As one of the largest employers in Boston, Beth Israel Deaconess Medical Center is an integral part of the state’s economic engine. Last year, spurred by a growth in surgery and sustained strength in other key clinical specialties, the medical center continued to make impressive financial gains with a positive bottom line of $34 million. In addition, we saw a rise in both total inpatient discharges and outpatient clinic visits. High-priority programs, such as cardiac, vascular, and thoracic surgery, also reported incredible progress, while the transplantation program remained the largest abdominal organ transplant center in New England.

Alongside this marked clinical growth, we have remained true to our basic values of exemplary service to our patients. Despite the high acuity of cases, our complication rates in areas such as cardiology and gastroenterology remain far below the national average. In addition, we have instituted a number of new programs to prevent medical errors, ensuring that our patients who entrust us with their lives are always safe in our care. We have also made tremendous investments to improve the quality of patient care through medical education and biomedical research. BIDMC is leading the field in the use of simulation technology to train clinicians in minimally invasive surgery. And our lease of space in the Center for Life Science (Lyme) building will promote the incredible efforts of our scientists, like those who are featured in the report that follows.

The medical center’s continued financial stability, growth, and high-quality service during this time is particularly gratifying to me as the end of FY’05 marks the beginning of my three-year tenure as chair of the Board of Directors. It confirms my belief that we have already embarked on an era of maximizing all the wonderful assets of this great institution. Our position would not be as promising as it is without the loyalty and generosity of all the members of the BIDMC community, and for that I thank you.

Sincerely,

Lois E. Silverman

People used to think of translational research as starting at the bench and going to the bedside, but it is really about creating partnerships with patients.
The stories you are about to read in this 2005 Annual Report—which highlights Beth Israel Deaconess’s success in bringing the fruits of our research to the patient—share a common theme: teamwork. Without this coordinated effort, the important work taking place at the medical center would not be possible. At BIDMC, we sustain a culture that fosters relationships between physicians and researchers. When doctors transcend departmental lines and work together, they become participants in innovation. Today’s interdisciplinary collaborations will yield tomorrow’s cures.

The pioneering research that takes place in laboratories across the campus is already changing the face of medicine by introducing novel therapies that will enable physicians to customize treatments to the individual. Translational research is revolutionizing the way patients receive care at Beth Israel Deaconess. Our goal is to replace the one-treatment-fits-all mindset with a biological customization of care that targets not only a person’s biology, but also the biology of his or her disease.

The stories presented here provide a tantalizing glimpse into what may be on the horizon for medical research and the role our physicians and scientists will play in this effort. I feel privileged to be a part of such a collaborative and caring community. I hope you feel equally proud of your involvement with this extraordinary organization.

Sincerely,

Paul F. Levy
Without translational research, the delivery of medical care would remain stagnant, untouched by the remarkable developments taking place in biomedical science each day. Because of our size and culture, we are in a unique position to strengthen and expand this critical bridge.
More Than a Theory

Five years ago, fresh off of a postdoctoral fellowship at Beth Israel Deaconess, Ananth Karumanchi, M.D., was eager to find a stimulating avenue of research where he could make his mark. On the surface, preeclampsia, an often life-threatening pregnancy complication, seemed an unlikely candidate for the talented young physician-scientist with a clinical background in nephrology—and now four years of vascular biology research training in the laboratory of Vikas Sukhatme, M.D., Ph.D. But to Karumanchi focusing on the maternal syndrome, which adversely impacts the kidneys and blood vessels, made “perfect sense.” It had it all: the scientific challenge, the combination of interests, and the chance to forge his own path. “His choice was partly to distinguish himself from me,” says Sukhatme, with a subtle smile, “which is the funny part about all this, as you will see, because we ended up working closer than ever.”

With his foray into the realm of preeclampsia, Karumanchi forged tight collaborative relationships not only with Sukhatme but with members of virtually every specialty at the medical center. Their collective willingness to think beyond the departmental boundaries of medicine and focus on disease as it affects the patient may provide a way to predict and eventually cure this long-elusive disorder and ultimately change the face of prenatal care. “It’s probably one of the most comprehensive stories of bench-to-bedside, true translational research,” says Benjamin Sachs, M.D., chief of obstetrics and gynecology at BIDMC. “And one that affects more people in the world than almost anything you could find. The burden of human suffering from this disease is enormous.”

Preeclampsia occurs in more than 5 percent of pregnancies, with affected mothers developing dangerously high blood pressure, edema, and protein in the urine. Left untreated, it can damage the woman’s kidneys, liver, and nervous system, causing potentially fatal seizures. In this country alone, one to three mothers die each week from preeclamptic complications; in the developing world, preeclampsia is the leading cause of maternal death. Because the only “cure” at present is to deliver the baby, the disease is also a major contributor to prematurity and stillbirths. Long defying researchers’ attempts to uncover its etiology, preeclampsia has been called the disease of a million theories, ranging from the infectious to the immunologic. “It’s one of the big unsolved mysteries in medicine,” notes Sachs, “not just in my field but in medicine as a whole.”

How Karumanchi broke this mystery wide open is a story of an unwavering work ethic, modern technology, and a collaborative culture, combined with a healthy dose of serendipity. On the advice of Franklin Epstein, M.D., a senior nephrologist who had been interested in the kidney problems associated with preeclampsia for decades, Karumanchi started by getting back to his clinical roots. “We made a paradigm shift compared to most of the research that typical researchers do in this area, where they decide to work on cell lines or in animal models,” he says. “We decided we were going to start with the patient.”

The willingness of Drs. Ananth Karumanchi, Benjamin Sachs, and Vikas Sukhatme to collaborate across disciplines has engendered landmark discoveries in Karumanchi’s pursuit of a cure for preeclampsia.
To make that decision a reality, however, would require cooperation from those directly involved in the delivery of obstetric care. Epstein and Sukhatme called Sachs on Karumanchi’s behalf to ask if he might have access to patients in the Labor and Delivery unit to pursue a hunch about the role of vasculature in preeclampsia. “I remember talking to them on the phone and saying to myself, ‘Oh my God, not another theory,’” recalls Sachs. But the more he listened and considered the reputations of the folks on the other end of the line, Sachs came to the realization that they had made him a request he couldn’t refuse—the potential clinical impact was just too great.

With Sachs on board and Kee Hak Lim, M.D., an expert in maternal–fetal medicine, as their departmental intermediary, Karumanchi and his sole postdoctoral fellow, Sharon Maynard, M.D., collected blood samples and placentas from delivering mothers. They then ran a microarray analysis to uncover which genes are more active in preeclamptic women compared to those without the disorder. Although the number of genes they found ranked in the hundreds, the researchers were able to narrow the field down to about 20 by ruling out those that didn’t involve secreted molecules (because the disorder was almost certainly caused by something that circulates in the mother). But how to decide which of the remaining genes to focus their efforts on? The most obvious answer would be to put the molecule into an animal model and see if it developed preeclampsia. “But you can’t do this with 20 genes,” notes Sukhatme. “It would take 20 years!”

Because of its unusual activity, one gene on the array stood out like a sore thumb. After four years in Sukhatme’s lab, Karumanchi was well acquainted with the molecule it produced: sFlt1, a naturally occurring protein that impedes the growth of blood vessels. Maynard quickly confirmed that circulating levels of sFlt1 were elevated in preeclamptic patients and fell after the delivery of the placenta. But was the relationship causal or just coincidental? Should they take a chance of following a false lead?

In the end, it would be Sukhatme who would relieve them of any misgivings. When his former fellow shared their results in a weekly meeting, Sukhatme had what is known in scientific circles as a Eureka! moment. At just that time, Sukhatme had been making the rounds to a number of scientific talks about “anti-angiogenic” cancer drugs, which work by inhibiting the growth of blood vessels that nourish tumors. He had heard, and later observed himself, that some of the patients in recent clinical trials for the drugs, which block the action of a particular vascular growth factor called VEGF, were experiencing symptoms of high blood pressure and protein in the urine. In other words, they were suffering from preeclampsia, presumably because the drugs had tipped the scales of anti-angiogenesis too far. Like the cancer drugs, the protein that had so intrigued Karumanchi and Maynard, sFlt1, was a VEGF blocker. By chance, the team had uncovered a common pathway that confirmed their instincts were right after all. They had a target they could run with.

“I think at the end of the day you have to work hard, and you have to be lucky,” reflects Karumanchi. “Obviously, everybody here works hard. But sometimes you get lucky, that’s all. And I think when you see something that is real, then lots of things fall into place.” Indeed, the pieces of the preeclampsia puzzle have been falling into place for the team ever since. That an anti-angiogenic factor like sFlt1 was involved made perfect sense in theory; toward

“There’s no question that seeing patients is extremely important in doing good translational research,” says Ananth Karumanchi, M.D. “That’s where you get your ideas. When patients tell you what’s wrong with them, that’s how you learn.”
the end of her pregnancy, a mother would need something to slow down the surge of blood vessel growth used for sustaining fetal development to avoid bleeding to death during birth. It appeared that in preeclampsia this brake is just applied too soon. But now Karumanchi needed proof.

He began with rats. By inducing pregnant rats to produce excess amounts of sFlt1, Karumanchi was able to generate preeclamptic symptoms, thereby creating the first animal model ever for the disorder. Importantly, he went on to demonstrate that sFlt1 was acting by depleting VEGF and another key protein, placental growth factor (PIGF), in the patients’ serum as well as in the animals. Now he was beyond just finding the source of preeclampsia; he was hot on the heels of a potential cure.

But it’s a long way from rats to humans. It was time to go back to the patient. Knowing that a broad-scale clinical trial to test for sFlt1 in pregnant women would be prohibitively expensive, Sachs remembered a NICHD (National Institute of Child Health and Human Development) study from the mid-1990s that examined whether calcium supplements might be effective in reducing preeclampsia in a large cohort of pregnant women (they weren’t). The next thing he knew, he was flying down to Washington, D.C., on a mission to convince this division of the NIH to let Karumanchi test his new therapeutic agent (albeit a naturally produced one) in pregnant women, the team is spurred on by the promise of what a cure could mean for the population to test what has become the overriding target for the research team—a cure.

With the help of the Technology Ventures Office (see page 28), BIDMC has made a licensing agreement with a division of Johnson & Johnson to develop and test a potential drug therapy for preeclampsia, namely a form of VEGF. With tests already confirming VEGF’s efficacy and safety in a variety of animal species, J&J recently submitted an Investigational New Drug Application (IND) to the FDA, which is the first step in launching the first-ever human clinical trials for a preeclampsia therapy. While no one underestimates the logistical and ethical complexities of testing a new therapeutic agent (albeit a naturally produced one) in pregnant women, the team is spurred on by the promise of what a cure could mean for the future of clinical care. “I say with absolute conviction that if the treatment trial works, Ananth and Vikas will have transformed the field of obstetric medicine around the world,” avers Sachs. In contrast, Karumanchi remains quietly modest, citing all the help he had along the way and his delight with the excitement his discovery has generated in the field of preeclampsia research. “We just keep our fingers crossed, pray, and do our best,” he smiles. “What else can we do?”

Useful may be a bit of an understatement; this circulating signal protein, commonly known as VEGF (pronounced vej Ef), is involved in the growth of new blood vessels in the body and likewise a host of biological processes—both normal and abnormal—that entail vascular development. If the acronym is an exotic mouthful, some of the diseases influenced by VEGF are likely more familiar: rheumatoid arthritis, psoriasis, inflammatory bowel disease, asthma, preeclampsia (and most notably, cancer).

It was VEGF’s association with tumor growth that lured Dvorak, who was ostensibly focused on immunology at the time, into the complex world of cancer research. While investigating a new form of cellular immunity in tumors, Dvorak noticed “something far more interesting”—an accumulation of blood clots around the tumor cells. How did they come to be there? He theorized that the tumor was producing an as-yet-unknown factor that caused nearby blood vessels to become permeable to blood, which leaked out and then formed clots. This factor would turn out to be VEGF. “We called it VPF, or vascular permeability factor, back then,” notes Dvorak. “And that’s still its most potent activity.”

Dvorak went on to show that the presence of this permeabilizing agent set off the very same sequence of events that the body uses to repair tissue after an injury, that is, growing new blood vessels. Unfortunately, cancers exploit this mechanism for their own purposes, overproducing VEGF and allowing the “healing” process to continue indefinitely. As a result, the tumor gets the new blood supply it needs to grow and spread. “It was a brand new observation, and it was a fundamental observation,” recalls Dvorak. “Others had hinted at it in the past, but they hadn’t appreciated its significance.”

In the end, Dvorak’s insights would lay the foundation for the field of angiogenesis, the growth of new blood vessels, which is considered one of modern medicine’s most promising hopes for curing cancer—so promising in fact that, in 2002, he stepped down from a 26-year stint as BIDMC’s chair of the Department of pathology to devote himself full time to this basic science. Dvorak still gets a charge at the prospect of learning more about how human beings are put together. “The intrinsic curiosity is certainly the thing that’s always stimulated me,” he says. “And one always hopes that you’ll have applications to human beings. I certainly wouldn’t be motivated to do it if I didn’t think that.”
We don’t want people to have sleepless nights, to feel like they’re not being treated like individuals. But if you don’t, in the end, prescribe the right treatment, it doesn’t matter how kind you are, it’s not going to work. Here, we try to ensure our patients get the best of both worlds.

Steven Freedman, M.D.
For two-and-a-half years, doctors at a local hospital were unable to account for Mario Cutone’s conflicting lab results. His blood tests showed significantly increased levels of prostate-specific antigen, a tumor marker used to screen for prostate cancer, but his prostate biopsies remained negative. The warning signs were there, but doctors couldn’t locate a tumor. After living with uncertainty, Cutone decided he needed answers and transferred his care to specialists at Beth Israel Deaconess Medical Center’s Prostate Care Center.

Unlike other facilities, the Prostate Care Center combines the expertise of specialists in urology, hematology, pathology, and radiology to provide patients with a continuity of care that starts from the moment of diagnosis and escorts them through the various phases of treatment. Martin Sanda, M.D., director of the Prostate Care Center, says Beth Israel Deaconess places a genuine emphasis on going the extra mile to make sure that doctors do what’s best for their patients. “We don’t assume that one 60-year-old prostate cancer patient is the same as the next guy. Every prostate cancer patient has a different situation,” says Sanda. “In the multidisciplinary Prostate Care Center, our doctors realize the importance of individualized care, and we cater to that reality. Prostate cancer care should not be generalized.”

Cutone says he never expected to feel a sense of relief to learn he had prostate cancer, but he found solace in his diagnosis. “You have peace of mind knowing what the problem is,” says the 64-year-old owner of M. Cutone Mushroom Co. “No one likes to hear the news, but at least you can direct yourself which way to go.”

The Prostate Care Center at Beth Israel Deaconess offers a multidisciplinary, personalized approach that focuses on putting patients at the center of their own care.

The Center’s integrated approach impressed Cutone from the start; he met with four doctors from varying specialities to discuss his care. When standard tests didn’t pinpoint the problem, Cutone’s new urologist, William DeWolf, M.D., chief of urology at BIDMC, collaborated with radiation oncologists to try the new 3-T MR. This instrument, one of only four in the United States, combines ultra-high resolution with state-of-the-art computer software to produce color-coded images that display benign growths in green and the area in or near cancerous lesions in red. The 3-T MR unexpectedly revealed not one but two different malignancies in Cutone’s prostate and bladder, which, due to their position, were impossible to detect using a traditional ultrasound. (Radiologists at BIDMC are also utilizing this kind of advanced imaging to define the extent of the cancer and to target therapy more effectively. For example, they are fusing MRI images with ultrasound imaging to give a more accurate, real-time image during prostate biopsies.)

The Critical Mass Effect

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Cutone was far from alone in trying to determine the best treatment path to take for this disease. According to the Prostate Cancer Foundation, cancer of the prostate—a walnut-sized male reproductive gland located below the bladder—affects one in six men in the U.S. It estimates that more than 2 million men are currently living with this disease. Although the exact cause of prostate cancer is unknown, doctors know that there are certain risk factors, such as age, race, and family history that can predispose some men to the disease.

To complicate matters, unlike many other diseases, there is no optimum treatment for prostate cancer. Irving Kaplan, M.D., co-director of the Prostate Care Center and a radiotherapist at BIDMC, says treatment is often “a choice between equals.” He adds, “We always present several options to the patient. It’s not like men’s socks where one-size-fits-all; it’s very individualized. Because of the unique aspect of prostate cancer, we have really worked more towards a multidisciplinary approach.”

Urology chief DeWolf says patients now have a broader menu of therapies from which to choose. “There are many ways prostate cancer can be treated depending on the stage and grade of the tumor,” he notes. “Not only do you have more options, they are more customized to your needs. Treatments are now more functionally adaptive to an individual’s situation.” Several years ago, even patients with early-stage prostate cancer might have undergone a prostatectomy, or removal of the prostate. But today their choices range from radiation therapy to hormonal therapy to no treatment at all.

Glenn Bubley, M.D., director of genitourinary oncology at BIDMC, said there have been incremental improvements in treatments for prostate cancer, but, as of yet, no “magic bullets.” The first line of defense for early-stage prostate cancer has traditionally been radical prostatectomy, however, brachytherapy, or seed implantation, has gained acceptance. This treatment involves embedding radioactive seeds—about the size of a grain of rice—that emit radiation only a few millimeters to kill nearby cancer cells without affecting healthy, surrounding tissue. But notes Bubley, “Since therapies have a finite duration of response, the more therapies we have leads to a longer and better survival for patients. We now have at our disposal newer hormone treatments, chemotherapy, and investigational agents that are helping patients live longer.”

Hormone therapy, which Bubley says is essentially “anti-hormone” therapy because it lowers testosterone levels, puts the disease into remission. Bubley is studying the effects of vaccines and other drugs for patients who stop responding to hormone treatment. One such treatment targets the adrenal gland; others use novel “targeted” therapy. Patients with low-grade and early-stage disease can also elect to participate in BIDMC’s active surveillance program. DeWolf says the program allows patients with minimal cancer to continue with their lives without the side effects of treatment, until the appropriate time becomes apparent.

“Physicians at the medical center are using new, high-powered MRI machines to pinpoint areas affected by cancer, according to Irving Kaplan, M.D., radiotherapist and co-director of the Prostate Care Center at BIDMC. Greater accuracy in diagnosis translates into the ability to deliver more precise treatments.”

continued from page 15
Recent advances in research have enabled BIDMC doctors to do away with the one-treatment-fits-all mindset and progress to a more customized and targeted approach to the diagnosis and treatment of prostate cancer. “Today there is a greater recognition that prostate cancer is biologically variable from one patient to the next,” Sanda says. “By understanding the biology of prostate cancer, we can improve clinical care.” However, he points out that recent national priorities have severely underfunded federal funding for cancer research. “There is a greater need than ever before for endowment funds,” he reflects. “Without it, we will not be able to keep the scientists who have been drawn to this field engaged so they can continue performing their valuable work.”

A sampling of the wide-ranging prostate cancer research at BIDMC shows just how valuable these efforts could be. While the widespread use of the prostate-specific antigen, or PSA, blood test led to the increased detection of early-stage prostate cancer, this “gold standard” may soon be replaced by more sensitive screening tests. Researchers at the medical center are trying to find new biomarkers to improve the detection of prostate cancer, and determine whether a person will respond to therapy. In a recent study published in The New England Journal of Medicine, Sanda and colleagues from the University of Michigan at Ann Arbor found that prostate cancer patients produce an immune response to an overexpressed protein found in the epithelial cells of prostate cancer. This autoantibody could be used as the basis for a more accurate screening test for prostate cancer.

To understand why some patients respond to treatment when others don’t, doctors at BIDMC have set up a repository to analyze patients’ tissue and blood samples. “It gives us the ability to go back and analyze tissue and blood samples years later for specific targets or markers,” Bubley says. “If patients have a recurrence of prostate cancer, doctors can look at previously ‘banked’ samples and may be able to target therapy more effectively. There may be something the cancer is producing that we didn’t even know about ten years ago that we can now test for.”

The basic science research being conducted at BIDMC is at the forefront of science and is helping drive the clinical care patients receive. Sanda is working on a genetically engineered prostate tumor vaccine that uses smallpox to stimulate the body’s immune system to better recognize prostate cancer cells and eliminate them. And Bubley says it is not farfetched to think that in the near future early prostate cancer will be managed as a chronic disease, like diabetes or hypertension.

As for Cutone, he will always be grateful to the team of specialists who brought him resolution during a time of great uncertainty. “The level of care I received at Beth Israel Deaconess was excellent,” he says. “I rest easier knowing that my doctors have everything under control.”

Men diagnosed with prostate cancer can now choose from a wide range of treatment alternatives, but sorting through the benefits and consequences of each treatment can sometimes generate undue anxiety. Should they delay treatment and choose active surveillance? Or should they elect for more aggressive treatment, like radiation? Nowadays, the choices are endless.

Marc Garnick, M.D., a physician at Beth Israel Deaconess Medical Center, has made it his mission to navigate patients through the maze of treatment options to help them make informed decisions. “My practice deals with trying to help patients go through the dilemmas of deciding what to do with prostate cancer once they have been diagnosed,” he says. “That stems from the fact that I’ve written a whole series of articles on screening for prostate cancer for different audiences, such as the American College of Physicians.”

Garnick has written several articles on the dilemmas of prostate cancer screening. While the use of PSA-based screening has aided in the early detection of prostate cancer, Garnick points out that there is no definitive evidence that aggressive treatment at the onset of prostate cancer leads to improved outcomes. “The predicament that a patient faces, especially those with early prostate cancer, is that we can quantify all the harms, difficulties, and side effects of treatment, but we can’t show them unequivocal data that we are doing them any benefit,” he says. “Most patients elect to undergo treatment because they want their cancer treated. Garnick says. “By presenting patients with a balanced view, they can make appropriate treatment choices that are based on the most current medical literature available.”
A lot of the really important breakthroughs we make here come from taking the blinders off and looking a little to either side. That’s the beauty of the hospital research environment—there’s always someone with the knowledge you need willing to share it.
Plagued with a sleep disorder that caused him to stop breathing and wake up 66 times each hour, Bob Daly was facing a life in constant decline. His fragmented sleep caused excessive fatigue during the day, he developed heart disease, and it wasn’t long before he had to retire from a 25-year career as a venture capitalist.

But a chance encounter with a doctor in the Division of Pulmonary, Critical Care, and Sleep Medicine at Beth Israel Deaconess led to an extraordinary collaboration that enabled Daly to play a significant role in developing an instrument pivotal in his recovery. The enterprise proved to be such a success that the Technology Ventures Office at BIDMC (see page 28) is using it as a model for how to advance promising technology to clinical utility.

A chain of random events was set in motion four years ago to bring Robert Thomas, M.D., a clinician specializing in sleep disorders, and Daly together. During that fateful morning, Thomas was in the office checking his mail when he overheard snippets of a telephone conversation between a secretary and troubled patient, who would turn out to be Daly. When Thomas heard the words “sleep apnea” and “tracheostomy,” a surgical procedure that creates an artificial breathing hole, he agreed to see the patient right away.

After seeing several doctors in and out of Boston who misdiagnosed him and prescribed an ineffective treatment for his condition, Daly had serious doubts that he would ever be properly treated. “The disease was killing me,” he says. “I had unbearable fatigue, and I couldn’t get through the day without sleeping a couple of times. My quality of life was basically zero. I found out later that part of the reason I was feeling so awful was because I was on this totally inappropriate and very dangerous therapy.”

Daly’s exhaustion was the result of untreated sleep apnea, a disorder that causes people to momentarily stop breathing during sleep. According to the National Institute of Neurological Disorders and Stroke, sleep apnea affects 18 million people in the U.S. If left untreated, it can increase a person’s chance of having high blood pressure, heart attack, or stroke.

Sleep apnea comes in three varieties: obstructive, central, and mixed. Obstructive apnea, the most common form of this disease, is characterized by loud, irregular snoring caused by partial or complete obstruction of the airway by tonsils, fatty tissue, or involuntary muscle relaxation during sleep. Central apnea occurs when the brain fails to send the necessary signals to the muscles that control breathing. In essence, the brain “forgets” to breathe. Daly had mixed apnea, which is the most difficult to treat because patients have a variable combination of obstructive and central sleep apnea. What doctors know now is that the conventional characterization of “mixed” apnea misses the majority of patients with combinations of obstruction and respiratory control dysfunction, a condition Thomas has named “complex.”
Despite his initial misgivings, Daly walked away from his first consultation with Thomas with a sense of renewed hope. "That was a good time for Bob to see me for this critical problem," Thomas says. "By then I had figured out how to differentiate people with pure obstructive disease and those with complex sleep apnea." He had a theory that people with complex sleep apnea behave like people who travel to high altitudes and experience disrupted sleep. At altitudes of 8,000 feet or higher, the number of oxygen molecules in the atmosphere is decreased and can cause symptoms, such as shortness of breath. "Oxygen has a stabilizing effect on breathing rhythm," Thomas explains. "At high altitudes you breathe more to keep the oxygen levels up, but that also lowers the carbon dioxide. It's been known for a long time that low carbon dioxide is what drives breathing fluctuations. When you are awake it's alright, but when you are asleep the brain seems to sense you are breathing too much and sends signals to stop breathing."

Continuous positive airway pressure machines have been around for quite some time, and effectively treat 70 to 80 percent of people with obstructive sleep apnea. But Thomas had the ingenious idea of designing a machine that delivered a precise combination of oxygen and carbon dioxide to treat patients with complex apnea.

The pair met one afternoon in the lobby of the Carl J. Shapiro Clinical Center. Over lunch, Thomas put his idea to paper, sketching on a napkin the blueprint for the instrument he hoped to build. As Daly's health continued to deteriorate, he became more determined to see Thomas's project succeed. When he learned that design houses were asking for six-figure development deals to build the machine, Daly remained undeterred. He simply stepped out to the garage of his Weston home and started to build it himself. "There was a lot I did not know, but I was a fast learner," says Daly, who took a few electrical engineering courses as an undergraduate at Brown University. "If I didn't know something, I would look it up on the Internet and within 30 minutes I would have the answer."

Two weeks later, Daly called Thomas to let him know he had constructed a prototype. "At the time his sleep apnea wasn't well treated, so I was amazed that he was able to undertake such a complex project," Thomas says. "At that time, it was more like a science project."

Over the next couple of months, doctor and patient refined different aspects of the instrument. They poured over medical literature and engaged in intense dialogue about the device, such as what it would have to do, what it would look like, and how much carbon dioxide would be required.

*I remember this look came over his face,* Daly recalls. *"When I came back a week later he told me he had a theory about how to treat these groups of patients, which, it turned out, I was a poster child for."*
Unlocking the Rhythm of Sleep

For Robert Thomas, M.D., luck and serendipity continue to be a driving force in his work. Six years ago, while monitoring patients in a sleep lab, Thomas noticed they spontaneously switched between two distinct states of sleep—characterized as stable or unstable—during non-rapid eye movement (non-REM), a sleep stage that comprises 80 percent of an average night’s rest.

His observations run contrary to the conventional concepts of non-REM, which are classified in grades of depth. What he needed was a way to validate his subjective findings with an objective and unbiased estimate.

Unbeknown to Thomas, Joseph Mietus, a BIDMC engineer, had developed an algorithm to track the interactions between heart rate and respiration with the hope of being able to diagnose sleep apnea and perhaps sleep stages. When his findings didn’t correlate with traditional non-REM sleep staging standards, he set the project aside. The crucial connection would lie waiting until Thomas “stumbled across” Ary Goldberger, M.D., a cardiologist and director of the Margaret and H.A. Rey Laboratory for Nonlinear Dynamics in Physiology and Medicine at BIDMC, who worked with Mietus. “What I was looking for, they had,” says Thomas. “And what they were hoping to find, I already knew.”

Thus began their ongoing collaboration to unlock the rhythm of sleep. The team developed a sleep spectrogram—a graph based on results obtained from an electrocardiogram, a device that tracks the heart’s electrical signals. “It turned out that breathing and heart rate are tightly modulated by a person’s sleep state,” Thomas says. “Graphically, we could see when a patient was awake or asleep, stable or unstable.”

Using this method, they were able to identify two different types of behavior during the course of a person’s sleep—stable and restless or unstable and around. Thomas says this new characterization of sleep is “intuitively much simpler and biologically more meaningful. Health is dominated by stability, and disease is dominated by instability.” Thomas says this cost-effective approach to assess stability and quality of sleep could lead to other important clinical applications, such as diagnosing sleep disorders or testing the efficacy of sleep aids and other medications.
Nothing Ventured, Nothing Gained

Few would argue that researchers at Beth Israel Deaconess are inventive and enterprising, willing to follow new ideas where they may lead in the name of improving patient care. But even for the most brilliant scientist, it can be a daunting task to translate inspiration into innovation. No one can deny that TVO’s work to make BIDMC’s research enterprise more entrepreneurial is a bit of a risky business. Laughs Chalek, “You’d do a lot better on Longwood Avenue in building parking garages than you would in trying to commercialize early-stage technology. It’s the highest of high-risk games, particularly when you’re on the front end like we are.”

Countless obstacles can derail a promising drug or technology before it can make the trip from the research lab to a patient’s bedside. Hence, the Technology Ventures Office (TVO), which was formed in 1998 under the leadership of Mark Chalek. Although much of its work takes place behind the scenes, the efforts of TVO have been indispensable for bringing the fruits of BIDMC’s research to patients in need. TVO is a unique group composed of professionals who can straddle the two worlds of biomedical science and industry and, with a blend of technological and business savvy, work closely with BIDMC’s researchers to develop and market their most valuable ideas. They safeguard intellectual property and help avoid possible litigation. They find creative ways to realize the commercial potential of ideas through strategic business partnerships. But, most importantly, they help BIDMC’s medical scientists focus on what they do best — medical science — by relieving them of the burden of having to decipher the intricacies of the business world and by subsidizing more of their research in the face of tightening profit margins and diminishing federal grants.

BIDMC’s obligations, however, are much more than legal. As recipients of federal funding, BIDMC scientists have a legal obligation to disclose their discoveries to their employer, and in turn, the medical center has a similar obligation to do what it can to help these discoveries realize their commercial potential. BIDMC’s obligations, however, are much more than legal. As a leading academic medical center with a vast research enterprise, BIDMC has an ethical responsibility to do everything in its power to improve the welfare of its patients. Transforming ideas and discoveries into tangible advances in clinical care is a natural outgrowth of that mission, whether or not the institution gains direct financial benefit. And, bucking the odds, TVO has in fact generated more than $20 million in revenue for BIDMC over the past five years by executing more than 100 new license agreements. Plus, Chalek notes, in the process, the medical center profits in more subtle and strategic ways. For one, TVO’s work enhances BIDMC’s reputation to current and prospective faculty as an institution that values the role of research in medicine. “One of the reasons researchers like to do this stuff here is because they like to work with us. We help them, and we add value,” he says. It also creates beneficial alliances with businesses that may help advance research efforts in unanticipated ways. “Like anything else, it’s a relationship business,” says Chalek. “You start with an agreement that may seem to be simple and mundane and straightforward, and you have success. And then the next thing you know, you’re talking about doing something more interesting, more long-term, more strategic.” All these assets help differentiate the medical center as an organization says Chalek. He points out that few teaching hospitals are known for their strength in the technology transfer area, and that TVO’s work is ensuring that BIDMC’s bench-to-bedside endeavors are on par with its status as a center of clinical excellence. “It’s a great institution with a great history with brilliant people doing innovative things every day,” states Chalek. “Why wouldn’t you want to have a service function that is really commensurate with that culture?”