taste or inhaling tobacco smoke into your lungs," Jed Rose says. "In discussing the issue of satisfying nicotine cravings, Dan wondered whether some sort of skin patch could be developed — similar to the transdermal scopolamine patch used for the prevention and treatment of motion sickness."

Jed Rose, Ph.D.
Photo courtesy of
Duke University Medical Center

This nicotine patch could potentially be used to reduce people's cravings for cigarettes, cigars and other tobacco products containing nicotine. "So we hatched a plan to develop the patch," Rose says. And the rest, as they say, is history.

Getting the Nicotine Patch to People Who Want to Kick the Habit

Working together with his brother and Murray Jarvik, Ph.D., then head of UCLA's Psychopharmacology Laboratory, Jed Rose initiated the research and development of the nicotine patch. Using himself as the first research subject, Jed Rose determined that nicotine could indeed reach the bloodstream when applied to his skin using a polyethylene patch. The team's first published study on the subject in 1984 demonstrated that the transdermal transfer of nicotine into the bloodstream had the desired effect of reducing nicotine cravings.

After years of experimentation on hundreds of test subjects, the team, with assistance from the Swiss pharmaceutical company Ciba-Geigy, developed a skin patch that would transmit low doses of nicotine into the bloodstream through a subject's skin at a rate corresponding to that of smoking. The patch could also be used in combination with a nicotine aerosol spray in development at the time that would mimic some of the sensations associated with inhaling tobacco smoke. The trio of researchers obtained the first of three patents on the technology in May 1990.

Ciba-Geigy licensed the new nicotine patch technology from the University of California Office of Technology Transfer and after gaining approval from the U.S. Food and Drug Administration, the company launched the Habitrol® patch as a prescription drug in 1991. It wasn't long before other prescription-based

transdermal nicotine patches entered the marketplace as well. In 1991 and 1992 other pharmaceutical companies began marketing their own nicotine patch products based on technologies licensed from other research institutions.

But it was the FDA's approval of over-the-counter nicotine replacement therapies in the mid-1990s that marked another significant step in the nicotine patch success story. Through much wider over-the-counter accessibility, use of nicotine patches increased by as much as 92 percent compared with prior prescription use. By 1999, an over-the-counter version of Habitrol was introduced to the marketplace by Novartis, a pharmaceutical giant formed from the 1996 merger of Ciba-Geigy and Sandoz. Because 70 percent of all smokers express a desire to quit smoking, the widespread over-the-counter availability of these and other nicotine replacement therapies has presented even greater opportunities to kick the tobacco habit.

Tremendous Benefits to Society

To say that nicotine patches have benefited society is like saying breathing oxygen is good for your health. Ample scientific and medical data show that nicotine patches have helped reduce the toll of smoking on society.

And it has been a heavy toll indeed. In the U.S. alone, one out of five adults — 44.5 million people — were smokers in 2004. Nearly one out of every five deaths is related to tobacco use, killing 438,000 Americans annually. Cigarette smoking is the primary cause of death and disease in the U.S., taking more lives than alcohol, car accidents, suicide, AIDS, homicide and illegal drugs combined.

The Centers for Disease Control estimate that adult male smokers lose an average of 13.2 years of life, while female smokers lose an average of 14.5 years of life because of smoking. According to one estimate, smoking annually costs Americans 1.1 million years of potential life lost before they reach 65.

Besides these tremendous human costs, the economic costs of smoking are staggering as well. In 1993, an estimated $50 billion in the U.S. was spent on smoking-related medical care. Lost productivity and earnings from smoking-related disabilities were estimated to cost an additional $47 billion.

Yet nicotine replacement therapies and the nicotine patch in particular have gone far in reversing these devastating trends. Numerous studies indicate that nicotine patches roughly double the rate of successful quit attempts. Successful quit rates for those using nicotine patches range from 9 percent to as much as 20 percent. According to one estimate, the annual number of successful quits achieved using over-the-counter patches alone in the U.S. was 13,566.

By helping thousands of smokers quit every year, nicotine patches generate significant annual net social benefits — an estimated $1.17 billion to $1.39 billion. What's more, the nicotine patch is considered highly cost-effective. Use of the patch produces a lifetime quitter at an estimated cost of $7,332, a tremendous bargain in light of

Nearly one out of every five deaths is related to tobacco use ... taking more lives than alcohol, car accidents, suicide, AIDS, homicide and illegal drugs combined.

University of California, Los Angeles

the tremendous cost to society posed by tobacco use, which amounts to $3,391 per smoker per year. It comes as no surprise that nicotine patches and other nicotine replacement therapies are more cost-effective than other common disease prevention approaches, such as the treatment of hypertension or high blood cholesterol.

Today Jed Rose continues to lead nicotine research as Director of the Duke Center for Nicotine and Smoking Cessation Research at Duke University in Durham, N.C., working alongside his wife, Frederique Behm, who was involved in his initial nicotine patch experiments years ago. Looking back, he notes a humble feeling of satisfaction when reflecting on the groundbreaking research that he, his brother and Murray Jarvik initiated.

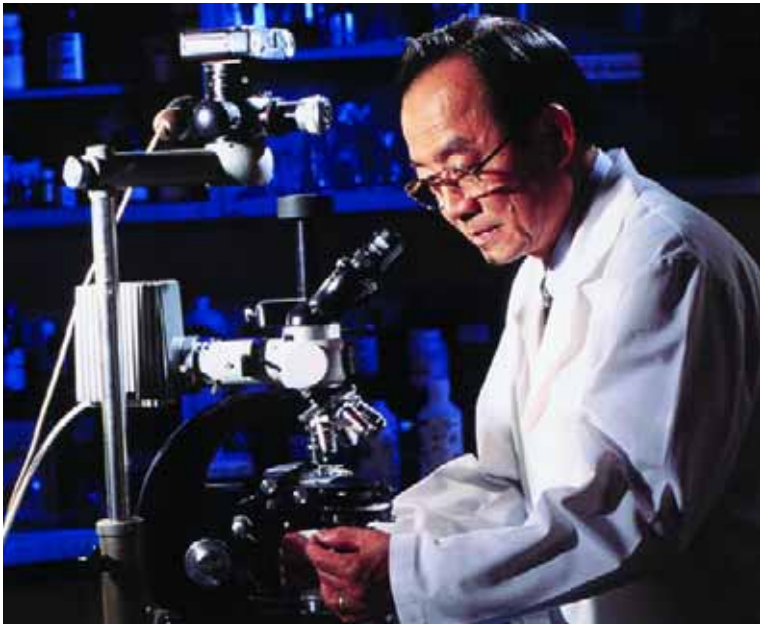
"It is very exciting and gratifying to know that our work has made a difference in people's lives," he says. "This shows the potential impact that clinical research can have on society."

— By Bill Shepard

Chapter 6

The PSA Test: Beating the Odds Against Prostate Cancer

Just decades ago, having prostate cancer was like a death sentence because diagnoses typically occurred in the late stages of the disease. But thanks to the prostate-specific antigen test developed at Roswell Park Cancer Institute, thousands have received early diagnoses and treatment.



T. Ming Chu, Ph.D.
Photo courtesy of Roswell Park Cancer Institute

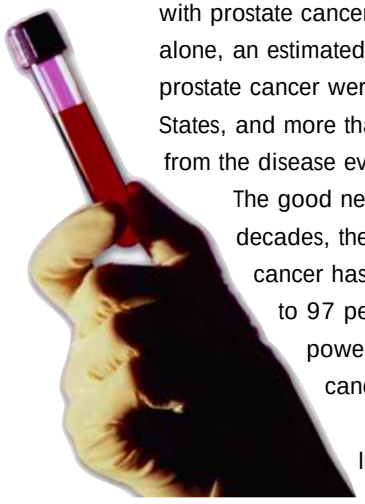
Roswell Park Cancer Institute

When Stanley Inhorn, M.D., visited his doctor for a routine checkup in 1992, he was in for an ominous surprise.

"My wife had encouraged me to get a PSA test during my visit to the doctor. I was 64 at the time and had not had one prior to that," says the former professor of pathology and preventive medicine at the University of Wisconsin-Madison's Medical School. "In retrospect, I'm glad she did."

The results of Inhorn's prostate-specific antigen, or PSA, test indicated he might have prostate cancer. Further follow-up tests and a biopsy confirmed that was, in fact, the case. He sought treatment and has been cancer-free ever since. Now retired, he is actively involved in public health issues including cancer prevention, and is one of more than 1.8 million prostate cancer survivors leading fruitful lives in the United States.

Prostate cancer is second to lung cancer as the leading cause of cancer death in American men. Roughly one out of six men will be diagnosed with prostate cancer during his lifetime. In 2005 alone, an estimated 232,090 new cases of prostate cancer were diagnosed in the United States, and more than 30,000 Americans die from the disease every year.



The good news is that over the past two decades, the survival rate for prostate cancer has increased from 67 percent to 97 percent. And one of the most powerful weapons against prostate cancer is the PSA test.

"The PSA test absolutely revolutionized the way we approach prostate cancer diagnosis," says Donald Trump, M.D., senior vice president for Clinical Research and chair of the Department of Medicine at the Roswell Park Cancer Institute in Buffalo, N.Y., where the initial research on the PSA test was conducted.

The PSA test is used to detect prostate cancer long before the symptoms appear, which typically occurs in the more advanced stages of the disease — often when it is considered too late for treatment.

"Before the PSA test came along, being diagnosed with prostate cancer was almost like a death sentence," says Richard Matner, Ph.D., director of technology transfer and commercial development at the Roswell Park Cancer Institute. "But the PSA gives prostate cancer patients an 'advanced warning' so they can consider various treatment options before the cancer spreads."

Administered to millions each year, this simple blood test has practically become routine for American men in their 50s and older. Besides being used for early detection, it is a valuable tool in monitoring the efficacy of treatments for those already diagnosed with prostate cancer, and it is an effective predictor of the disease's recurrence.

How the PSA Test Works

Prostate-specific antigen is a protein produced by the walnut-sized prostate gland surrounding the urethra in men. When prostate cancer or benign conditions occur, PSA levels increase — so higher PSA levels are used as a marker to detect the disease. The PSA test measures the

level of PSA in the blood. Once a patient's blood is drawn, PSA levels are measured in the laboratory, indicating whether or not he might potentially have prostate cancer.

Though PSA levels alone do not offer enough data to distinguish between benign or cancerous prostate conditions, physicians and their patients use PSA test results to determine the next steps in checking for other signs of cancer.

Age is a major risk factor for prostate cancer. More than 70 percent of all prostate cancers are diagnosed in men older than 65. Race is a factor as well; prostate cancer is twice as common among African-American men as it is among Caucasian men. The American Cancer Society recommends that doctors offer the PSA blood test and the digital rectal examination yearly, beginning at age 50 for men who do not have any major medical problems, and beginning at age 45 for men at high risk.

An Ambitious Research Effort

The PSA test's origins can be traced to the pioneering work of researchers led by T. Ming Chu, Ph.D., at the Roswell Park Cancer Institute. In 1979, Chu and Ming C. Wang, Ph.D., Luis A. Valenzuela and Gerald P. Murphy, M.D., D.Sc., reported the discovery and purification of the PSA. Working with Lawrence D. Papsidero, Ph.D., the following year, Chu demonstrated the presence of PSA in the blood of prostate cancer patients. Together with Manabu Kuriyama, M.D., Chu developed a test to detect PSA in 1980, and in 1981 Chu worked with Murphy to further evaluate and refine the clinical value of PSA. The U.S. Patent and Trademark Office awarded Chu, Wang and Papsidero a patent for the PSA test in 1984.

Research Corporation Technologies Inc., based in Tucson, Ariz., acquired patenting and licensing rights to Chu's PSA test technology, and licensed it on a nonexclusive basis to Hybritech Inc., a pioneering San Diego biotech company that is now part of Beckman Coulter in Fullerton, Calif. Hybritech developed the first commercially viable PSA test, approved by the U.S. Food and Drug Administration in 1986. This test was approved only for monitoring the progress of prostate cancer patients undergoing treatment. In 1994 the FDA approved the PSA test for use as a screening tool for the general public.

The PSA Test's Impact and Benefits

Since the introduction of the PSA test as a monitoring and screening tool, prostate cancer survival rates have dramatically increased. In one study conducted in 1991, 32 percent of the prostate cancers identified by biopsies would have been missed if the PSA test had not been used as a screening tool. A 2005 study indicated men who receive yearly PSA tests are three times less likely to die from prostate cancer compared to those who don't have annual screenings.

"There is no doubt that thousands of men would not be alive today if the PSA test had not come along," Trump says.

Though Trump and others point out there isn't enough hard data available to scientifically prove that PSA tests lower prostate cancer mortality rates, those studies are now under way. Some in

"There is no doubt that thousands of men would not be alive today if the PSA test had not come along."

— Donald Trump, Roswell Park Cancer Institute

Roswell Park Cancer Institute

the medical field harbor reservations about false positives and negatives associated with the test, but proponents point to the PSA test's role in thousands of early diagnoses — crucial in helping prostate cancer patients beat the odds against the disease through successful treatment. Additionally, the PSA test continues to be refined and enhanced as a result of ongoing research.

Economically, the PSA test has had a significant impact as well. "Overall, 20 companies ended up licensing the PSA test technology from RCT, which led to significant job creation and generated millions in sales," says David A. Wiersma, Ph.D., a senior associate at Research Corporation Technologies. "The PSA test remains the biggest-selling commercial diagnostic test of its kind," Wiersma adds.

What began as an ambitious research effort in Roswell Park Cancer Institute's laboratories more than a quarter century ago clearly has become one of technology transfer's greatest success stories.

Just ask Stan Inhorn, who soberly notes, "I might not be here today if I hadn't taken that PSA test."

— By Bill Shepard

Chapter 7

Google: Better Understanding the World

Developed by former Stanford University computer science graduate students Larry Page and Sergey Brin, Google has become the gold standard among Internet search engines.

Stanford University

Though the brain as a biological entity has long-term and short-term functions, the American brain seems to prefer the latter. Short-term viewpoints — the stage on which pop stars' and politicians' careers rise and fall — also shape the ever-changing landscape of Internet technology, where information can go from news to history in a matter of hours.

At the heart of this world is the search engine Google, which accounts for nearly half of all Web searches, and whose founding dates back to a distant age when Web sites numbered in the millions rather than billions. Yes, the search engine whose name has become a verb has not always existed. In fact, in the mid-1990s, it was just an idea floating around the ether of two Stanford University dorm rooms.

From Dorm Room to Boardroom

Web search tools did exist in those primitive days. Yahoo! matched queries against entries in a human-compiled directory of Web sites. Lycos and WebCrawler performed automated searches using keywords. But Stanford computer science graduate students Larry Page and Sergey Brin — son of a University of Michigan professor and native Muscovite who had a habit of disagreeing with about things — saw a more organic principle for conducting searches, one based on the structure of the Web itself.

Seeing the Web as a family tree composed of links, Page and Brin developed PageRank™, the algorithm that lies at the heart of Google's technology. PageRank responds to queries based on two criteria: importance and relevance. Previous search engines ranked query results simply by number of mentions found. A Web site is important, Google's logic says, to the extent that other Web sites link to it. A Web site is relevant to a particular query if its content — and the content of sites it links to — match the query. These calculations are carried using the patented algorithm of PageRank.

First disclosed to Stanford's Office of Technology and Licensing in 1996, Google quickly grew in popularity. By 1999 Google held $25 million in investor equity and was performing 6 million searches a day. Now, it performs more than 50 million searches a day. But what really sets Google apart from competitors is not numbers but user experience — trusted, pop-up-ad-free results in less than a half-second that have become the gold standard among search engines.

Unlimited Impact

The impact of some inventions is felt only by a select few, but Google's dizzyingly democratic online empire — the very word stands for the number one followed by 100 zeros, signifying the amount of information it synthesizes — offers something for everyone: lava lamps to literature, bargain shopping to blogging, advertising to

office goods, even cultural Zeitgeist. The underlying whimsy speaks to No. 9 of Ten Things About Google listed on its Web site: "You can be serious without a suit."

Headquartered in Silicone Valley, with offices on five continents and an international management team, Google subscribes to a creative, collaborative approach to problem solving. Technological milestones notwithstanding, Google's greatest contribution to the economic sphere might be cultural, or even multicultural, joining the worlds of work and play.

Beneath the laid-back, left-coast culture of the company is an entity that's become the poster child for economic success in the information age. For starters, it employs more than 4,000 of the world's best and brightest technological and financial players. Its stock, sold for $85 per share during its initial public offering in August 2004, is expected to sell for $600 a share by the end of 2006, according to a Piper Jaffray stock analyst.

A December 2005 survey of Internet users conducted by S.G. Cowen & Co. shows Google as their primary search engine, the search engine of choice for those with yearly household incomes over $60,000 and the leader in paid search revenues. An estimated $825 million in 2005 capital expenditures and $489 million in 2005 research and development won't hurt the economy either.

'Now, You Just Go to Google'

As Google pays financial dividends to share holders, it pays rewards in time saved and dependable results to the world of information technology. "A decade ago, there used to be a dozen different search engines (of equal worth) out there," says Kathryn Motoviloff, an information researcher at Lucent Technologies in Murray Hill, N.J. "Now, you just go to Google." Those who track down information in the ultracompetitive telecommunications sector have come to rely on Google's speed and accuracy.

Looping back to academia, where it was born, Google has become nearly indispensable to librarians, professors and students alike. "I turn to Google almost immediately when working on a reference question. It is not difficult to quickly develop search strategies that can deliver good basic information on a topic," says Kevin Kurdylo, librarian and archivist at the Max Kade Institute of German-American Studies at the University of Wisconsin-Madison.

Further facilitating research, Google Scholar allows password-controlled access to university libraries' online resources. Similarly, Google's partnership with the Online Computer Library Center's Open WorldCat program makes public library resources readily available to users via links to their home library. "Library users are starting with Google and stopping with Google," says Stefanie Morrill, technology coordinator for the South Central Wisconsin Library System.

But it's not just ease of research. The research

"Library users are starting with Google and stopping with Google."

— Stefanie Morrill, South Central Wisconsin Library System

Stanford University

itself has the potential to be deeper, fuller and richer because of the encyclopedic range of images, music and words Google provides. Scholarship has always been about advancing the cause of knowledge. To the extent that more material is digitized, the world's vast storehouse of knowledge — most of which was previously cloistered in special collections — can become easily interwoven into the global tapestry of knowledge. Google's partnerships with Stanford, Harvard University, the New York Public Library and others in Google Book Search makes their collections of public domain accessible to users worldwide and helps all of us better understand our world.

— By John Motoviloff

Chapter 8

Flying Without Fear: Sonic IR Identifies Cracks in Airplanes

Researchers at Wayne State University found a way to discover cracks in layered structures, which promises good things for the airline and other industries — and for the people who depend on them.

Injecting ultrasound into an aircraft engine turbine blade with a handheld ultrasonic gun.
Photo courtesy of Skip Favro, Ph.D., Wayne State University

Wayne State University

Electrical and computer engineering professor Xiaoyan Han doesn't spend a lot of time worrying about little cracks in airplanes as she flies across the country at 30,000 feet. But the thought of what would happen if an engine fell off or the fuselage peeled open in mid-flight has crossed her mind. That's why Han's research gives her some comfort.

Han and fellow Wayne State University faculty members Skip Favro and Robert Thomas have developed an ultrasound technology called Sonic IR that can detect cracks as small as one-thousandth of an inch. The professors began working on the effort about five years ago and received their first patent in 2002.

Now, the U.S. Federal Aviation Administration and aircraft manufacturers are studying the ultrasound technology. "I hope this will be applied to airplanes soon," Han says. "It could make them safer."

She says the technology is especially good at discovering cracks in layered structures. "If they are below the surface, it's hard to find them," Han says. "But with Sonic IR, we can locate delaminations and disbonds quite easily."

A Wayne State student tests for fuselage cracks. Photo courtesy of Skip Favro, Ph.D., Wayne State University

Making the Skies Even Safer

Favro, a research scientist in the Detroit-based university's Institute for Manufacturing Research, says he thinks flying in airplanes is safe. "But clearly, there is a great interest in the aviation industry because the results of a failure can be catastrophic," says Favro, whose institute is working with the FAA.

"I think the airline industry does a pretty good job," he says. "But some things do sneak up. Little cracks do tend to get bigger." Favro explains that the FAA's aging aircraft program began after the fuselage of Aloha Airlines flight 243 came apart in 1988. The accident, which occurred 24,000 feet over Maui, killed one flight attendant and injured eight passengers.

David Galella, project engineer at the FAA technical center in Atlantic City, N.J., calls the Sonic IR technique "very promising because of its ability to potentially detect crack tips, which can be the source of the friction." In airplanes, he says, cracks often grow away from their starting points at the heads of fasteners or rivets.

"We've developed a couple of different prototypes and are trying to understand the best applications for the technology," he says. "We certainly hope to see the technology implemented within this decade."

Galella says Sonic IR could supplant some of the technologies already in use. "Our jobs here are to find improvements," he says. "Whether or not a technology is picked up depends on a number of things including cost benefits. But we certainly think this technique has a lot of potential for aircraft."

Technology Has Applications in Various Industries

Meanwhile, Sonic IR — for which Wayne State has six patents — is being adapted for uses with

pipelines, power plants, transmission towers and in the automotive industry. "Who wouldn't be interested in this technology?" Favro asks. "Cracks are everywhere and they can cause a multitude of problems."

Siemens Power Generation Inc. is using Sonic IR to test the power turbine parts it makes for utilities and their electricity generation plants. "Wayne State's work is a major step forward from the historic processes of finding natural or propagated cracks. It is unsurpassed, a powerful new technology," says Paul Zombo, head of nondestructive evaluation technologies for the Orlando, Fla.-based company.

Zombo, whose company has named its version of Sonic IR SIEMAT, for Siemens Acoustic Technology, says the old techniques did not define cracks as well. The company uses SIEMAT to test new parts and service-exposed parts that have been in use at power plants. "This gives you a more accurate analysis of the true defects in a part," he says. "It gives us a better 'truth,' so you can estimate the real remaining life of the part."

Zombo says the technology can work on a variety of metals, ceramics and composites. It is also easier to use than previous devices. "Before it was squiggly lines on an Oscilloscope," he says.

"This is an imaging method, so you can actually see the defect. You can also superimpose your data onto a finite element analysis model and apply stresses and loads to see if the crack is dangerous or benign. It's great," Zombo says.

The technology has many applications outside the utility industry, too. "Obviously, aeroframes and aeroturbines would be two of them," Zombo says. "I can see why airlines and the FAA are interested."

Zombo declined to speculate how much money the Wayne State technology has saved his company. "That's hard to say," he says. "But just from a comparison standpoint, we have a much higher probability of finding defects and we can do it in about 50 percent of the time it used to take."

Another company that has licensed the technique is Indigo Systems Inc., which has introduced it under the trade name Thermosonix.

The Wayne State technology also can replace time-consuming and environmentally toxic dye-penetrant methods of looking for cracks. "They soak what they are testing in a bath of a horrible dye," Zombo says. "But first they have to clean the part, etch it with acid, soak it in a fluorescent dye, clean it again and then look at under a UV light. Frankly, it is a pain in the rear end," he says.

Sort of Like Rubbing Your Hands Together

Favro says the Wayne State technology blends the diagnostic powers of ultra-high frequency sound waves and thermal imaging, using infrared radiation to detect heat. The technology is based on friction, he says. When sound waves are sent through a material — whether it's fiberglass, laminate or steel — it moves. But if there is a crack, the two sides don't move in unison. Instead, one side will rub against the other.

"A byproduct is heat, just like when you rub

"This is an imaging method, so you can actually see the defect. You can also ... apply stresses and loads to see if the crack is dangerous or benign."

— Paul Zombo, Siemens Power Generation Inc.

Wayne State University

two sticks together in that Boy Scout trick," says Favro, a former Scout himself. "It's not a lot different than rubbing your hands together on a cold day to keep warm." To locate the crack, researchers use an ultrasonic welder. To capture the image, they use infrared video camera. The heat that the crack produces is depicted in pixels of an image on a computer monitor.

Another benefit that intrigues developers is the technique's ability to detect what are called fatigue cracks, which X-ray examination sometimes misses. When under stress, many critical components used in aviation are highly vulnerable to fatigue cracks, which is one reason that the Wayne State technology shows such promise for aircraft design and manufacturing.

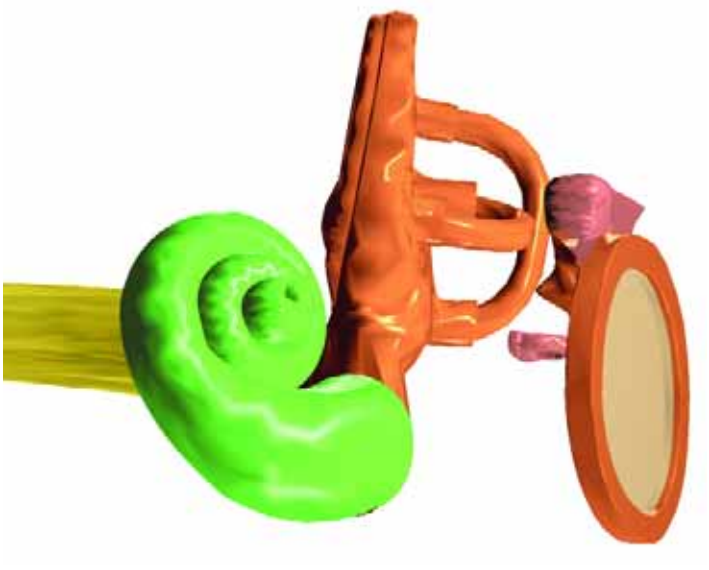
Favro says the best thing about this technology — and what makes it superior to existing techniques — is that it can detect cracks from any angle. "Using flash lamps, we could see the disbonds and delaminations that were parallel to the surface, but we couldn't see the cracks that were perpendicular to the surface," he says. "Now we can. This is much better."

— By Brian E. Clark

Chapter 9

Cochlear Implant Brings Sound and Language to Thousands

An electronic hearing device developed by neuroscientists at the University of California, San Francisco gives the gift of sound to thousands of people who have lost their hearing and brings normal language to people who have been deaf since birth.



Anterior view of inner ear anatomy.

University of California, San Francisco

Michael Merzenich, Ph.D., led research on cochlear implants. Photo by Susanna Friedrich

One of the most remarkable technologies ever developed for people with hearing loss is the cochlear implant. An amazingly complex, micro-machined electronic device that stimulates the acoustic nerve to replace the excitatory function of a pathologically destroyed ear, the cochlear implant has led to restored hearing in people with advanced hearing loss and established normal language use in people who have been deaf since birth. Though the device has been somewhat controversial within the deaf community, it is nothing short of a miracle for people who use it.

Michael Merzenich, Ph.D., and his colleagues at the University of California, San Francisco led research on the development of cochlear implants in the1970s and 80s. Merzenich, a neuroscientist, has spent his career investigating the neural origin of higher brain functions and the remediation of human neurological dysfunction and disability. His lab focuses on defining the neural bases of learning, recognition and memory, defining the mechanisms that underlie functional disabilities, and developing strategies for remediating learning-disabled children and adults. The cochlear implant is one of a number of commercial products that has emerged from those varied interests and pursuits.

"It is the most sophisticated electronic device that's implanted into humans," Merzenich says of the product. The university licensed the technology in 1988 to a cardiac pacemaker manufacturer, which created a subsidiary called Advanced Bionic, now a subsidiary of Boston Scientific, to develop and market the technology.

Merzenich and his team developed novel strategies to electrically stimulate the auditory nerve array in the inner ear with patterned stimulation that generated sensory inputs designed to simulate those generated in a normal, intact ear. Though the Merzenich team was the world-leading research group in this area, they didn't patent their inventions until they began to search for a company that could manufacture the device.

Studies Began in the 1950s

Researchers had been working on the problem since the 1950s, wondering whether it might be possible to replace the electric signals from the missing hair cells in people who had hearing loss, especially those who had intact auditory nerves. Initial efforts to create a cochlear implant were met with a great deal of skepticism and daunting technical obstacles.

In parallel, the communication industry had been working to reduce the information in a speech signal without losing its intelligibility. Spearheaded largely by AT&T's Bell Laboratories, these early voice coders simplified the designs of the coding stages for the cochlear implant. Merzenich's inventions were based in part on that technology.

Merzenich says that the first patent was very general, covering the basic idea behind the technology: the patterned replacement of sound that would simulate the activation that occurs in an intact ear. The ear of a non-hearing person lacks the tiny hairs that act as transducers to stimulate the auditory nerve, creating sound. The cochlear implant directs the electrical simulation input of

complex sounds. Later patents described specific features that were critical to the successful application of the device.

Distinct From Hearing Aids

Cochlear implants are not the same as hearing aids. Surgically implanted to replace the function of the ear, they are used in patients whose deafness is complete, or almost so. Hearing aids amplify sounds and are created to target specific areas of the auditory nerve to make up for hearing loss.

In contrast, the cochlear implant stimulates the whole auditory nerve array with patterned electrical signals to simulate normal nerve input in a way that would be expected to generate sound in an intact ear. It is more sophisticated, complex and costly than a hearing aid; it also is extremely difficult to manufacture, requiring complex micromachining, microfabrication and engineering.

"Each implant has hand-fabricated components and very complicated electronics," Merzenich says. "The engineering development in this product has been substantial." Merzenich estimates that each device costs $5,000 to $10,000 to manufacture with appropriate quality assurance. "Quality assurances are crucial," he says, "because these devices are designed to last a lifetime."

The implant was developed for those with the most severe hearing loss, but it is being applied more and more frequently to patients with marginal hearing. One of the most famous people to receive a cochlear implant is radio talk show host Rush Limbaugh, whose career was on the line because his hearing loss was so severe.

The cochlear implant technology, while embraced by the medical community, has met with some resistance in the deaf community. Merzenich says it is difficult for deaf families — especially those who have always been deaf — to deal with a hearing child, or even to understand why anyone would want to treat the non-hearing child.

"It isn't surprising that deaf individuals can be a little insulted by the notion that deafness is an unacceptable condition that demands treatment," he says. "It's not an entirely unjustified fear that deaf children implanted with the device can become aliens in their own families and communities."

Understanding Sounds

The "ah-ha" moment for Merzenich and his colleagues came in 1979 or 80, when patients equipped with the technology, sitting in a sound room, "began to understand everything the scientists were saying to them through the cochlear implant-mediated hearing alone."

When a deaf person with a cochlear implant is first exposed to speech, they usually cannot understand what they're hearing, according to Merzenich. "Speech sounds distorted or robotic," he says. "But, in time, about 90 percent of the patients come to understand almost everything that's said to them."

More than 20,000 patients have received Cochlear implants since the technology was patented in 1980.

— By Jill D. Ladwig

The cochlear implant stimulates the whole auditory nerve array ... to simulate normal nerve input in a way that would be expected to generate sound in an intact ear.

Chapter 10

Discovery of a Fundamental Lung Function Leads to Higher Survival Rates for Premature Infants

A University of California, San Francisco professor dedicated his career to studying how lungs work, then created a treatment that helps babies suffering from respiratory distress syndrome breathe. The result is a dramatic decline in infant mortality caused by RDS.

The research of John Clements, M.D., led to Exosurf.
Photo by Elisabeth Fall; courtesy of the University of California, San Francisco

University of California, San Francisco

Not long ago, thousands of newborn babies died in hospitals every year because of a mysterious affliction called respiratory distress syndrome. Up until the mid-1950s, doctors didn't know the cause of this heartbreaking ailment. That's when professor John Clements began to make inroads into doctors' understanding of the human lung that eventually led to a cure for RDS.

Clements had been in the U.S. Army's Medical Research Unit during the Korean War. A trained biochemist and physiologist, Clements had been assigned the task of understanding how nerve gases affect the lungs. His research focused on the defensive aspects of chemical warfare — providing better treatment for soldiers who had been exposed and trying to figure out whether they could be protected against the noxious gas. The knowledge Clements sought for the battlefield would eventually save thousands of lives — not soldiers' lives, but babies' lives in hospital nurseries around the world.

"My studies on lung mechanics led me to think there was a surfactant there," Clements says, more than a half-century later.

Finding It Was Just the Beginning

A surfactant is a substance that reduces the surface tension of liquid containing it. It accumulates at the surface of the lung and occupies the surface of air spaces, which are typically wet and would otherwise have high surface tension. The lung secretes this surfactant to allow the lung to expand in breathing and remain air-filled.

"I guessed it was there, tested for it, and I found it was there," Clements says. "It turned out to be very interesting, very complex — and it took me another 25 years to really understand it," he adds with a laugh.

Clements is now an emeritus professor at the UCSF Cardiovascular Research Institute and the Department of Pediatrics. "It's only one molecule deep," he says about the qualities of lung surfactant. "It's like a sheer nightgown covering the surface of the airspaces of the lung, but it is absolutely critical to life."

Intrigued, Clements has spent decades investigating the structure, function and biology of lung surfactant. The problem for newborn babies, especially those born pre-term, is that this life-supporting mammalian function doesn't become active until late in pregnancy, around 28 to 32 weeks.

"Preemies with RDS don't have a surfactant," Clements says. "They have not begun to secrete the protective surface that will enable them to keep their lungs expanded."

The Connection with Infants

Around the same time Clements was beginning to explore and publish articles about lung surfactant, Mary Ellen Avery, a pediatrician interested in RDS, and Jerre Meade, a pulmonary physiologist who knew about Clements' research, decided to see if infants with RDS lacked surfactant. Working at Harvard University, they consulted with Clements to learn his methods and in 1959 published data indicating that babies who died with RDS did, in fact, lack surfactant.

Between that time and 1982, Clements

explored the intricacies of surfactant in the human lung, using his research knowledge to consult with clinicians about how best to care for premature infants. It was during this time that one of the nation's first intensive care nurseries was developed at UCSF, with expert input from Clements.

"I consulted on the research aspects of neonatal care, especially in terms of physiology and basic science," he says. "We brought many supportive measures — blood transfusions, artificial oxygenation and others developed in adult intensive care — to bear on the problems of sick newborns." Other universities including Columbia University and Vanderbilt University also were introducing these types of facilities, Clements says.

Around 1980, a Japanese pediatrician, Tetsuro Fujiwara, created an artificial surfactant from cow lungs and found it worked well in 10 infants with RDS. Clinicians from the Specialized Center of Research on Pulmonary Disease at UCSF asked Clements what surfactant he would advise for a larger clinical trial. Clements, who was a little concerned about putting animal materials into human lungs, told them that he would design a synthetic substitute for them. Two weeks later, he presented a substance named Exosurf.

Clement's synthetic surfactant was licensed by Burroughs-Wellcome in 1986. Clements says a friend persuaded the pharmaceutical company, now GlaxoSmithKline, to take a look at the substance. The company shepherded the product through the U.S. Food and Drug Administration approval process, from pre-clinical work through human clinical trials.

But it wasn't an easy road to market. According to the University of California Office of Technology Transfer, the Exosurf invention was disclosed just before the passage of the Bayh-Dole Act in 1980, meaning the university had no legal right to license it. And the preference of the National Institutes of Health for non-exclusive licensing was incompatible with the company's need for exclusivity. So several years of negotiation ensued before the university could offer exclusive rights.

Trials Showed the Impact Was Immediate

When Exosurf finally went into human clinical trials, the impact of the drug on the welfare of newborn babies was immediate. "During the first trials of Exosurf, infant mortality was reduced one-half to one-quarter of what it was with the standard treatment," Clements says.

Exosurf, and other surfactant substitutes developed more recently, have contributed to a dramatic drop in the infant mortality rate in this country and around the world. Between 1988 and 1993, infant mortality in the United States dropped by 16 percent — a remarkable decline in such a short time frame.

In honor of their achievements, Clements and the Burroughs-Wellcome scientists who assisted in the development of the drug received the 1997 Discoverers Award from the Pharmaceutical Research and Manufacturers of America, a membership organization dedicated to the research and introduction of new medicines.

— By Jill D. Ladwig

"During the first trials of Exosurf, infant mortality was reduced one-half to one-quarter of what it was with the standard treatment."

— John Clements, Exosurf inventor

Chapter 11

Tiny Monitor Gives Diabetics Frequent, Automatic Readings

The first non-invasive continuous monitoring device, pioneered at the University of California, San Francisco, helps patients better manage diabetes.

University of California, San Francisco

In 2002, many people with type 1 diabetes rejoiced when they learned that a new technology offered relief from being a human pincushion. Diabetics who were tired of pricking their fingers to check their blood sugar levels, or ignored or avoided the process altogether — and, by doing so, increased their chances for hypoglycemia — had a new, portable, convenient option.

That non-invasive score-keeper was the GlucoWatch® Biographer™, the world's first wristwatch monitoring device, which incorporates technology invented at the University of California, San Francisco. As a supplement to finger-prick devices, the easy-to-use GlucoWatch has helped diabetics and their doctors become better informed about the patient's disease.

Staying in tight control of glucose levels is key in managing diabetes. Physicians usually advise doing blood checks by finger prick four to seven times a day; but because of the inconvenience, some patients draw blood only once a day, if at all.

The trade-off for this relaxed attitude can be deadly. Patients who do not actively manage their diabetes could suffer long-term diabetes-associated complications including blindness, hypertension, stroke, heart disease, kidney disease and amputation.

In 2005 the World Health Organization estimated about 500 million people worldwide suffer from diabetes and only about 40 percent have been diagnosed. More than 20 million people, or about 7 percent of the U.S. population, have the disease and about a third of those are undiagnosed and untreated.

In 2002 — the year that GlucoWatch Biographer was introduced — 224,092 deaths were attributed to diabetes complications, and these numbers are considered low because many older people have multiple chronic conditions. In the same year, the annual economic cost of diabetes was estimated at $132 billion.

Easy-to-Use Tool Changes the Landscape of Glucose Monitoring

Scientists at the UCSF spent eight years developing and patenting the technology behind the GlucoWatch Biographer, a first-of-its-kind glucose monitoring device. Blood glucose monitors can offer substantial benefits that other traditional sampling methods don't provide.

For diabetics who want to better manage the disease by tracking glucose levels in a non-invasive, easy-to-read way, the small, portable technology invented at the UCSF has changed the landscape of diabetic monitoring.

In addition to the convenience of being able to wear the monitor, the GlucoWatch Biographer also warns patients before their glucose levels become too low or if there is a sudden, rapid drop in glucose levels. The technology has been an important step toward improving diabetes management.

The U.S. Food and Drug Administration approved the GlucoWatch Biographer in 2001 as a supplement to — not a replacement for — blood testing through finger pricks. It has helped patients make better decisions about diet, medication and physical activities. The frequent readings show how various activities such as

exercises, stress, sleep, taking medications and eating meals affect glucose levels. Most important, it can warn patients of low blood glucose levels, which can be fatal.

"The pain-free, wrist-watch device automatically checks sugar levels by transmitting tiny imperceptible electric currents through the skin," explains Yashwant Vaishnav, Ph.D., business development and intellectual property manager with the systemwide Office of Technology Transfer at the University of California. "The concept for the first-of-its-kind technology was developed in 1987, and in 1995 the university licensed the technology to Cygnus Inc. of Redwood City, Calif."

In 2001, Cygnus began marketing the device in Europe, and in 2002 the second-generation model, the GlucoWatch® G2™ Biographer, became available in the U.S. for adults and pediatric patients.

The forerunner of recently released self-monitoring devices, the GlucoWatch G2 Biographer provides noninvasive readings by measuring glucose collected through the skin as opposed to the traditional finger-prick method of collecting readings from whole blood. The Biographer provides frequent automatic glucose readings — as often as every 10 minutes for up to 13 hours.

Noninvasive diabetes management begins when the patient places an adhesive AutoSensor, a thin disposable pad, to the back of the watch and straps the GlucoWatch Biographer on the forearm. The sensor adheres to the skin, collects glucose in tiny gel discs in the sensor, then displays the readings on the watch's face.

"Readings are taken noninvasively through the sensor by extracting glucose from interstitial fluids between the skin cells," Vaishnav says.

Though automatic glucose monitoring devices are not for everyone, they can make it easier for diabetics to gather and review information. In addition to convenience, Vaishnav points out, there is another significant benefit for users of the GlucoWatch Biographer[1]. "The technology gives the user an archival record. Worn like a watch, it calculates, displays and stores frequently recorded glucose readings," he says.

And a patient doesn't have to be a computer programmer to use the data management system. Before purchasing a glucose monitoring device, patients' physicians or diabetes educators can help discern what information they want patients to record. The technology lets patients scroll back to see glucose readings over a few hours and download the information to a personal computer to save, print out and interface with physicians' computer systems. The GlucoWatch G2 Biographer can store up to 8,500 readings, and the information, once transferred to a computer and plotted as a graph, can offer a good visual picture of patients' histories.

Spawning the Next Generation of Self-Monitoring Devices

In connection with a sale of certain assets by Cygnus to Animas Corp., a leading maker of insulin infusion pumps and related products, the University of California consented to the assignment of the GlucoWatch license agreement from Cygnus to Animas. Animas is dedicated to improv-

"The pain-free, wrist-watch device automatically checks sugar levels by transmitting tiny imperceptible electric currents through the skin."

— Yashwant Vaishnav University of California System

[1] The Regents of the University of California do not endorse any specific product or service.

University of California, San Francisco

ing diabetes management and making insulin pump therapy easier for patients with insulin requiring diabetes and healthcare professionals, and is currently selling GlucoWatch products.

The interest that ensued when the GlucoWatch Biographer was first introduced is still evident today. The University of California's pioneering technology opened the door to other continuous monitoring products that have been and are expected to be introduced to the marketplace as a direct result of the GlucoWatch Biographer.

Some new products include the DexCom® Inc. Short-Term Sensor Continuous Glucose Monitoring System, the Medtronic Inc. MiniMed Long-Term Sensor System™ and Guardian® RT Continuous Glucose Monitoring System, and the Abbott Laboratories Freestyle Navigator™.

"The Regents of the University of California maintains ownership of the technology," Vaishnav says. "While there are other newer products on the market, GlucoWatch was the first commercially available product of its kind."

— By Sharyn Alden

Chapter 12

Glass Fiber Reinforcement Provides Dental Material Strength and Flexibility

Two researchers at the University of Connecticut Health Center create a new dental composite named FibreKor with the strength characteristics of a stealth bomber's surface, and aesthetic characteristics that please dentists and patients.

Photo courtesy of Charles J. Burstone, D.D.S., University of Connecticut Health Center

University of Connecticut

What might stealth bombers and some modern dental bridges, crowns, splints and posts have in common? At first glance, not much. But if you look below the surface of FibreKor®, a dental composite, and the skin of the bomber, you'll find tiny glass reinforcing fibers that make both durable and strong.

Two University of Connecticut Health Center researchers — materials scientist Jon Goldberg, Ph.D., and orthodontist Charles Burstone, D.D.S. — collaborated in the late 1980s to create the fiber-reinforced material now used by dentists around the world in a number of dental devices.

The Old State of the Art Was Metal

"Before we did this, the state of the art was metal," Burstone says. "But metal is not transparent and, unfortunately, has the undesirable effect of darkening the tooth."

Once technicians build the base of a FibreKor bridge or crown, they coat it with an existing plastic restorative material to complete the artificial tooth that is strong and natural looking — without requiring a metal base. Posts and splints also are advantageous because they look like real tooth enamel. And dentists can use FibreKor to make some dental devices right in their offices on a while-you-wait basis.

Photo courtesy of Charles J. Burstone, D.D.S., University of Connecticut Health Center

This high-quality and flexible product is the first commercially successful dental application of a fiber-reinforced composite, and it's an ideal fit in the field. "People had tried to use polymers in the past. But they didn't have the rigidity or other attributes needed for dentistry," Burstone says. "But by putting in fibers, we discovered that you could have both pleasing aesthetics and the desired mechanical properties."

Going Outside the Literature

To find answers for their endeavor, the pair went outside dental literature — to the U.S. Air Force. "We looked at how they made the skin of stealth bombers," he says. "And we found some of the information there.

"I don't know if this is the gold standard for dentistry," Burstone says. "But the polymer products look much better than metal, certainly."

Goldberg says he and Burstone have been working together for nearly three decades. "We go way back," chuckles Goldberg, who chose to specialize in dental materials when he was a graduate student at the University of Michigan. He received his Ph.D. in materials science from the University of Michigan Schools of Dentistry and Engineering.

"I had a number of opportunities, but I liked the challenges that dentistry posed," he says. "I also liked the people in the dental school." He began his collaboration with Burstone when

he joined the University of Connecticut Health Center faculty.

A Long Way From Stainless Steel

In one of their first projects, they developed a titanium alloy that was used to replace stainless steel wires traditionally used in orthodontics. "The great thing about it was that it had a lot more flexibility," he says.

Then, they turned their attention to what became FibreKor. "We looked over materials available and settled on fiber reinforced composites," he says. "What we initially developed, though, was not used for the orthodontic application that we'd originally intended. We had hoped to use fiber-reinforced composites for orthodontic wires as a follow-up to the titanium wires."

But they didn't give up because they were convinced that what was eventually marketed as FibreKor would be useful in dentistry. So they set about refining their discovery.

"In a sense, it was a kind of serendipity," he says. "Once we had it in hand, we saw that it could be used for various dental applications like bridges and posts." The idea of using fiber-reinforced composites had never been successfully applied to dentistry. "It was a puzzle that had yet to be figured out," Goldberg says.

"But the defense industry had made strides, so we researched what the military had done. Then we were able to properly identify a dental need and, then, adapt FibreKor to retain the characteristics we wanted," Goldberg says.

Burstone and Goldberg received their first of two U.S. patents in 1988.

Initially, Dentists Were a Tough Crowd

Even after they came up with their prototype, the materials didn't immediately gain acceptance in the dental world. "To be honest, it was like a number of things we have done," Goldberg says. "At first, we could not get people to adopt it … It takes a combination of having a fairly well developed prototype and a commercial partner with interest in that area. It took off when that partner was identified," he says.

That partner was Pentron, a small company in Wallingford, Conn., and one of the world's prominent makers of dental materials. Pentron signed the first of two exclusive licenses with the University of Connecticut in 1996, and introduced the first fiber-reinforced composite materials to the dental market in early 1997.

Pentron Helps Get Dentists' Attention

Joe MacDougald, chief operating officer of the privately held Pentron, was involved with negotiating the original licenses with the university. He calls FibreKor a "great technology" and says his company liked the material because it replaced less attractive metal materials.

"FibreKor posts have much of the strength of metal," he says. "Moreover, it bonds better than metal and it's easier for dentists to use. They can apply the Splint-It® version of the material chair-side in strips to stabilize or repair teeth in

"FibreKor posts have much of the strength of metal. … Moreover, it bonds better than metal and it's easier for dentists to use.

— Joe MacDougald, Pentron

University of Connecticut

the office. And it replaces the metal understructure of the crown and gives just as strong support," he says. "With a composite up above, the substructure and the tooth can match each other."

Pentron first introduced FibreKor to replace metals for crowns and bridges. Its second product, Splint-It, became available in fall 1997 to hold groups of teeth together to compensate for a lack of gum or bone support. Dentists also use it to splint teeth together to simplify and make more aesthetic orthodontic treatment and retention.

Pentron's third product, the FibreKor post, was unveiled in 1998 as an alternative to traditional metal posts that support the construction of a crown after root canal procedures.

Root Canal Posts Are the Biggest Application

Golberg says FibreKor's biggest application is in dental posts. He estimates that fiber-reinforced composites comprise 20 to 30 percent of root canal posts. "If you have a root canal, but not enough tooth left to properly restore, a post will provide the additional retention necessary for a crown," he says.

FibreKor is gaining in popularity for several reasons, Goldberg says. "Aesthetics is one big issue," he says. "Metal post creates a shadow in the tooth because it is darker. But polymers also bond better than metal … And anything you do with teeth, you want to have a good bond."

Finally, the processing is easier. "You don't have to do metal casting and you don't have high-temperature metal handling," he says. "It's a winner."

— By Brian E. Clark

Chapter 13

Scientists Find Promising Treatment for Neglected Killer Diseases

A University of Washington and Yale University collaboration yields a set of chemical compounds that may hold the key for treating infectious parasitic diseases including Chagas' disease and malaria. The compound was licensed to a nonprofit pharmaceutical company that is developing a drug for use in Latin America.

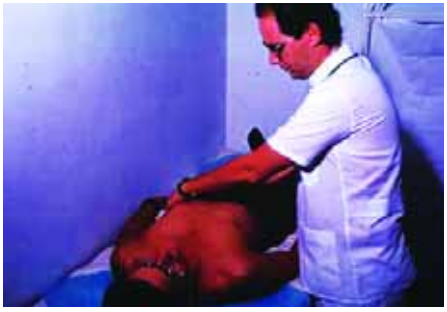
The Rhodnius prolixus, or kissing bug, spreads Chagas' disease when it bites. Photo by Sinclair Stammers; courtesy of the World Health Organization and the Special Programme for Research and Training in Tropical Diseases

University of Washington / Yale University

Some of the world's most intractable diseases are predominant in the developing world. These illnesses are known as neglected diseases because, though they have a significant impact on vulnerable populations, they receive little attention from the medical community or the pharmaceutical industry. One of these neglected killers is called Chagas' disease.

Chagas' disease is an insect-borne, parasitic illness that infects and kills millions of people every year, according to the World Health Organization. Chagas' is endemic in 21 Latin American countries and a major cause of heart failure in the region. Caused by the parasite *Trypanasoma cruzi*, it is most often transmitted by an insect known as the kissing bug. Humans, as well as wild and domestic animals, carry the parasite, and the insects infected with *T. cruzi* frequently live in the thatched walls and roofs of homes, making it especially challenging to eradicate.

Controlling the disease is difficult, costly and risky. It depends largely on treating homes in affected areas with residual insecticides and, in general, improving housing by replacing traditional thatch-roofed dwellings with more modern plastered walls and metal roofs. Management of the illness now entails blood screening to prevent transmission through transfusion. Some drug treatments are available as well.



Chagas' is endemic in 21 Latin American countries and a major cause of heart failure in the region. Photo by Mark Edwards; courtesy of the World Health Organization and the Special Programme for Research and Training in Tropical Diseases

Finding a Treatment for the Disease, Not Just the Symptoms

But the standard drug treatments for Chagas' leave much to be desired. Most are aimed at fighting the infection, which manifests in the heart and gastrointestinal tract of the victim. The drugs are difficult to administer and highly toxic, leading to severe side effects in many patients. And no existing medicines have consistently cured patients, according to a report from the Institute for OneWorld Health, a nonprofit pharmaceutical company whose purpose is to develop affordable treatments for neglected infectious diseases around the world.

A collaborative research effort among scientists at the University of Washington and Yale University recently brought forth a non-toxic drug therapy for Chagas'. The team included Andy Hamilton and Junko Ohkanda, both chemists at Yale; and Fred Buckner and Wesley Van Voorhis, infectious disease experts, and Michael Gelb and Kohei Yokoyama, chemists, at University of Washington.

"It was a wonderful collaboration between organic chemists and parasite biologists that came about through reading the literature and recognizing potential connections," says principal investigator Andy Hamilton, who has since become a provost at Yale. "Big problems nearly always involve collaborative solutions

because no one person or institution can have all the answers."

Fred Buckner, of the University of Washington Medical School, agreed. He has worked for years with a group of chemists led by Michael Gelb to develop compounds to treat infectious diseases caused by protozoan pathogens.

"They would make the compounds and we would test them against the parasites to see if they would do anything. Some turned out to be active against targets that were different that what we designed them to do, but we determined the mechanism of action and showed them to be active in an animal model," Buckner says.

Collaboration Goes Beyond the Laboratory

The original patent application described "compounds and methods for treating infections caused by bacterial protozoal and fungal agents," says Aline Flower, of the University of Washington TechTransfer Invention Licensing.

"We developed, in collaboration with parasitologists, compounds that target the Chagas' disease agent in animal models, and we are seeing some very encouraging data," Hamilton says when asked about the potential application of the compound.

Buckner and his colleagues had made inroads targeting these diseases, working toward cures or vaccines. "We had discovered that protozoan parasites contain the enzyme protein farnesyltransferase," he says. "This same enzyme plays an important role in cancer cells, which meant a lot of research laboratories were developing drugs against it. We were working on the hypothesis that protein farnesyltransferase inhibitors might work against parasites," Buckner says.

In the meantime, Hamilton and his colleague at Yale were working on a similar problem from another angle. "This was the result of many years of fundamental research in trying to get a novel molecular structure to target a specific enzyme," Hamilton says. "It's a question of how one synthetic molecule could recognize a biological molecule in a process called molecular recognition."

Perhaps just as important as the chemical compound the researchers discovered, Hamilton says the two universities and the nonprofit pharmaceutical company have developed an integrated model for drug development. "We hope, as we make progress in the pre-clinical stage, OneWorld Health will help us pull together the necessary funding to allow the clinical and preclinical development of these compounds," he says.

Alan Carr, senior licensing associate at the Yale Office of Cooperative Research, says that an inter-institutional agreement between the University of Washington and Yale enabled the institutions to structure a deal with OneWorld Health to license the compound affordably.

Like the drug compound, this model for drug development, borne of innovative university technology transfer, could well have a lasting impact on people around the world.

— By Jill D. Ladwig

"Big problems nearly always involve collaborative solutions because no one person or institution can have all the answers."

— Andy Hamilton, Yale University

Chapter 14

Just a Simple Swab, and No More Cavities

Innovative technologies developed at the University of Florida that can eliminate dental cavities and possibly major bacterial infections have the potential to affect the entire human population.

Photo courtesy of Jeffrey D. Hillman, D.M.D., Ph.D.

University of Florida

David Day, director of the Office of Technology Licensing at the University of Florida, boils it down to a simple explanation: "A single swab of the mouth could result in the total elimination of cavities."

Though the compelling story behind this concept began several decades ago, well before his tenure at the university, Day is now involved with the process that may soon make this treatment a reality. About 15 miles from his office on the Gainesville, Fla., campus resides a small biotechnology startup called Oragenics Inc. that is poised to launch two very promising, and potentially revolutionary, products.

The two technologies — Replacement Therapy and Mutacin 1140 — share a common background and are the result of more than 25 years of work by Jeffrey Hillman, D.M.D., Ph.D. Hillman's research on the action of bacteria that cause tooth decay began at the Forsyth Institute in Boston and continued when he moved to become professor at the University of Florida College of Dentistry.

Jeff Hillman, left, and Bob Zahradnik founded Oragenics in 1996.
Photo courtesy of Jeffrey D. Hillman, D.M.D., Ph.D.

By the mid-1990s Hillman had conceived of an approach to oust cavity-causing bacteria that take up residence on teeth. The key to the technology's success was to replace the destructive bacteria with a genetically engineered strain of bacteria incapable of causing decay. Once replaced, the decay-causing bugs are virtually powerless to come back.

Hillman worked with the Office of Technology Licensing to obtain an exclusive worldwide license to the technology, named Replacement Therapy. With the help and business expertise of fellow dental researcher Robert Zahradnik, Ph.D., the two colleagues founded Oragenics in 1996. Early growth and development phases moved forward, and less than seven years later the company announced the successful completion of its $3 million initial public offering.

Envisioning a Global Treatment

Though small in size — Oragenics now has 11 employees — the company continues to grow and change as excitement about its products increases. In September 2005 Zahradnik was named president and chief executive officer of Oragenics; just before that, the company achieved a major milestone as it began a Phase I clinical trial of Replacement Therapy designed to evaluate the safety of the technology. Zahradnik is optimistic and echoes Day when describing the potential impact. "The best way of looking at this technology," he says, "is that one painless treatment can offer a lifetime of protection."

Zahradnik says that to date Oragenics has received $5 to $6 million in investments; he also says that investors must view a technology of this nature on a global basis. Indeed, from a public health perspective, Replacement Therapy can

address the needs of numerous developing countries and could improve the dental health of 5 billion people worldwide.

Replacement Therapy has such enormous potential because tooth decay is so prevalent. According to Hillman, tooth decay is the most common chronic infectious disease in the world; essentially everybody has it. Yet at the present time there is nothing available to help prevent tooth decay. Despite the typical hygienic precautions followed by most people for the past 25 years — using fluoridated water, brushing thoroughly and undergoing regular cleanings — tooth decay continues to thrive. In unindustrialized countries where fluoride and cleanings are not readily available, Replacement Therapy could have a tremendous impact.

"Replacement Therapy has a major advantage over these approaches because there is no patient compliance required," Hillman says. "Replacement Therapy can be done in the dentist's chair. The dentist just swabs the replacement strain (of bacteria) on the patient's teeth for five minutes, and that's all you need to do. When the patient leaves the chair, nothing else will have changed except that the chance of tooth decay and incidence of cavities will be dramatically decreased."

The science behind Replacement Therapy is based on the fact that most human tooth decay is caused by a naturally occurring bacterium called Streptococcus mutans. These bacteria sit on the surface of teeth and convert sugar that we ingest to lactic acid that, when excreted by the bacteria, dissolves the mineral that makes up tooth enamel and dentin. Hillman succeeded in genetically engineering a strain of Streptococcus mutans that produces a small amount of antibiotic capable of eliminating all other strains of Streptococcus mutans. Moreover, through recombinant DNA technology, this modified strain can no longer produce lactic acid. Topical application of the patented strain of Streptococcus mutans to a person's teeth actually displaces any decay-causing strain of Streptococcus mutans. This approach has been described as fighting fire with fire.

Potential Reaches Far Beyond Fighting Cavities

During the course of developing Replacement Therapy, Hillman recognized the tremendous potential of the particular antibiotic he engineered into the replacement strain. A second major focus by Oragenics is Mutacin 1140, a novel broad-spectrum antibiotic peptide that has proven to eliminate some of the most dangerous and stubborn infectious bacterial strains worldwide. In laboratory studies, Mutacin 1140 has demonstrated potency against essentially all gram-positive bacteria and certain medically important gram-negative bacteria including those responsible for strep throat, common pneumonia and staphylococcal infections. In particular, multidrug resistant Staphylococcus aureus and Enterococcus faecalis, which are notorious for causing infections in hospital settings, have met

Replacement Therapy can address the needs of numerous developing countries and could improve the dental health of 5 billion people worldwide.

University of Florida

their match in Mutacin 1140. "This antibiotic has the potential to treat such infections, which might otherwise lead to death of the patient," Hillman says. Approximately 100,000 patients died last year from infections they acquired during hospitalization.

The patented antibiotic peptide, also held under license from the University of Florida, is now in its preclinical phase of development and may obtain fast track status after application to the FDA as an investigational new drug. Zahradnik is optimistic that if all goes as planned, clinical trials will begin within a year from now.

"We plan to position it as a drug of last resort, and it can be used in hospital settings to treat infections not responsive to current antibiotics," Zahradnik says. "These multidrug resistance strains are of major concern in hospitals, but Mutacin is very effective in killing them. It has a unique mode of action compared with other antibiotics on the market so it fills a very important niche."

Replacement Therapy and Mutacin 1140 show great promise and are generating quite a bit of excitement. Following the completion of clinical trials, expected to take approximately four years, Replacement Therapy will hopefully receive approval from the U.S. Food and Drug Administration and become the first line of defense in tooth decay around the world.

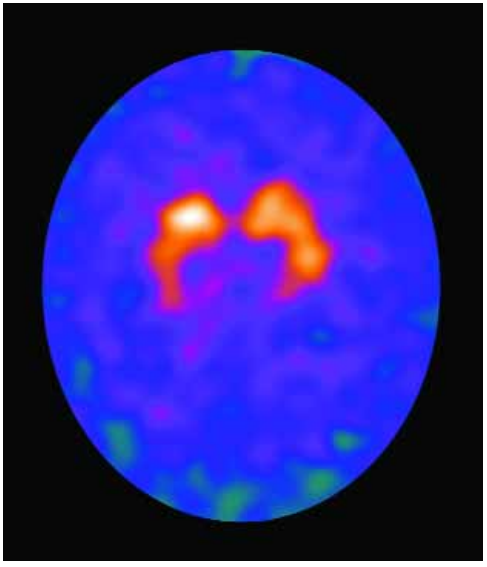
That leaves just one problem: if a simple, painless topical treatment can offer kids a lifetime of protection, can we no longer threaten that eating too much candy will cause cavities?

— By Nicole Resnick

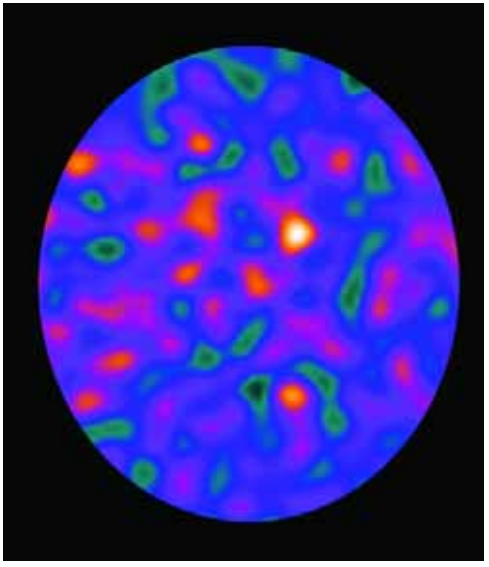
Chapter 15

Accurate and Definitive Diagnoses: the Story, and the Promise, of Altropane

A fortuitous discovery of a molecule that can differentiate between normal and abnormal levels of brain cells that bear dopamine transporters may hold the key to more accurate and early diagnoses of Parkinson's disease and attention deficit hyperactivity disorder.



Representative normal human SPECT brain scan using Altropane.
Image courtesy of Boston University Medical Center



Representative SPECT brain scan using Altropane of a person with early- to mid-stage Parkinson's disease.
Image courtesy of the University of Pennsylvania

Harvard University

Imagine waking up one morning with a sudden and unexplained twitch in your little finger. Too persistent to ignore, you go to your general practitioner where you learn that you may have some kind of movement disorder. The twitches, tremors and shakes may not go away — in fact they may get worse. Even scarier, there is a good chance that your condition will be misdiagnosed, and the treatment you really need is not necessarily the one that will be prescribed.

Welcome to the frustrating world of movement disorders. Doctors who treat patients with these symptoms face this conundrum everyday. Patients with Parkinson's Disease — a highly debilitating neurodegenerative disease — as well as patients with other disorders that appear to be the same thing but are actually of a very different etiology suffer because of a lack of accurate and reliable diagnostic tools. Approximately 140,000 people in the U.S. alone come to their physicians every year with new, undiagnosed movement disorders like Parkinson's Disease and essential tremor. Medical journals report misdiagnosis rates of 30 to 40 percent, if not higher.

"There has been a crying need for a long time now for earlier and more accurate diagnosis of Parkinson's disease," says Ken Rice, executive vice president and chief financial officer of Boston Life Sciences Inc., a Boston-area company that is playing a huge role in helping to solve this problem. Research into the progression of Parkinson's disease has shown that by the time a patient is symptomatic, 70 to 80 percent of the neurons that control movement in the substantia nigra part of their brain have died. Because there is no cure for the disease, all that is available to patients and their families is a plan for managing the symptoms — and even this phase is relatively short. "That is why earlier detection and intervention of PD can make a big difference," Rice says. "It would allow for an extension of the symptom management phase and translate into better quality of life for patients."

Understanding Diseases on a Molecular Level

That's where Altropane®, a highly specific imaging agent presently undergoing evaluation in Phase III clinical trials, comes in. The groundwork for Altropane was laid in the late 1980s, when Bertha Madras, Ph.D., professor of psychobiology at Harvard University, was researching the action of cocaine in the brain. Madras fortuitously discovered that a certain molecule, by virtue of selectively binding to a protein — the dopamine transporter — could accurately differentiate between particular cells in the brain. A somewhat simple concept, but the information it revealed was quite powerful. "I'll never forget that moment," Madras recalls. "When the lab technician showed me the results of the experiment, I nearly fell off my seat. I immediately realized the impact of these results, and it sent off a cascade of ideas in my mind."

This binding molecule, called a tropane, was the first to accurately identify neurons in the brain that bear dopamine transporters, specialized

proteins that transport the chemical dopamine into cells. Neurons that don't have dopamine transporters on their cell surface were clearly and cleanly ignored when introduced to the tropane. The implication for Parkinson's patients is that those with the disease have very low levels of dopamine transporter-producing cells; they mysteriously die off. So, the brains of Parkinson's patients, compared with normal brains, as well as those with non-Parkinson's movement disorders like essential tremor, look very different when put to this test.

The clinical application of this discovery involved joining forces with a team of chemists who specialize in modifying molecules to make them imaging agents, or proteins that become detectable by nuclear medicine tests such as positron emission tomography, or PET, scans. Collaboration with fellow Harvard scientist, chemist and inventor David Elmelah, Ph.D., helped to overcome this hurdle, and the team was ready to find a partner to support product development. They enlisted the expertise of Peter Meltzer, Ph.D., scientist and president of Organix in nearby Woburn, Mass., and the collaboration between academic and industry science led to the further development of Altropane.

The final version of Altropane includes a radioactive label (Iodine-123), enabling its visualization by clinicians in live humans when imaged by single photon emission computed tomography, or SPECT. SPECT imaging is more widely available and less expensive than conventional PET scans, making it accessible to most hospitals with nuclear medicine departments. Moreover, SPECT can provide imaging of Altropane almost immediately after it is injected, enabling quick and accurate diagnoses.

Early Diagnosis Can Slow Progression of Disease

The technology transfer office at Harvard University worked with the scientists as they recognized the potential of Altropane, and Boston Life Sciences, headquartered in Hopkinton, Mass., acquired the rights to develop, manufacture and commercialize the agent. Following the completion of several large early-stage trials, Altropane is now in pivotal Phase III trials specifically designed to test the molecule's ability to differentiate between Parkinson's disease and other non-Parkinsonian movement disorders manifested by shaking and tremors.

"We're very excited about Altropane and its promise in reducing the high error rate associated with the diagnosis of PD and other movement disorders," says Rice of Boston Life Sciences. The company is very committed to bringing the product to market and has made a substantial investment in the clinical development of Altropane. "First and foremost, the Parkinson's community is a very dedicated group of people who want nothing more than to find a cure," Rice says. "Anything we can do to help alleviate the uncertainty by providing a more accurate tool for diagnosis is hugely important."

Clinicians who diagnose and treat Parkinson's patients say Altropane could have a significant

"In terms of a patient's quality of life, it is so important to get the appropriate medicine early on."

— Burton Scott, Duke University Medical Center

Harvard University

impact. "In terms of a patient's quality of life, it is so important to get the appropriate medicine early on," says Burton Scott, Ph.D., M.D., associate clinical professor in medicine and neurology at the Movement Disorders Center at Duke University Medical Center. "We want to eventually use neuroprotective drugs for those patients who are susceptible to PD. That goal has been the Holy Grail in PD research for quite some time. In the foreseeable future, when we have effective therapies that can slow down the progression of PD — and I'm confident that they will be forthcoming — the correct diagnosis of the disorder will be even more critical."

The acceptance of Altropane also promises a more widespread means of identifying and diagnosing Parkinson's Disease patients so that they receive adequate treatment earlier. "Altropane allows more clinicians to make an accurate diagnosis without requiring movement disorder specialists," says Alan Fischman, M.D., director of nuclear medicine at the Massachusetts General Hospital and an investigator involved in clinical trials of Altropane in Parkinson's Disease patients. "By allowing doctors who are not necessarily experts in the field of movement disorders to make a definitive diagnosis, it moves the treatment out of major academic centers and out into the community. Because of this, Altropane can significantly augment the field."

Attention deficit hyperactivity disorder, or ADHD, is another highly prevalent medical problem characterized by abnormal levels of dopamine transporter-producing neurons in the brain. Like Parkinson's Disease, the level of dopamine transporters in the brains of ADHD individuals differs from those without the disorder. In the case of ADHD however, dopamine transporters levels are elevated, not reduced. Boston Life Sciences is now sponsoring clinical trials to test the accuracy of Altropane in diagnosing this disorder.

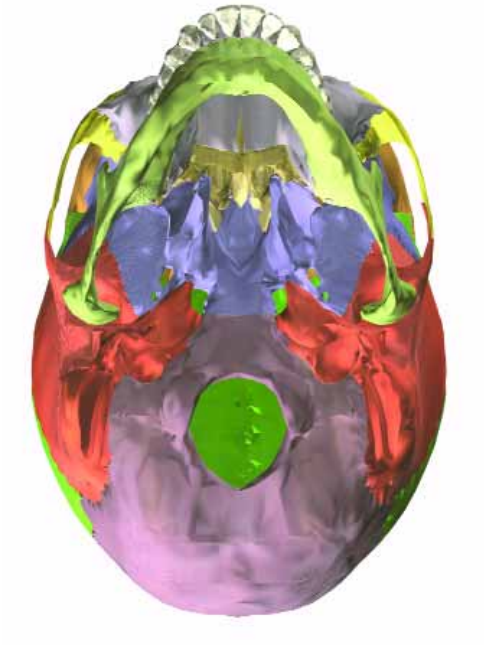
ADHD, which affects more than 5 million children in the United States and as many as 2 to 4 percent of adults, has been a controversial medical issue because of inconsistencies in the clinical diagnosis and concern about the reported abuse of behavior-modifying medications for the disorder.

— By Nicole Resnick

Chapter 16

InstaTrak Helps Doctors Operate in Confined Spaces

Boston University and Brigham and Women's Hospital deliver an electromagnetic, three-dimensional surgery system that provides real-time images to surgeons performing sensitive surgical procedures.



InstaTrak guides doctors during sensitive ear, nose and throat surgeries.

Boston University / Brigham and Women's Hospital

Fresh out of Boston University Medical school in 1991, Maurice Ferre, M.D., could have gone the usual path and headed off for a residency. But Ferre, who 15 years later is a businessman with a medical degree, chose instead to accept a fellowship at the university's Health Care Entrepreneurship Program, under the direction of Richard Egdahl, M.D., and John Valentine.

"It was a unique model," says Ferre. "It was an entrepreneurial residency, and it fit in perfectly with what I wanted to do. While in medical school, I also took a lot of business courses and got a double degree in public health."

Once at the center, Ferre began working with Frenenc Jolesz, M.D., and Ron Kininis, M.D., of Brigham and Women's Hospital, on a project that led to the commercially successful InstaTrak® system, an electromagnetic, image-guided surgical technology.

InstaTrak also resulted in the creation in 1993 of Visualization Technology Inc. through Boston University's Health Policy Institute. It refined the system and focused the technology initially on ear, nose and throat surgeries. VTI estimates that it holds 80 percent share in that market.

"Because of my training, I can communicate well with the medical community," he says. "That has been a big advantage for me."

System Shows Three-Dimensional View

Ferre says the InstaTrak system provides a three-dimensional view of a patient's CT scan combined with real-time information about the location of surgical instruments during operations. "Essentially, what we did was bring a military technology — one used for helping pilots guide missiles while flying F-16s — into the operating room," says Ferre, who was the company's founding CEO.

"We were able to build on that technology to track tumors and work in very confined spaces," he says. "Another way of putting it is that we were the first company to bring electromagnetic GPS tracking technology to the operating room. We used CT scans and MRIs as road maps," he says. "We used a tracing technology to track surgical instruments in relationship to tumors and important structures like the optic nerve. It was the perfect marriage."

VTI has since expanded to cranial, spinal and orthopedic procedures and today is used in more than 800 surgical centers in the United States and abroad. The company was sold in 2002 to General Electric, the world's largest imaging company, for more than $50 million.

Technology Doesn't Require Line of Sight

Ferre says most image-guided surgery systems available today are based on optical tracking, which uses an infrared camera and LED array that facilitate the communication between the camera and the surgical instrument.

VTI's technology is electromagnetic so it requires no line of sight between the instrument and the cameras. With an optical system, someone in a crowded operating room could block

that path and interrupt the ability to track the instrument. But with VTI's system, the transmitter and receiver can see each other even without an optical line of sight.

Ferre praises Egdahl and Valentine for serving as mentors while InstaTrak and VTI got off the ground. Valentine served as a director of the company until its sale. "They set up an incubator at Boston University that was geared toward people like myself," he says. "So I was able to explore business opportunities in the medical world. They nurtured my ideas and I was able to run with one: InstaTrak."

Enter the Angel Investor

Valentine also introduced Ferre to Tom Rosse, an entrepreneur in the medical device industry who put millions of his own money into VTI when it was in its earliest stages. He also followed up with more financial help. "Tom was an angel investor who believed in the process," Ferre says. "I could not have done it without him. Eventually, we built the company to more than 150 employees before we sold it."

Ferre has since moved back to his native city, Miami, to do it all over again. He now is founding CEO of Mako Surgical Corp. "It's an orthopedic robotics company," Ferre says. "We're trying to take surgical robotics to the next level. In a sense, it's kind of like what we did with InstaTrak." He says the company just closed on a $20 million round of financing, the largest round for a medical device firm in the state of Florida.

"Maurice is a real entrepreneur and we became very good friends," says Valentine, who now serves as vice chairman of the board of Boston Medical Center, BU's affiliated teaching hospital. "He liked the ideas that two doctors had at the Brigham who were working on brain surgery and he got very excited about it."

Though Ferre understood the technology much better than his mentor, Valentine says Ferre knew little about raising money. To start VTI and get InstaTrak off the ground, Valentine arranged meetings with financiers, including Tom Rosse, who put in the first $1 million. Valentine describes Rosse as his own angel network.

"Tom Rosse is an extraordinary guy," Valentine says. "He believed in this and never blinked when we needed more money. That's the kind of backer you need."

Taking InstaTrak to ENT

Valentine also helped guide Ferre to a market that could support VTI. "At first, the application we were considering focused on the brain," he says. "But I looked at the number of procedures done and it wasn't enough.

"As a doctor, Maurice could see a lot of applications," Valentine says. "But my thinking was that we needed to grind out some salable products." InstaTrak was well-suited for ear, nose and throat work, Valentine says, and the next step was to bring in several engineers who began to write the necessary software.

"When you go up the nose, you usually can't see where you are operating," he says. "When you're up there cleaning out debris, you can get

The InstaTrak system provides a three-dimensional view of a patient's CT scan combined with real-time information about surgical instrument locations during operations.

Boston University / Brigham and Women's Hospital

awfully close to the optic nerve and the brain." Because surgeons do not want to damage vital structures, they sometimes had to repeat surgeries, Valentine says. "With InstaTrak, though, they know exactly where they and their surgical instruments are.

"Our technology has a screen showing the patient's head and it puts the sharp end of the instrument right in the cross hairs. It reduces the number of times you have to do surgery over and that's big."

When GE became interested in buying VTI, it also looked at a dozen other systems, Valentine says. But they were all optical, and InstaTrak had the advantage of being electromagnetic. "Ours was the best," he says. "I've heard some doctors say that anyone who doesn't use InstaTrak should be sued for malpractice, that's how much many of them like it."

— By Brian E. Clark

Chapter 17

Mind Over Matter: the World of the Rheo Knee

Adapting to user walking style and terrain via a microprocessor that sends signals to magnetic fluid in the artificial joint — and optimizing control over time — the Rheo Knee helps below-the-knee amputees enjoy active lives.

Photo courtesy of
the Massachusetts Institute of Technology

Massachusetts Institute of Technology

An irony lies deep at the heart of modern society. Though technology is an outgrowth of our vigorous imagination, it can, at times, take on a life of its own. With gigabytes of empowering information at our fingertips, microprocessors far smarter than we are, clappers that turn off lights and clickers that open garage doors, it's easy to become complacent and become overwhelmed by our own creations.

However, some wills appear to be made of sterner stuff. There are inspiring stories — of a triple-amputee-turned-triathlete; of a soldier who, after losing his legs to a landmine in Afghanistan, fulfilled his dream of running alongside the president of the United States; and of a mountain-climber, amputated below the knees, who was able to climb again. It is people like these who refuse to let their handicaps define who they are, who reclaim what is theirs. It is people like these — and many others — for whom the Rheo Knee™ makes all the difference.

Technology as Healing

The hypotheticals above aren't hypothetical. They're flesh-and-blood Rheo Knee wearers. In fact, that very mountain climber is one of the principal investigators of the Rheo Knee, Hugh Herr, Ph.D. A graduate student and aspiring mountain climber, Herr was stranded on Mount Washington in minus-20-degree temperatures for four days in 1991. He suffered severe frostbite that ultimately resulted in the amputation of both legs.

After being fitted with conventional prostheses, Herr wondered how he could get back to his old passion. The answer was technology. Not satisfied just getting around, Herr, now director at the Massachusetts Institute of Technology's Biomechatronics Group, invented a specialized foot device that allowed him to get back to mountain climbing. After that, as part of a personal quest to extend technology as a means for healing, he led a team of MIT researchers in the invention of the Rheo Knee, a microprocessor-controlled artificial knee.

A Smarter Knee

Artificial knees have used microprocessors for about a decade, and these can be programmed to give the user a more natural gait compared with conventional leg prostheses, which cause users to stumble and limp. But Rheo Knee is unique, even among other microprocessor-controlled knees.

Artificial intelligence is an important feature that sets the Rheo Knee apart from other prosthetic devices. The Rheo Knee adapts automatically to the individual's personal walking style and continually learns while optimizing control over time. The Rheo's Dynamic Learning Matrix Algorithm™ constantly learns from and responds to changes in the user's walking pattern and the surrounding environment. As the range of walking speed and activity increases, the Rheo Knee adapts appropriately, optimizing cadence response for individuals as they progress to higher levels of function.

Built-in sensors measure how far the knee is bent and how much pressure it is bearing. This feedback is communicated, as frequently as 1,000 times per second, to a magnetic fluid made up of oil and tiny iron particles inside the artificial joint. A magnetic charge is cast across the fluid and as more tension is exerted, the magnetic field becomes stronger and the chain formed by the iron particles becomes more rigid.

Wearers of the Rheo Knee are freed from thinking, and worrying, about their knees. Instead, the knee thinks so the user can act. Ossur, the Icelandic company that manufactures and distributes the Rheo Knee, is pleased with its reception since coming onto market in February 2005. "Sales have gone through the roof," says Tabi King, marketing communications manager of Ossur North America.

The Rheo Knee's intelligence hasn't gone unrecognized by the media. *Discover* and *The Wall Street Journal* have reviewed it, *Fortune* and *Time* listed as a top 2004 invention and *Popular Mechanics* awarded Herr its Breakthrough Leadership Award in September 2005.

A Soldier's Story

Amputees hail from every walk of life and number 1.6 million in the U.S. alone. National Guardsman Sgt. Mike McNaughton is part of a special and growing segment of this population: soldiers returning from Iraq and Afghanistan. In January 2003, while leading a mine-removal team that had cleared an astonishing 150,000 antipersonnel and 47 antitank mines in just seven months near Bagram, Afghanistan, McNaughton saw a flash of smoke and tasted TNT on his lips.

"We have an amputee!" he heard the medics yelling. He knew from Army training not to look at his injury, but he also knew he had lost a limb and that his life would never be the same. "I flew up in the air and all I could think was that I had just spoken with my wife two hours before," McNaughton recalls.

McNaughton, who had volunteered for mine-removal duty, was rechecking an area declared mine-free and had rejoined the military after Sept. 11, 2001, has never been one to take the easy way out. After receiving a Purple Heart, undergoing 11 operations, spending four months in Walter Reed Army Medical Center and eventually losing his right knee, McNaughton — during a visit from President Bush — announced that he would run again. After being fitted with a prosthetic knee in 2004, McNaughton made good on his promise and ran alongside the president for a mile around the South Lawn track.

Seeking a full recovery, McNaughton was fitted with a Rheo Knee in 2005. "Before the Rheo, I used a C-Leg, another micro-processor knee with technology that's almost 10 years old. The C-Leg is like a car with a governor on it, but the Rheo is like one without one. The Rheo is the Lamborghini of prosthetics. Because of its artificial intelligence, it knows my walking style. The Rheo does the thinking and adjusting for me, even when I'm walking down ramps and stairs. It's like a part of me, an experience I haven't had with other prosthesis."

McNaughton, now an operations manager at the Department of Homeland Security in Baton

"The Rheo is the Lamborghini of prosthetics. ... It's like a part of me, an experience I haven't had with other prosthesis."

— Sgt. Mike McNaughton, U.S. National Guard

Massachusetts Institute of Technology

Rouge, plays soccer with his kids, has run marathons, and plans to complete the New York Marathon in a few years. And he and his wife had a baby boy in December 2005.

The Future: Keep Moving Forward

As McNaughton trains for marathons on his Rheo Knee, Herr and his colleagues — at the helm of an emerging discipline called biomechatronics, the interfacing of robotic prosthetics with the human nervous system — are busy developing a prosthetic ankle that might be viewed as the successor to Rheo Knee.

Herr, as part of a $7.2 million U.S. Department of Veterans Affairs research project designed to help returning amputee soldiers, will have three small sensors implanted in his leg below his knee. These sensors measure electrical impulses given off as the amputee-user flexes leg muscles in ways that once moved the ankle; this feedback is conveyed to a computer chip that activates the prosthetic ankle's motor. Though this device may sound futuristic, its application and value for veterans and others comes down to the most basic of human impulses. And it's what compels Herr to do what he does for himself and others everyday: the desire to keep moving forward.

— By John Motoviloff

Chapter 18

Giving the Gift of Speech

No one knows for sure what causes stuttering, which affects 3 million people in the United States. But a trio of researchers from East Carolina University developed a device that has helped thousands of people who stutter become more fluent, enabling them do things they previously considered off limits.

Photo courtesy of East Carolina University

East Carolina University

For most of her life, Carol White of Ocean City, Md., lived in relative silence. That's because she has been affected by stuttering since she was 2 years old. Though she had undergone speech therapy when she was younger, stuttering remained a barrier to doing things that most people take for granted.

"I didn't use the telephone unless I really had to, and I'd often avoid situations that involved talking to people," she says. But that all changed in 2003, after she saw an intriguing report about the SpeechEasy® fluency device on ABC's "Good Morning America" news show.

"I thought I'd give it a try, and I'm glad I did," White says. The device, which can be worn like a hearing aid, helps reduce stuttering. In White's case, it almost has eliminated her stuttering entirely. "I'm doing things I wouldn't have dreamed of doing before," she says.

Case in point: the 61-year-old is now a real estate agent — a profession requiring a significant amount of communication and interaction with others. For thousands like White, the SpeechEasy device has opened doors to new opportunities.

Professors Andrew Stuart, from left, Joseph Kalinowski and Michael Rastatter have helped thousands who stutter. Photo courtesy of East Carolina University

The Product of Extensive Research

Having dealt with the challenges of being a person who stutters severely himself, Joe Kalinowski vowed he would try to find a way to help others affected by stuttering. After receiving a Ph.D. in speech pathology from the University of Connecticut, Kalinowski went on to Dalhousie University in Halifax, Nova Scotia, where he and Andrew Stuart, Ph.D., conducted extensive research on delayed auditory feedback, or DAF. DAF is based on the choral speech phenomenon, in which people who stutter enhance their fluency when they speak in unison with others.

Using DAF, those who stutter are able to hear their own voices with a slight time delay, and by speaking in unison with their own voices, they achieve greater fluency. Though speech experts had known about DAF for decades, Kalinowski and Stuart made great advances in using it to reduce stuttering. One of their key discoveries was that shortening rather than expanding the delays in auditory feedback enhances fluency in those who stutter. So instead of slowing down speaking rates, which previously was thought to increase fluency, DAF could be used to enhance fluency even when speaking at faster rates.

But it was at East Carolina University in Greenville, N.C., where Kalinowski, Stuart and Michael Rastatter, Ph.D., broke new ground in their research about the effects of DAF and frequency auditory feedback, or FAF, on stuttering. FAF allows users to hear their own voices with a slight shift in pitch — either higher or lower. The

trio demonstrated both DAF and FAF could enhance fluency levels in various situations, from casual daily conversations, to phone calls, to speaking in front of audiences.

However, there was just one problem: providing people who stutter with a discreet, easy-to-use device incorporating DAF and FAF. Previously, large equipment or bulky portable devices using DAF technology were used to reduce stuttering.

"But carrying around a cumbersome, visible device makes you look 'different,' which is not very desirable for many who stutter," Kalinowski explains. If only such a device using DAF and FAF could be small enough to fit in an ear, like a hearing aid.

With this vision in mind, the team of researchers received help from East Carolina University's Office of Technology Transfer to obtain a patent for their concept in 1999. Then the Greenville-based Janus Development Group Inc. obtained the license and set about finding a company to produce the small, portable device.

"That was the challenge — taking this great idea that was on paper and bringing it to life," recalls Darwin Richards, a former Janus Development Group president involved in the project. But Janus succeeded in creating various prototypes and eventually brought the SpeechEasy device to market in June 2001.

Today, three different models are available: behind-the-ear, in-the-canal (fitting in the ear canal with a visible outer shell); and completely-in-canal (placed completely in the ear canal). The device has been enhanced with features that reduce distracting non-speech-related sounds and is completely customizable for each individual user. Thousands, including Kalinowski, use the device with varying degrees of success.

"I never spoke on the telephone until 2002, after I started using the device," Kalinowski says. "For many like me, it has made a tremendous difference."

Impact of the SpeechEasy Device

As of November 2005 more than 5,600 SpeechEasy devices have been sold worldwide. Approximately 75 to 80 percent of those who tried the device experienced an improvement in their speaking abilities, reducing stuttering by 50 to 90 percent. Though some experience immediate improvements in fluency, many experience improvement over time. Maximum benefits generally occur as users become more familiar and comfortable with the device.

During more than 10 years of experimentation and peer-reviewed research, the research team has demonstrated the power of DAF and FAF to reduce stuttering. A one-year longitudinal study has indicated that the SpeechEasy device effectively maintains fluency in those who stutter. Longer-term studies also are underway to determine the device's effectiveness in a broad cross-section of the population.

As Kalinowski, Richards and others point out, the SpeechEasy device is not a cure for stuttering. "It's similar to wearing glasses,"

"I never spoke on the telephone until 2002, after I started using the device."

— Joe Kalinowski, SpeechEasy inventor

East Carolina University

Richards says. "It helps you compensate for the problem. But if you do not wear the device, you may experience stuttering again, so we recommend wearing the device as often as possible to get the best results."

Some users require little or no training when they first begin to use SpeechEasy, and they become fluent rather quickly. But others need training, and may ultimately have limited or no success in using it. Those who have learned traditional speech therapy techniques and use them while wearing SpeechEasy devices have noted higher levels of fluency enhancement and more natural-sounding speech. These traditional therapy techniques include reducing speaking anxiety through relaxation, or gaining control by slowing speech and gradually increasing it.

For the 3 million people who stutter in the United States, the SpeechEasy device offers a glimmer of hope. "I'm not a shy person, so now that I've been using this device, I haven't been holding back," White says.

— By Bill Shepard

Chapter 19

Cystic Fibrosis Discovery Hailed as a Medical Milestone

The discovery of the cystic fibrosis gene by researchers at The Hospital for Sick Children in Toronto and the University of Michigan leads to improved health care and global scientific knowledge.

Lap-Chee Tsui, Ph.D., in his laboratory.
Photo courtesy of Robert Teteruck, The Hospital for Sick Children

The Hospital for Sick Children / University of Michigan

Sixteen years ago, Grant Boyle's birth was a familiar routine in a world of medical challenges and sickly children. Like other parents, John and Marylynn Boyle of Toronto were thrilled to learn their firstborn child was healthy.

But 13 months later, it became obvious that Grant was not thriving. Though they knew he wasn't well, he suffered from symptoms that parents unfamiliar with cystic fibrosis wouldn't have recognized. The baby's skin had a salty taste, he wasn't gaining weight as he should and he suffered from a constant bowel dysfunction.

When his parents started down the diagnostic path that would lead to The Hospital for Sick Children in Toronto, John Boyle says, "We didn't know anything about cystic fibrosis, including any of the symptoms connected with the disease."

Cystic fibrosis, a debilitating inherited disease that is usually manifested in children and affects approximately 1 in 2,000 live births in North America, often results in premature death. In the U.S. about 1,000 new cases are identified each year. As Grant's parents discovered, the defective gene blocks chloride transport, and as a result of this gene defect, the body produces an abnormally thick mucus that affects the lungs. The disorder is often a precursor to life-threatening lung infections.

John Boyle would learn that he, along with millions of others in North America, are unknowing, symptomless carriers of cystic fibrosis. He also would learn that nothing a parent does causes the disease.

Grant was born in the same month in 1989 that the cystic fibrosis gene was isolated and characterized at The Hospital for Sick Children, Canada's most research-intensive hospital. The University of Toronto-affiliated hospital is the largest pediatric academic health science center in Canada and one of the largest in the world. Its clinicians are widely known for treating a huge number of patients with cystic fibrosis.

Researchers Isolate Mutant Gene

Thanks largely to the world-class research team of scientists and physicians, the defective gene responsible for cystic fibrosis was found in human chromosome No. 7. Before the discovery, scientists knew that the faulty gene was somewhere in the 22 pairs of autosomal chromosomes, not the x or y sex chromosome. But Lap-Chee Tsui, Ph.D., Jack Riordan, Ph.D., and others in collaboration with the University of Michigan's physician-geneticist Francis Collins, M.D., and his research team, took the research to a new level when they cloned and sequenced a gene encoding a protein known as cystic fibrosis transmembrane regulator, or CFTR. They found a mutant form of the CFTR gene known as Delta 508, which causes about 70 percent of the clinical incident of the disease.

During eight years of intensive research, they narrowed the field from an enormous pool of genes — now known to number about 30,000 along the DNA molecule. The discovery provided the first structural evidence that the defective CF gene leads to a malformation of the protein that

regulates chloride transport across epithelial cells. This milestone discovery of the cystic fibrosis gene was a supreme example of how research can benefit people worldwide and lead to better health care.

"During the collaborative research, looking for the CF gene was somewhat like looking for a needle in a haystack. When the gene's position was found, it set the stage for the development of CF carrier tests," says Stuart D. Howe, Ph.D., director of business and partnership development at The Hospital for Sick Children.

The discovery has enormous impact on families worldwide. The breakthrough opened the door to a screening test to identify people who unknowingly carry the defective gene and pass it along to their children.

Diagnosis, Treatment and Testing

Grant's diagnosis started with a sweat test to assess the salinity of his skin. When the first test was negative, his parents were relieved, but when it was run again, it confirmed the baby had cystic fibrosis. His father, though not affected by CF, is a carrier of the Delta 508 gene.

"I was in Ottawa on business when I learned I was Delta carrier. I didn't recognize the connection with CF," John Boyle says. "I thought the test results had something to do with the heart." Back home, the reality that Grant has cystic fibrosis, hit hard. "When I read that CF affects the lungs, is always fatal, and that it typically happens when children are young, I fell apart inside."

When Grant spent a week at The Hospital for Sick Children while his medications were adjusted, two life-changing things happened. First, Marylynn Boyle learned she was pregnant with her second child. "By then I knew there was a one-in-four chance that the unborn baby would have CF. I wasn't terribly concerned, but everyone around me was worried," John Boyle recalls.

Before the 1989 gene discovery, parents were alerted to the possibility of having a baby with cystic fibrosis only if they already had an affected child. But as a result of the breakthrough cystic fibrosis gene discovery, doctors can identify carriers and conduct genetic tests on unborn babies to offer parents a prenatal diagnosis. The sophisticated diagnosis shows if the fetus has a known mutation of the cystic fibrosis gene. At the 12-week mark in her pregnancy, Marylynn Boyle was tested and learned the baby did not have cystic fibrosis.

The genetic screening not only provided knowledge of the baby's health, it also unleashed enormous comfort and joy for the family. James, the baby Marylynn was carrying when Grant was diagnosed with cystic fibrosis, is now 14. The couple's third child, 8-year-old Jacklynn, does not have cystic fibrosis, but genetic testing has determined she is a cystic fibrosis carrier.

There was a second thing that happened during Grant's stay at the hospital. "By the end of the week, I saw many kids far sicker than Grant," John Boyle says. "At the end of the week, I actually felt jubilant when I realized that, when compared to other children, Grant is fairly healthy. Because the CF team is exceptionally

"Because the CF team is exceptionally proactive and dedicated, they have helped Grant live life to the fullest."

— John Boyle, whose son was diagnosed with cystic fibrosis as an infant

The Hospital for Sick Children / University of Michigan

proactive and dedicated, they have helped Grant live life to the fullest."

Grant continues to do just that. But when he was 12 cystic fibrosis caused his lung to collapse. The event was extremely alarming, John Boyle says. "CF kids may look normal one day, but the following day they may be ill or dead because of a time bomb inside of them."

When Grant lost the function of his lung, John Boyle asked the hospital staff if there was someone they could call. "They humbly replied that when it comes to CF children, other hospitals call them. We felt privileged to have this extraordinary CF team working for us."

Worldwide Impact

Today, children and parents throughout the world benefit from the CF testing. The Hospital for Sick Children and the University of Michigan entered an agreement that allows the hospital to manage international licenses while the University of Michigan manages licensing activities in the United States.

"The decision to license non-exclusively has encouraged competition among diagnostic laboratories," says David Ritchie, Ph.D., senior technology licensing specialist at the University of Michigan. "Seventeen companies are producing CF testing kits, about half are not on the market yet but expect to be in the next five years."

Licensing of the cystic fibrosis testing occurred in 1994, and in the last four years the licensing has become profitable, allowing both institutions to reinvest in new research. With every diagnostic kit sold, a small percentage of each net sale is returned in royalties. Patent protection was established for the gene, the protein derived from it and the mutation. Numerous non-exclusive licenses for the diagnostic test have been granted in Canada, the U.S. and Europe.

"The widely available CF diagnostic testing offers valuable 'yes or no' information. Families now have the opportunity to make intelligent decisions about deciding to have children and, depending on the test results, what the risks might be," Ritchie says. Now that newborns are automatically tested for cystic fibrosis, the technology has had a direct impact on the licensing of the test. "If you want to do CF testing, use of the Delta 508 mutation must be included in the testing panel because it is present in 70 percent of CF patients," Ritchie says.

CF research was funded in the U.S. by Cystic Fibrosis Foundation of America, the Howard Hughes Medical Institutes and the National Institutes of Heath. In Canada, funding was received from several government and private grantors including the Canadian Institute for Health Research, formerly the Medical Research Council, and the Canadian Cystic Fibrosis Foundation. Royalties derived from the Delta 508 tests are shared with a number of the grantors.

Today, Grant Boyle is an outgoing 16-year-old high-school student. His father says he goes full tilt. Last summer he spent a month in Africa with a humanitarian organization. "He's a great musician, a professional actor and fully connected with life," John Boyle says. "He doesn't think

about his CF much, which is a lesson for his parents."

Still, if it hadn't been for the hospital's CF clinical care and research, combined with life saving drugs and physical therapy, it might be a different story.

"The hospital has superb technology driven clinical care, and outstanding CF research and empathetic skills," says John Boyle. "As parents we demand the best care for our kids, and as CF parents, we are grateful that the hospital is gifted when it comes to CF research and knowledge."

— By Sharyn Alden

Chapter 20

Early Detection and Improved Protection Against Osteoporosis

Early research of collagen, a major component of bone, led to the discovery that discrete fragments of bone that were expelled from the body could indicate bone breakdown, the hallmark of osteoporosis. The technology has had a major impact on the ever-growing arena of osteoporosis detection and treatment.

University of Washington

Osteoporosis has garnered much attention in the past few decades as important research breakthroughs have led to more effective treatments for this highly prevalent and often silent disease. The condition, which affects more than 10 million people in the U.S. alone, is characterized by a gradual softening and breakdown of bones.

In the high risk population of peri- and post-menopausal women whose estrogen levels can quickly decline, the rate of bone loss can be especially fast. Some women can lose as much as 10 percent of their bone mass in a single year, and in the long term this deterioration can seriously compromise bone health.

Because osteoporosis is a preventable medical condition, efforts to ramp up early detection and screening are now linked with efforts to develop more effective treatments to stop bone resorption. Drugs like Fosamax®, Evista®, Actonel® and Premarin® are now widely prescribed and contribute to the multi-billion-dollar osteoporosis market.

Yet with new treatments come new challenges. Osteoporotic drugs may be abundant, but clinicians who prescribe them and patients who take them need to know if these medications are actually doing their job. Is bone breakdown slowing? Are fragile bones gaining back the advantage as bone growth is stimulated?

Innovation Inside and Outside the Lab

One technology transfer success story helps to answer such questions. The story begins in the 1980s in a research laboratory at the University of Washington's Department of Orthopaedics and Sports Medicine. While pursuing studies on collagen, a key component of bone and cartilage, David Eyre, Ph.D., professor and director of research, discovered a group of discrete protein fragments that were reproducibly appearing in urine samples. Chemical analysis revealed that the fragments were type 1 collagen peptides, and they derived from bone degradation. Eyre and his colleagues then developed monoclonal antibodies that could bind to the peptides and an immunoassay, which could accurately reveal the presence of the peptides in human urine.

Further development of the technology led to a prototype test for measuring stable end products of collagen breakdown. Eyre named the test NTx — later commercialized as Osteomark® NTx — for the origin and chemical composition of the peptides (they are cross-linked N-telopeptides of type 1 collagen), and recognized the promise of the technology. Because levels of NTx in urine correlated with rates of bone degradation, the test might aid in the detection of individuals at risk for developing osteoporosis, as well as help monitor the effectiveness of anti-osteoporotic medications.

In an innovative technology transfer arrangement with the University of Washington, Eyre sought the help of Seattle legal and business expert Ray Cairncross to form a startup company and eventually move NTx into the public domain. The company, called Ostex International Inc.,

was founded in 1989 and acquired the exclusive license for the technology from the university. As part of the agreement, Eyre chose to continue pursuing his academic research at the university and retain his status on the faculty. In the meantime, Cairncross and his law firm organized a group of local investors and generated enough capital in the first round of financing to move forward with the development of the Osteomark NTx technology.

Though Ostex functioned as a virtual company early in its history, Eyre soon announced that his product was ready to be commercialized and the time had come to create physical space and hire personnel. As chair and chief executive officer of Ostex, Cairncross again succeeded in raising funds in a second round of financing, and the emphasis turned to building the company and optimizing the NTx technology.

Ostex International hit the ground running and went public just six years later, raising more than $30 million in its initial public offering. The first product, designed to test for NTx in urine samples, led to a second modified assay that measures collagen peptide fragments in human blood. Samples are acquired for the test in a clinician's office, then sent to centralized laboratories for results. Scientists developed several different versions of the original Osteomark technology in quick succession, and they received approval from the U.S. Food and Drug Administration.

When Osteomark first went commercial, Eyre remembers feeling that his vision had finally become a reality. "It was very satisfying," he says, "to know that our basic research had translated directly into a product that could improve human health."

New Product Delivers Results in Five Minutes

The most current version of the Osteomark technology, the NTx Point-of-Care device, is perhaps the most revolutionary. The device allows clinicians to test patients' urine for the presence of collagen peptide fragments right in the physician's office, so a result is available within five minutes. Its ease of use means that patients can be tested every three to six months for a more updated status of their disease and assessment of their response to therapy. Most importantly, the disposable handheld kit allows physicians and patients to confer and make decisions about osteoporosis treatment based on the test results during that same appointment.

The Osteoporosis Education Project in East Syracuse, N.Y., was selected as one of four test sites nationwide to participate in clinical trials designed to evaluate the Osteomark NTx Point-of-Care device for home use. Susan E. Brown, Ph.D., C.C.N., and director of the project, points out that one of the most critical aspects of evaluating bone degradation in osteoporosis patients is the rate of bone loss.

"It's helpful to monitor when changes occur, and how fast they occur, in people undergoing bone breakdown," Brown says. "Is a patient currently losing bone? Is the patient continuing to lose bone, or is it something that happened in the past? Now we can distinguish those who are losing bone at

"Now we can distinguish those who are losing bone at a rapid rate, rather than at a more normal, moderate rate."

— Susan E. Brown, Osteoporosis Education Project

University of Washington

a rapid rate, rather than at a more normal, moderate rate."

Brown's assessment of the utility and impact of the Osteomark technology complements Eyre's perception of the changing emphasis in osteoporosis treatment. "The standard for bringing new drugs to market in the pharmaceutical industry has relied on measurement of bone resorption. It used to be that DEXA (dual energy X-ray absorptiometry), which is typically performed only once every one or two years, was the exclusive test," Eyre says. But he says that mindset is changing as doctors begin to focus on a patient's bone quality, rather than simply bone density and mass.

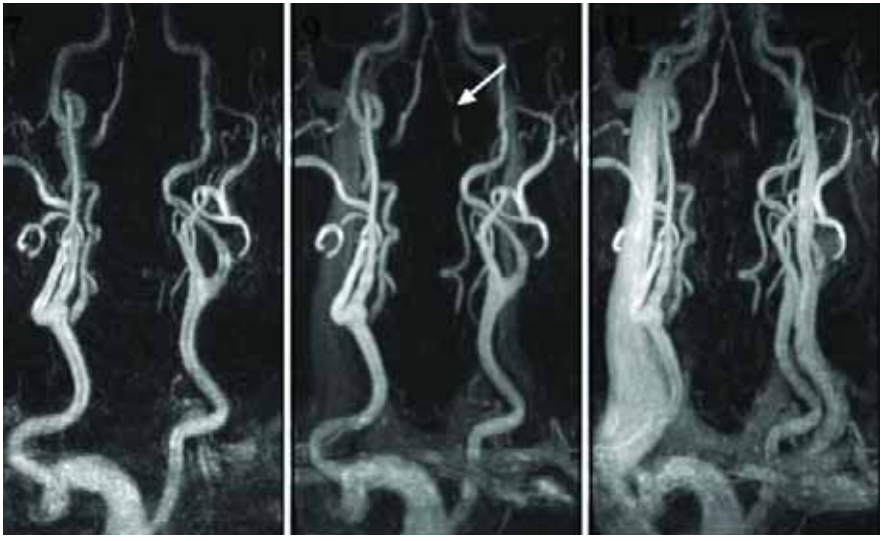
Since the development of the NTx point-of-care device, Ostex International was acquired by Inverness Medical Innovations Inc., based in Waltham, Mass. The merger, completed in 2003, provided Inverness Medical Innovations with the intellectual property rights in the field of osteoporosis testing, and the Osteomark technology continues to provide a valuable way to quantify bone degradation in osteoporosis patients.

— By Nicole Resnick

Chapter 21

TRICKS Changes the Face of Medicine

TRICKS, a three-dimensional imaging technique invented by University of Wisconsin-Madison medical physics professor Charles Mistretta, takes the unknown and makes it known.



Images of the carotid and vertebral arteries using the TRICKS method for contrast enhanced magnetic resonance angiography. Note the slow flow in the left vertebral artery (arrow)

University of Wisconsin-Madison

Gary Baron of East Lansing, Mich., repeatedly felt painful cramping in both legs when he walked. There was nothing about Baron's physical appearance that would foreshadow narrowing of the arteries, but his medical history told another story.

Baron, 63, had previously been diagnosed with angina, which led to his need for a cardiac catheter and a three-vessel bypass graft. So he had an ultrasound test to see how well the arteries in his legs were working.

After Baron had the test, his surgeon referred him to physical therapy. Though he showed some improvement during the therapy, he still experienced pain in his legs. Fortunately for Baron, he was about to get some assistance from time-resolved imaging of contrast kinetics, or TRICKS™, a new three-dimensional imaging technique that takes the guess work out of contrast-enhanced MRI procedures.

Every year, between 8 and 10 million people are affected by peripheral vascular disease. But before the invention of TRICKS at the University of Wisconsin-Madison, visualization during the MRI process was limited. TRICKS entered the marketplace in 2003.

Before TRICKS was introduced, when doctors looked at images of blood flow in areas like legs and ankles, the resulting information could be confusing. The old technology would miss some arteries or not be able to show the physician when the flow in the artery had backed up and started going in the wrong direction. The process also took a long time, well over two hours.

"TRICKS has helped us see what arteries are affected, how bad the arteries are, and if the patient needs vascular surgery," says Kevin DeMarco, M.D., an associate professor in the Department of Radiology at Michigan State University. "TRICKS also helps us see the very small arteries in the calf and foot, even down to three millimeters."

DeMarco has used TRICKS in different areas of his work: in private practice in East Brunswick, N.J., with the University Radiology Group, and at MSU. He learned of TRICKS through national meetings of the International Society of Magnetic Resonance Medicine. "When I first heard of inventor Charles Mistretta's early work with vivid three-dimensional images, it sounded exciting," he says.

Images Display Like Scenes in a Movie

In the 1980s, the X-ray technique became the gold standard for diagnostic images. Then in the 1990s, radiologists used MRI exams, sometimes injecting a contrasting agent into the patient to better enhance the study. The trouble was that the results sometimes were confusing to interpret. The reason was timing.

In diagnostic imaging, timing is everything. Think of multiple scenes running in sequence, like photographing water flowing over a waterfall or revolving scenes in a movie. TRICKS records fast-evolving images, or scenes, critical to making an accurate diagnosis pertaining to blood clots and vascular problems. With the old technology, the camera takes multiple shots, often missing a

crucial snapshot in time. TRICKS acts more like a video camera, recording all the events during an MRI exam, not just static, frozen images. The technology allows doctors to capture the images they need to make a diagnosis.

Charles Mistretta, a professor in medical physics at the University of Wisconsin-Madison at the time TRICKS was patented in 1996, is also a professor of radiology at the university today. "We devised a lot of different technologies to get the timing right," he says.

Today, radiologists all over the world are using TRICKS, a system that's simpler, more robust and more reliable than previous technologies. "It used to take us 30 seconds to generate one image, and that image couldn't decipher dynamic events," explains Mistretta, who says his UW team of scientists was inspired by Thomas Grist, M.D., chair of the UW Radiology Department. "It was obvious that to better track blood flow in the legs and ankles, we needed a time-resolved series."

The result of Mistretta's invention was TRICKS. "It has a major advantage over the old MRA X-ray technique because it provides three-dimensional images and it has a 400 percent increase in speed," he says.

TRICKS, patented by the Wisconsin Alumni Research Foundation and licensed to GE Healthcare of Waukesha, Wis., was incorporated in 2003 into GE's Signa EXICTE™ 1.5 T MR unit. The following year GE included TRICKS technology in its 3.OT MR unit.

As part of EXCITE, TRICKS helps doctors diagnose blood clots and other vascular concerns with faster, safer, non-invasive MRI studies. Its primary advantage is that it produces a series of time-resolved images rather than just one.

Technology Produces Economic and Societal Benefits

Introduced in 2003, two major MRI companies now manufacture TRICKS, including GE Healthcare. "We're very excited about the technology," says Jerry Shattuck, a licensing manager with WARF. Shattuck says WARF also is in negotiations with a third major MRI manufacturer. "We expect sales to increase as the technology continues to gain acceptance in the marketplace," he says.

TRICKS continues to help doctors make important decisions — decisions that directly impact their patients' lives. "I see people with a particular type of pain, They have cramping in their legs usually after walking just a few blocks, but the pain usually goes away when they're at rest," DeMarco says.

When Baron, a patient with bilateral pain, saw DeMarco, the total exam time with TRICKS was less than an hour. Previously, the MRI exam was typically three to four hours. "We usually had to have the patient return for a second two-hour session," DeMarco says.

Before the availability of TRICKS, patients like Baron might have had to undergo an invasive conventional angiogram, usually performed in an operating room or hospital angiographic area. The procedure involves inserting a catheter into

"(TRICKS) has a major advantage over the old MRA X-ray technique because it provides three-dimensional images and it has a 400 percent increase in speed."

— Charles Mistretta, University of Wisconsin-Madison

University of Wisconsin-Madison

the artery in the groin with a chance of injuring the artery and making the patient's foot cold. "While that may happen only a very small percent of the time, that's a 100 percent inconvenience and frustration for the patient," DeMarco says.

With the invention of TRICKS, "we're getting closer to the gold standard. It answers questions like how narrow the arteries are in the calf and feet 80 to 90 percent of the time," DeMarco says. In Baron's case, TRICKS answered the question of whether he needed vascular surgery.

The good news for Baron was that surgery wasn't necessary. He continued physical therapy, which eventually led to a positive outcome. "Without TRICKS we would have been less certain what route to take between surgery or physical therapy." DeMarco says, "With TRICKS, the diagnostic process was simpler, faster and safer."

— By Sharyn Alden

Chapter 22

Taxol Reshapes the War on Cancer

A Florida State University professor invents the process to make the best-selling cancer drug in history — and while he's at it, helps save the endangered Pacific Yew tree. Since the introduction of synthetic Taxol, more than 2 million women worldwide have taken the drug to fight ovarian and breast cancer.

Photo courtesy of Florida State University

Florida State University

The nurse points a flashlight in the patient's eyes and from miles away, Karen Curtin, an R.N. in electronic nursing, is helping examine the hospital patient. From Curtin's vantage point, sitting at a desk with six computer screens and monitoring 30 patients simultaneously at several Chicago area hospitals, life is magical.

"Electronic nursing is an exciting area of medicine," says Curtin, who works in the intensive care unit with Provena Health Care and monitors critically ill patients via computer from a central location, "Every day I remind myself how lucky I am to be alive and be able to help others."

Four years ago, Curtin, a single mother with two children from Orland Park, Ill., was working as an intensive care nurse for St. Francis Hospital in Blue Island, Ill. In her free time she enjoyed all forms of exercise.

She still tenses up when she recalls Dec. 4, 2001, when she was running on a treadmill. "The running produced a pain in my left breast. Later, taking a shower, I felt a painful lump. I had been an ICU nurse for 13 years so I told myself, I'm 31, there's no history of breast cancer in our family, so it's probably nothing. But another voice inside knew something was wrong. Terribly wrong."

A few days later, Curtin learned she had breast cancer. Last year the American Cancer Society estimated that more than 210,000 people would be diagnosed with breast cancer and that more than 40,000 of them would die. Curtin was proactive and immediately had an ultrasound, followed by a lumpectomy. Exactly a month after discovering the lump in her breast, she underwent nine hours of a mastectomy and tram-flap reconstructive surgery.

"Eleven of my 30 lymph nodes were positive for cancer," she says. "I found out I am her-2 positive, which is a very aggressive form of cancer." During what Curtain calls her "big surgery," her breast, including the nipple, was removed, and on the same day, she underwent reconstruction surgery that included abdominal muscle tunneled under the skin to support a new breast area. The recovery from the surgery took weeks, followed by several grueling rounds of drug therapy. In her characteristically understated manner, she says 2002 was probably the most difficult year of her life.

Reaching the Turning Point

When Curtin started cancer treatment — she had enrolled in a national drug therapy study — she underwent 12 weeks of chemotherapy, and four rounds each of Adriamycin and Cytoxan. "I was horribly ill through this process and when my medium-length hair fell out, my illness really hit home. My kids were supportive, but they were horrified. My son kept telling me to put my wig back on."

But when Curtin started taking Taxol by IV drip once a week for 12 weeks, her life started to change. "Taxol was the turning point in getting my life back," she says. "Compared to other drug therapies I had taken, it was a relief to take Taxol and not have side affects."

Curtin, one of the people who have reacted well to Taxol, says, "When I look back on the months of cancer-fighting treatment that I went

through, I credit Taxol with being the milestone that started making a difference in my recovery." After her Taxol treatments, Curtin had radiation treatments five days a week for 25 days.

Breakthrough Leads to Wide Availability

Though millions of people have heard of Taxol, chances are most do not know the connection to Florida State University and the phenomenal story behind the drug's invention. The active compound that would become Taxol, or paclitaxel, which the National Cancer Institute described in 1990 as the most vitally important cancer drug in 15 years, was first discovered in the 1970s from the bark of the endangered, ancient Pacific Yew tree. But there was a problem. To produce a cancer treatment, the bark of the trees had to be harvested, and the harvesting killed the trees.

By 1988 the NCI released results of Taxol's Phase II trials of ovarian cancer. According to the report, at least three of every 10 persons found their tumors had shrunk using Taxol. The result was a huge demand for the drug. To offer it to all ovarian cancer sufferers in the U.S., doctors would have needed 240 pounds of Taxol. That production level would have required the harvesting of 360,000 Pacific Yew trees, the habitat of the spotted owl, also an endangered species.

Enter professor Robert Holton, a Florida State University chemist who had returned to FSU, his alma mater, in 1985 and was excited about seeking a solution to the Taxol supply problem. His work at FSU was deemed nationally significant when just two later, his laboratory was working with support from the U.S. National Cancer Institute.

There are many stories about Holton's discovery, as well there should be. Holton's work at FSU is legendary in the world of cancer-fighting technology. His breakthrough occurred with his 1991 invention of synthesizing paclitaxel using compounds found in the needles and twigs of the common English Yew tree. Holton's perseverance paid off. His relentless determination to help cancer patients resulted in a synthesizing process that didn't kill the Yew tree. The process that started with needles and twigs and ended with a medical breakthrough is in some ways an expression of Holton's character.

"Professor Holton is a dynamo. He is driven to attack cancer," says John Fraser, director of the Office of Intellectual Property Development and Commercialization at Florida State University.

Holton's invention at FSU was subsequently licensed to Bristol-Myers Squibb, which introduced the drug as Taxol in early 1993 after it received approval from the U.S. Food and Drug Administration. Because of Holton's work at FSU, Taxol became the most important cancer-fighting drug to come along in 15 years.

Impact Heard Around the World

When Bristol-Myers Squibb used the FSU semi-synthesis process in bringing the drug to the marketplace, it was a major step forward in fighting ovarian cancer. Though it is not

"When I started taking Taxol, I felt more human again. It was Taxol that got me back to being a mom."

— Karen Curtin, Nurse and cancer survivor

Florida State University

effective for everyone, Taxol has had a far-reaching social and economic impact since its introduction. More than 2 million women worldwide have taken Taxol. By 1998, the FDA approved its use not only for first-line ovarian cancer therapy, but also for first-line metastic breast cancer therapy when used in combination with Herceptin. Today, it has extended use as a second-line treatment for AIDS-related Kaposi's sarcoma.

"When Taxol was first introduced, it was a golden bullet. It had a staggering impact on the treatment of cancer," says Fraser, a University of California, Berkeley-trained biochemist. "And years later, it still is a front-line therapy for treating breast cancer and ovarian cancer."

One of the offshoots of Holton's work is Taxolog Inc., a private company set up as an FSU startup with a technology transfer license to develop and bring to market other Taxol analogs invented at FSU.

Within months of her Taxol treatments, in October 2002, Curtin was back at work saving lives. While the computer pushes data at her, informing her about the critically ill patients she's monitoring, she recognizes how fortunate she is to be alive, thriving and helping others do the same.

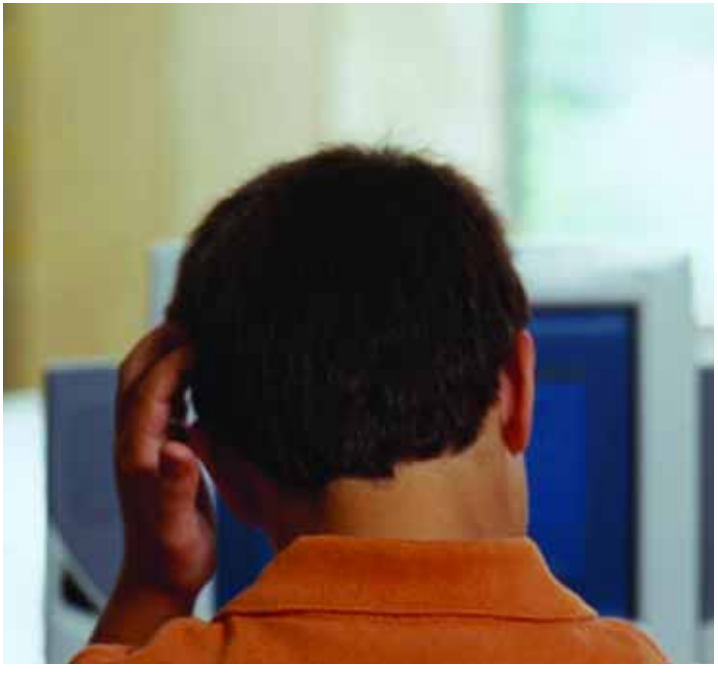
There were many elements that played a part in her recovery, but without missing a beat, she says, "When I started taking Taxol, I felt more human again. It was Taxol that got me back to being a mom."

— By Sharyn Alden

Chapter 23

A Breakthrough Treatment for Sufferers of Psoriasis

Researchers at Harvard University's Dana-Farber Cancer Institute join forces with a Boston-area biotechnology company to develop a new treatment for psoriasis. Their joint studies of immune molecules and functions yield an effective therapeutic that provides relief for this painful illness.



Dana-Farber Cancer Institute

"I have had chronic plaque psoriasis since I was 4 years old and it usually covered my entire body. Oftentimes, it was difficult to deal with since friends and strangers weren't very sympathetic," says one individual.

Another reports, "I was diagnosed with chronic plaque psoriasis … It started out as a small patch … but then it was out of control covering my face, arms and legs. Since I frequently missed work — not wanting to show my face looking the way I did — my job was in jeopardy."

Yet another patient describes, "In my early 20s, my friends were dating, building careers, and enjoying life. Meanwhile, I could barely stand to look at myself in the mirror."

The patient testimonials speak volumes. Living with a medical condition like chronic plaque psoriasis is one of those things that you have to personally experience to understand. It is not a life threatening illness, nor is it a disorder that can rely on public health campaigns to raise awareness, understanding and sympathy. Instead, it is a painful and oftentimes disfiguring illness that can seriously compromise the patient's quality of life. When a therapeutic called Amevive® became available, those lives got better.

Biogen Idec, a global biotechnology company headquartered in Cambridge, Mass., is the present manufacturer of Amevive. The discovery that led to the development of this biologic therapy goes back almost 20 years when the company joined forces with Harvard scientist Timothy Springer, Ph.D. Springer, at that time an associate professor at Dana-Farber Cancer Institute, a teaching affiliate of Harvard Medical School, and now a professor of Pathology at Harvard's CBR Institute for Biomedical Research, was studying molecules of the immune system with a particular focus on the immune pathways involved in fighting cancer.

Collaboration Between Academia and Industry Advances Research

Springer's research strategy entailed making monoclonal antibodies to proteins that are present on the surface of human white blood cells, called T lymphocytes or T-cells. By screening for antibodies that could block the ability of lymphocytes to kill their target cells, Springer reasoned he might discover new proteins with important biologic activity.

With the help of graduate student Michael Dustin, Ph.D., now an investigator at the Skirball Institute of Biomolecular Medicine at New York University, Springer identified three novel proteins called lymphocyte function associated antigens, or LFAs, and named them LFA1, LFA2 and LFA3. Then, they conducted rigorous cell biology experiments to figure out how and why these proteins normally functioned. "We knew that since these were important in normal lymphocyte function, when the immune system got out of control, they should be able to block or dampen this over activity," Springer says. "We thought that blockers of these molecules would be good therapeutics for a whole range of autoimmune diseases."

Springer turned to the technology transfer office at Dana-Farber for some assistance. He

researched his options for collaborations with industry to determine the most efficient way to develop LFA3 as a therapeutic agent. What resulted was the implementation of a funded research agreement with Biogen, a local biotechnology company. Biogen sponsored several subsequent and key steps in the development of LFA3 that were carried out by Springer and colleagues at Dana-Farber. This research led to the generation of intellectual property owned in part by Dana-Farber and Biogen. The intellectual property was eventually licensed exclusively to Biogen which then initiated an internal research program to develop clinical products.

"This was a fine example of collaboration and partnership between academia and industry," says Anthony del Campo, vice president for research and technology ventures at Dana-Farber. "Amevive represents an excellent technology transfer story and shows how discovery and innovation at the academic level can eventually make it to the marketplace."

With the help of scientists at Biogen, the protein sequence of LFA3 was used to identify a LFA3 cDNA clone. Researchers then used this clone to develop a fusion protein that interacts with a particular receptor (CD2) on T-cells, serving to inhibit the binding of endogenous LFA3. By inhibiting T-cell activation, the LFA3 fusion protein effectively interferes with the T-cell mediated inflammatory response. This type of inflammatory reaction is precisely the underlying etiology of psoriasis.

Therapy Targets Overactive Immune Cells

Though a detailed picture of all the molecules and pathways that converge to trigger psoriasis is not yet known, scientists understand that malfunctioning T-cells travel to the surface of the skin and cause an inflammatory reaction. Skin cells respond by multiplying seven to 12 times faster than normal, forming itchy and painful psoriatic plaques on the skin surface. Often cracked or blistering, these plaques can develop anywhere on the skin, though they usually appear on the scalp, knees, elbows and torso. Typically chronic and with no real cure, this autoimmune disease affects about 2 percent of the population worldwide; in the U.S. alone, 4.5 to 6 million people have a moderate to severe form of chronic plaque psoriasis.

The LFA3-fusion protein received approval from the U.S. Food and Drug Administration for the treatment of patients with moderate to severe psoriasis in January 2003 and is marketed by Biogen, now Biogen Idec, as Amevive. Its generic name is 'alefacept,' a mnemonic for L-F-A-cept. Since its approval this biologic therapy has provided treatment for more than 12,000 patients. Designed to target overactive immune cells, Amevive is administered by injection, either intramuscularly or intravenously, once a week for a total of 12 injections per treatment course.

Psoriasis affects about 2 percent of the population worldwide; in the U.S. alone, 4.5 to 6 million people have a moderate to severe form of chronic plaque psoriasis.

Dana-Farber Cancer Institute

The deeply personal testimonials Amevive users share on a Web site devoted to this therapy explain how their quality of life has improved. There is hope that many of the other immunologic proteins found to mediate T-cell responses will provide the key to treating a host of autoimmune diseases for which there are now no effective therapeutics.

— By Nicole Resnick

Chapter 24

Dental Research Yields Powerful Product in the Fight Against Periodontal Disease

A therapeutic use for a well-known family of antibiotic drugs is the basis of a revolutionary treatment. An ingenuous series of experiments by dental researchers at SUNY Stony Brook leads to Periostat, which works by inhibiting the human host response to dental plaque.

SUNY Stony Brook

Certain organs in our body — the heart and lungs for example — seem to receive more attention than others when it comes to health and maintenance. Teeth on the other hand, are something that many of us take for granted. It usually isn't until later in life when teeth may become susceptible to chronic problems, and require painful and costly procedures to save them.

Considered a silent condition with few symptoms in its early phases, periodontal disease can sneak up on adults. In too many cases, by the time periodontal disease is diagnosed, it is quite advanced. In the U.S. alone, more than 65 million adults — one out of every three — suffer from periodontal disease, and its escalating incidence makes it the second largest health-care problem after the common cold.

There is no cure for periodontal disease, but a product called Periostat® has proven to be revolutionary in the management and control of this disease. The discovery of Periostat was the result of a fruitful collaboration that began 30 years ago in a dental research laboratory. At that time, Lorne Golub, D.M.D., M.D. (honorary), Nungavarum Ramamurthy, D.V.M., Ph.D., and Thomas McNamara, Ph.D., of the Department of Oral Biology and Pathology in SUNY Stony Brook's School of Dental Medicine were investigating a specific family of enzymes known to break down collagen, a connective tissue that is a primary component of our bones, skin and teeth.

Bacterial Infection Isn't the Culprit

Before the line of experimentation spearheaded by Golub and colleagues, efforts to combat periodontal disease focused on the bacteria that build up around teeth known as dental plaque. Researchers understood that the body's natural immune response helped fight the plaque-causing bacteria, but a big breakthrough in the field was the discovery that enzymes produced by these immune cells and other human host cells — rather than the bacterial infection — were in fact responsible for the actual breakdown of the gums and bone that support teeth. In other words, it was the body's own host response to the bacteria that was causing the most damage and initiating the destruction of soft tissue and bone in the mouth.

Golub and colleagues began experimenting with ways to inhibit the host derived tissue-destructive enzymes such as collagenase using an already well-known compound: tetracycline. Though tetracycline works as a powerful antibiotic when used at certain doses, the molecule exerts a completely different mode of action when used at lower non-antibiotic levels. The investigators focused on a type of tetracycline called doxycycline and found that it effectively inhibited the activity of the enzymes, classified as matrix metalloproteinases, that break down collagen and gum tissue.

Perhaps most critical was their demonstration that this property of doxycycline occurred at low, non-antibiotic doses and therefore would not create drug-resistant strains of bacteria. They also chemically modified the tetracycline molecule to eliminate the antibiotic activity of the drug and created new compounds called chemically modi-

fied tetracyclines, or CMTs, some of which showed enhanced anti-enzyme properties.

The Research Foundation of SUNY went on to file several patents for these discoveries, which represented a new therapeutic use for an old family of drugs. The first product was named Periostat, and a startup company was launched in 1992 after it purchased the exclusive license for the technology. Under the guidance of its first chief executive officer, Brian Gallagher, CollaGenex Pharmaceuticals Inc., located in Newtown, Pa., committed itself to developing innovative medical therapies in the dental and dermatology markets.

Gallagher continued to lead the company, taking it public in 1996, and Periostat received approval from the U.S. Food and Drug Administration approved in October 1998. Today the product remains the only FDA-approved matrix metalloproteinase inhibitor drug and systemic treatment for periodontal disease. "Periostat is the most successful chronic prescription product ever launched in the dental market," says David Pfeiffer, CollaGenex's senior vice president of sales and marketing. "Before Periostat, the only prescriptions written by dentists were for short-term analgesics and antibiotics."

Millions Rely on Periostat for Improved Oral Health

The acceptance of this therapy is reflected in its widespread use by dental clinicians worldwide. To date, more than 4 million prescriptions have been filled for Periostat.

One of the most important features of Periostat is that it works systemically in patients. Whereas other periodontal therapies are effective only at specific tooth sites, Periostat is delivered to all tissues supporting the teeth simultaneously, offering a whole-mouth approach to the treatment of periodontal disease. The product is highly regarded as an adjunct therapy to the conventional, non-surgical standard of periodontal care, mechanical scaling and root planing, which is designed to physically remove bacteria and deposits from tooth surfaces.

The enzyme-suppressing technology behind Periostat and its systemic effects have led the Stony Brook investigators and others to explore and identify its therapeutic potential in a wide range of medical diseases that share a similar etiology with periodontal disease. Inflammatory diseases characterized by destruction of the body's connective tissues, cardiovascular disease, cancer metastases and diabetes-related complications are some examples where Periostat-related technology holds the promise of delivering powerful therapies.

Clinicians who prescribe Periostat say it has changed the way they practice. Maria Emanuel Ryan, D.D.S., Ph.D., professor and director of clinical research in the Department of Oral Biology and Pathology at SUNY Stony Brook, can attest to the change that this technology has meant to her practice. "As a clinician, I now have a new way to manage my patients. By administering Periostat as a pill twice a day, it amplifies or gives a boost to the response that I can achieve by mechanical scaling and root

"Periostat is the most successful chronic prescription product ever launched in the dental market."

— David Pfeiffer, CollaGenex Pharmaceuticals

SUNY Stony Brook

planning alone," says Ryan. "For a lot of people who may not have responded well to traditional periodontal therapy, we now can achieve a positive response with Periostat and can better manage their disease, in some cases without any surgery. I find that all modes of therapy, both non-surgical and surgical, have been improved in patients who are taking this medication."

Ryan also has witnessed firsthand the improved quality of life that patients enjoy thanks to Periostat. "To a lot of patients who didn't have much hope, this treatment gives them the hope that they can better manage this disease and maintain their teeth," she says.

Though periodontal disease has not been considered life-threatening, it recently has been linked to an increased risk for a number of systemic conditions such as heart and respiratory diseases, diabetes and adverse pregnancy outcomes. "There is no known cure for periodontitis — it requires a lot of work to control the disease — and many patients become despondent over this," says Ryan.

"But Periostat really provides us with another tool to better manage this disease and has spared many patients from needing dentures or implants. In the end, patients always prefer to keep their own teeth."

— By Nicole Resnick

Chapter 25

Shelter From the Storm

Using the Growth and Decay Storm Tracker algorithm developed by researchers at Massachusetts Institute of Technology's Lincoln Laboratory, StormVision software helps develop forecasts pinpointed to individuals' exact GPS coordinates.

Image courtesy of WeatherData Inc.

Massachusetts Institute of Technology

It strikes ground 25 million times a year in the U.S. alone. It can be five times hotter than the surface of the sun, and just one strike can generate a billion volts of electricity. Causing hundreds of casualties every year and capable of shutting down a New Mexico microchip-making plant or a New Bedford fishing vessel with equal aplomb, lightning is a natural-born killer second only to floods in the death toll it exacts.

Thanks to technology transfer — Marilyn Wolfson, Ph.D., and a team of Massachusetts Institute of Technology researchers developed the Growth and Decay Storm Tracker algorithm used in WeatherData Corp.'s StormVision software — people and institutions can now prepare for, instead of just react to, dangerous electrical storms.

Pushing the Envelope

It's not just lives that are at stake, but dollars as well. Thirty-four percent of all businesses suffer costly lightning-related power outages every year. The airline industry, with its tight scheduling requirements and imperative of passenger safety, is an especially vulnerable segment of the $4 trillion of U.S. economy subject to severe-weather hazards such as lightning. Compounding this vulnerability to nature was a roiling pot of contention in the late 1990s over who was to blame for historically high delays. The public blamed the airlines, the airlines blamed the Federal Aviation Administration and everyone agreed that more accurate forecasts were needed.

Consulting with air traffic controllers and commercial airlines, Wolfson and a group of researchers at MIT's Lincoln Laboratory found that convective, or electrical, line storms were the principal cause of delays. Line storms are one of two types of convective storms; the other being air-mass storms. Air-mass storms are small-scale, diffuse, and random in occurrence. But line storms — forced by frontal boundaries between warm and cold, or dry and moist air — are larger and more predictable. Working with FAA funding, Wolfson and her team developed a ground-breaking convective weather forecasting tool, the Growth and Decay Tracker, to address this problem.

To understand the Growth and Decay Tracker algorithm, it is helpful to look at the model of storm prediction it superceded. For the past several decades, conventional forecasters have predicted the path of line storms by extrapolating from the collection of the air-mass cells within them. However, Wolfson says the envelope, or edges, of the storm are a much more accurate predictor of the storm's path than the air-mass cells themselves. This is because the moving storm envelope, forced by a frontal boundary, causes new storm cells to grow while old ones decay as it travels. Hence the Growth and Decay Tracker, aptly named, is a much more reliable basis for predicting convective weather than earlier models.

The Growth and Decay Tracker, tested extensively at U.S. airports between 1998 and 2002, maintains its accuracy out to one to two hours and has proven as much as 50 percent more accurate in predicting line storms than conventional models. In the age of destructive storms such as hurricanes Rita and Katrina — and in a personal and business world where every minute

counts — the Growth and Decay Tracker did not come a minute too soon. Continuing the process of technology transfer with a license from the MIT Technology Licensing Office, WeatherData of Wichita, Kan., then developed a patented software called StormVision, available only from WeatherData, which is part of the forecasting products and services this 38-person company offers to business and institutional clients.

Manage and Mitigate, Stay Competitive

"Discoveries like Wolfson's allow us to predict weather with greater and greater accuracy," says Mike Smith, chief executive officer of WeatherData. "We are at the point now where it is very rare that a completely unforecasted event affects our clients. However, there is still work to be done. We would like to be able have the 30-minute accuracy we have now out to four hours. So, there are opportunities for the academic and private sectors to partner and maximize their respective strengths. This technology allows people and business to manage and mitigate operations, rather than just react to the weather. It allows them to be truly proactive."

What's the big deal about a few lightning bolts? In the Industrial Age, when manufacturing meant gargantuan lathes and bulky die-casts machining out heavy metal parts, operations continued as usual despite the weather. In today's business world of clean rooms and microprocessors, however, a few minutes warning can make all the difference.

The case of Swedish mobile phone manufacturer Ericsson, now axiomatic in business circles for the need to be proactive rather than reactive in regard to weather management, illustrates the point. In March 2000, lightning struck an Albuquerque, N.M., manufacturing plant that supplied Ericsson with cell phone microchips. Soot from the ensuing fire, which lasted a mere 10 minutes, contaminated the plant's clean room. Ericsson, unable to quickly find another microchip supplier, recorded a $2 billion dollar loss in 2000, and has yet to recover. With better contingency planning, and increased lead-time and accuracy made possible by StormVision, this accident could have been avoided.

Ericsson's lesson did not fall on deaf ears. High-profile clients such as GM, Toyota and Daimler-Chrysler now contract with WeatherData, which uses Storm Vision and other technologies to give its clients customized, up-to-the-minute forecasts. Clients receive cellular phone or pager alerts when severe weather — particularly lightning and tornados — is headed for their GPS coordinates.

"It helps us protect our employees," says Les De Bora, GM's security manager for service parts operations. "It gives us added security. We take shelter when we truly need to but don't have to take it needlessly." Shutting down the assembly line because of severe weather can easily cost an automaker hundreds of thousands of dollars. StormVision® helps make sure these closures happen only when necessary.

On another playing field across the country, athletic departments find StormVision to be a

"We are at the point now where it is very rare that a completely unforecasted event affects our clients."

— Mike Smith, WeatherData Inc.

Massachusetts Institute of Technology

lifesaver. "It's a great weight taken off our shoulders," says Rhonda Kelly, assistant athletic director for Florida State University. FSU receives cellular phone or pager alerts from WeatherData if a severe storm touches down within 15 miles. "Fifteen minutes more of practice is a big deal in NCAA athletics," says Kelly. "It allows us to keep practicing and stay competitive."

In the Final Analysis

From the great Armistice Day storm of November 1940, which left duck hunters clinging to frozen cattails on the upper Mississippi River, to the August 2005 flooding in New Orleans in the wake of Hurricane Katrina, Mother Nature shows no signs of abating. The argument can even be made that because of changes in the natural world, weather has become more severe. All the more reason people and businesses need to stay ahead of the storm.

— By John Motoviloff

The surprising and inspiring stories behind 25 great innovations that have changed the way we live.

- How did a mountain climber invent a better, more perfect prosthetic knee?
- What do stealth bombers and dental crowns have in common?
- How did a simple test help save millions of men's lives?
- Why is sand an ideal water purifier?
- How could an apple breathe new life into a section of the U.S. economy?

Learn the answers to these questions and more. *25 Technologies That Changed the World* is a must-read for people interested in research and discovery, technology transfer or economic development as well as anyone who has wondered: "Where did that come from?"

Honeycrisp apples, Google, the V-chip, nicotine patches and Taxol are products derived from technology transfer that have become household names. Others such as Exosurf, the PSA test, Altropane, Rheo Knee and SpeechEasy may not be as well-known, but have affected society profoundly — saving lives and improving well-being. The stories are immensely human, from the first spark of wonder and discovery to the final product. Without the tireless work and commitment of academic researchers on campuses across the globe, there would be no products and no stories to tell.

Read more about academic innovation and technology transfer at

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