

breakthrough

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All Sides Pointing Toward the Patient

Reversing the Domino Chain

A "Knock-In" Mouse

What I Did This Summer

Taking Care of His People

When Wounds Don't Heal

Medicine is a public trust
THE JOHNS HOPKINS CENTER
FOR INNOVATIVE MEDICINE

breakthrough



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BRINGING PEOPLE TOGETHER, THINKING DIFFERENTLY, MAKING THINGS HAPPEN

I like summer. At an academic medical center that never closes, there's never a time when "school's out," and we all get to sleep late and head for the pool. We always work hard. But in the summer, the structured pace eases up a bit around here. We have fewer meetings, not so many talks and lectures. This is the time, for many of us, for writing – working on grants, finally getting around to writing papers, having a little more time to study, to think about our research, to plan ahead. This summer, for instance, I was able to work on something that I've been thinking about for a long time. It has taken shape – literally, it's a pyramid – as a new model for medical education, with the patient as the primary focus (see page 4). I'll come back to that in a moment.

At the Center for Innovative Medicine, these quieter weeks are also the time for our Advisory Board members – a group made up of people who are willing to think differently – to do some summer reading. It's hardly ever medical stuff; instead, we look for books outside our field that help us think creatively. Books on leadership, on innovation, on ideas. We don't meet over the summer as a group; instead, we recharge, reflect, refocus – and when fall rolls around, we're ready to go. We start by talking about what we all read. I thought that you, as our partners in this mission to reshape academic medicine, might be interested in some of the books that have given us so much to think about. They include:

- *A Whole New Mind: Why Right Brainers Will Rule the Future*, by Daniel H. Pink
- *Diffusion of Innovations*, by Everett M. Rogers
- *Team of Rivals: The Political Genius of Abraham Lincoln*, by Doris Kearns Goodwin
- *Made to Stick: Why Some Ideas Survive and Others Die*, by Chip Heath and Dan Heath

Why cores matter: Another aspect of the CIM that you may have noticed is that we value cores, and we have several, including the Lowe Genomics Core, the Amos Proteomics Core, and cores in histology and cell sorting. Cores allow us to achieve critical mass. When the right people come together, with different skills and areas of expertise that complement each other, and when we add smaller funds to other funds – and add those to funds that come as a blessing from the generous philanthropists who have done so much to help us make life better for patients, we begin to see results that are much more exciting, and that happen much faster, than they would if Dr. A plodded along in her little corner of the world, and Scientist B toiled away in a lab, and Equipment C was used by just a few people in one specialty. Bringing people together. Thinking differently. Making things happen, for the greater good of patients. This is our mission.

In this issue of *Breakthrough*, among other stories, you'll see how a young medical student is learning to know her patients as people, and how the good work made possible by the Greek philanthropist, Mrs. Aliki Perroti, has strengthened our ties with the beloved Greek community here in our own neighborhood. One of Bayview's great strengths is the deep relationship we have with our local community. And this brings us back to the exciting new model that we are beginning to create for academic medicine, reshaping the traditional triangle of "patient care, research, and teaching" into something stronger: A pyramid, with all sides pointing toward the patient.

David B. Hellmann, M.D.

4

All Sides Pointing Toward the Patient

The familiar triangle model of academic medicine gets a 21st-century upgrade, and a new focus – the patient

New Hope for Understanding a Tough Disease: A "Knock-In" Mouse

In every way but one, it's a plain old mouse – with the potential to help some very sick people.

7

8

What I Did This Summer: Learned About People

Behavior is hard to change. Lives are complicated. Textbook answers don't always cut it.

Taking Care of His People

A benevolent hawk watches over Baltimore's Greektown, and gives back to Bayview.

10

- 12 When Wounds Don't Heal
- 15 One Step Closer
- 16 Friends of CIM

WE BELIEVE

Medicine belongs to the public. Our mission is to create a different kind of academic medicine, to tear down ivory towers, share knowledge and dedicate ourselves toward one goal – making life better for patients.

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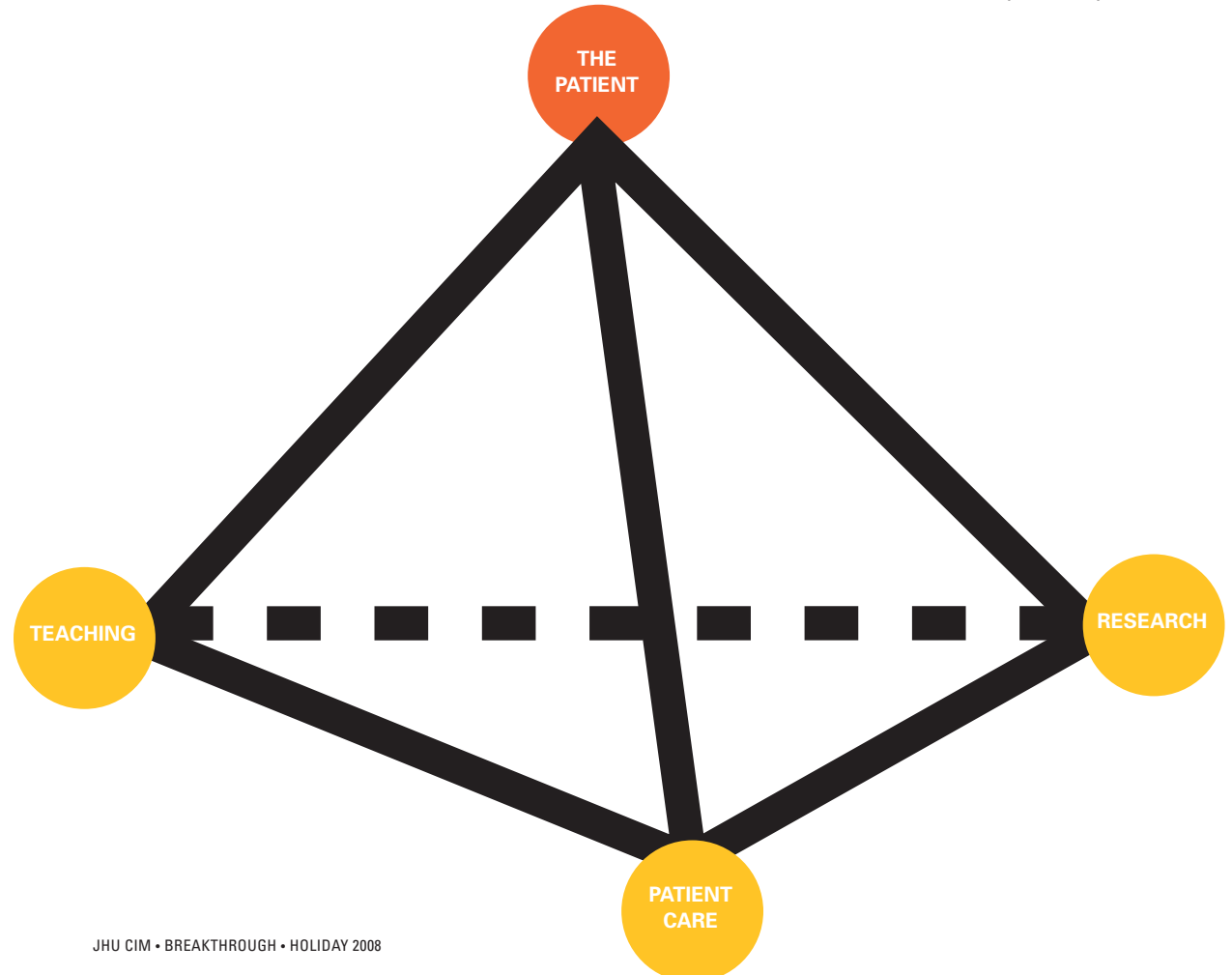
All Sides Pointing Toward the Patient

What's the difference between a triangle and a pyramid? For academic medicine, the answer is that the old, familiar triangle model – which did its job well for more than a hundred years – needs a 21st-century upgrade. The two-dimensional triangle needs to grow, to make more room for patients and the community.

Pick any academic medical center, and chances are, a triangle figures into the logo somewhere, with the three-sided mantra: Teaching. Patient care. Research.

But something is missing, says David B. Hellmann, M.D., M.A.C.P.: An epicenter, a single priority instead of three separate missions. He proposes adding a new dimension to the model – making it a pyramid, with all sides pointing toward the patient. “Only one side of the traditional triangle explicitly focuses on the patient. The assumption is that the other two sides are focused on helping patients, but unfortunately, this is not always the case.” Research, especially, tends to become an end of its own, and in the race for academic excellence, the idea that science is a means of achieving the greater goal – helping patients – can get pushed aside.

“The triangle was a great Hopkins innovation,” continues Hellmann, the Aliko Perroti Professor of Medicine, Vice Dean of Johns Hopkins Bayview



“At the base are all the people – everybody, our whole work force – at the academic medical center. The pyramid rests on a bedrock foundation of people working together for one greater good – the patient.”

Medical Center, and Chairman of the Department of Medicine. “It came about as an answer to problems of 19th-century medicine – the lack of science, and the huge distance between the best, the average, and the worst-trained doctors.” (See side story.)

Since then, academic medicine has become uniformly better in some important aspects, and great in others. But patients should be foremost, continues Hellmann, “and clearly, they’re not.” For example: “Nearly half of Americans do not believe their doctor knows them as a person. That’s not acceptable. Worse, only half of the care provided in the U.S. is judged to be appropriate. The primacy of the patient needs to be explicit in every aspect of what we do.”

Over the years, an increasing emphasis on scientific achievement has skewed the triangle academically, says Hellmann. “Research dominates the pathway to professional rewards. Not teaching doctors how to be caring clinicians, not being caring clinicians. Research receives the lion’s share of the support for infrastructure.”

The current model does little to promote collaboration, as well, and instead spawns jealously guarded academic fiefdoms and turf battles – again, because scientists lose sight of the bigger picture, and of what should be their goal. “There should be many opportunities for collaboration and synergy between clinical and basic researchers, and among health care workers in different fields,” says Hellmann. “But by definition, the sides of the triangle meet only at one point. Also, the triangle emphasizes the special role of physicians, but doesn’t highlight the critical work of nurses, physical therapists, pharmacists, administrators, and other staff.”

BUILT ON BEDROCK

The main components are good, says Hellmann; the model just needs to be reshaped into a pyramid, with the patient, or the public trust, as the pinnacle. The three-dimensional pyramid also shows the countless opportunities for collaboration, as

How the Triangle Came to Be:

It Started at Hopkins

The academic medical center as we know it was born at Johns Hopkins. The hospital opened in 1889 with the goal of being “a model of its kind.” Before launching the medical school, the founding professors – there were just four – took the time to think carefully about what they wanted to achieve. In a time when medical education was often sketchy, they wanted to combine the best of the great hospitals and universities in Europe with a new way of teaching – the opportunity for students and residents to learn by doing.

The Hopkins model established three key elements:

- Science is the basis for medical knowledge.
- Rigorous preparation in science is the prerequisite for beginning medical education.
- The teaching hospital, an innovative fusion of hospital and medical school, is the best training ground for internship and residency.

They got it right. In fact, the Hopkins model was so successful that in 1910, Abraham Flexner’s famous report on medical education held it up as the ideal, and recommended that all American medical schools either adopt it, or be shuttered and closed.

And, as historian Kenneth Ludmerer, the first Alike Perroti Visiting Professor of Medicine, noted, Americans listened – because in the early 20th century, Americans viewed medicine as a public trust, and cared deeply about the types of doctors its schools were training. The Hopkins model became the standard throughout the United States.

“The triangle of academic medicine, which began here at Johns Hopkins, has served American medical schools and the public well,” says David B. Hellmann, M.D. “Many marvelous advances in medical research and patient care are the product of this triangle.”

The new pyramid model takes these good components and reworks them so they function better, with the patient as the primary focus.

all sides are connected. “At the base are all the people – everybody, our whole work force – at the academic medical center. The pyramid rests on a bedrock foundation of people working together for one greater good – the patient.”

Johns Hopkins Bayview is uniquely suited as the birthplace for this new model, Hellmann adds, because of its rich heritage. “Not only are we the home of many Centers of Excellence, with \$100 million in external funding, numerous award-winning teachers, and groundbreaking educational programs such as our Aliko Initiative (see page 8), but this special place has never lost its beginnings as Baltimore City Hospital, with deep and vibrant community ties. These two strands of institutional DNA – one from Johns Hopkins, and one from Baltimore City – give us great potential, a once-in-a-lifetime chance, to create a new model for academic medical centers in the 21st century.”

How does one go about transforming a formidably entrenched culture and organizational structure? One step at a time, says Hellmann. Some of these steps, well under way, include:

- **The Aliko Initiative**, an innovative program to change medical education by giving doctors the time and opportunity to get to know their patients as individuals;
- **The Miller-Coulson Academy for Clinical Excellence**, which gives academic medical centers the tools to define, measure, and reward the most gifted, caring physicians (see page 15);
- **The creation of scientific and clinical research cores**, powerful building blocks that create critical mass and generate scientific momentum (see letter, page 2).

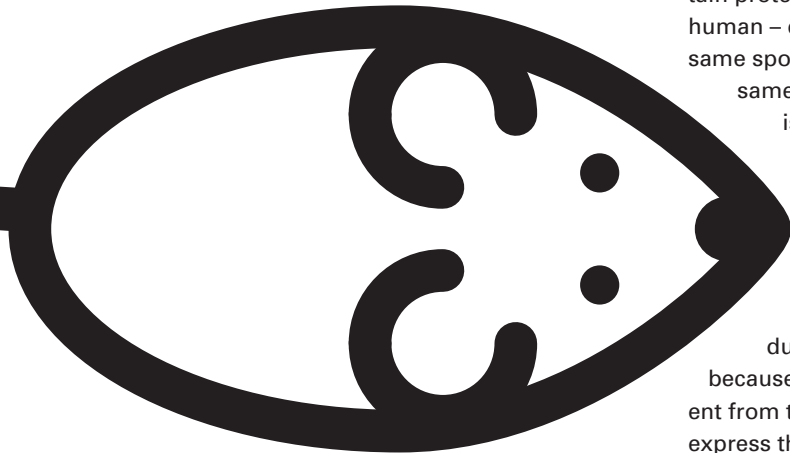
Finally, any new blueprint must be carried out by general contractors, says Hellmann, and several groups are already taking on this role, including the Center for Innovative Medicine. “Unlike the ancient pyramids, which were set in stone, the Bayview pyramid model will be a living one, where the faculty and staff are constantly seeking ways to raise the pinnacle of patient health higher and higher.” ■

“There are an estimated 20,000 genes, and we’re going to exchange one of them in a mouse for a human gene. So this mouse will have 19,999 mouse genes, and one human gene.”



New Hope for Understanding a Tough Disease: A “Knock-In” Mouse

Wegener’s granulomatosis is a complicated disease that causes inflammation in the blood vessels, which can restrict blood flow and damage organs. Although there are drugs, including corticosteroids and medications to suppress the immune system, treatment is not always perfect, the disease can recur, and its complications can be severe.



Rheumatologist Felipe Andrade, M.D., Ph.D., wants to understand the molecular biology of this disease, so he can figure out why this happens – and discover new ways to treat it. But he’s been frustrated by a huge roadblock: Unlike many diseases, Wegener’s does not have a good animal model for study. Among other challenges, this means that drugs that seem to show promise in the research laboratory have not proven helpful in people, and symptoms in people have not been effectively duplicated in experimental studies.

All that may be about to change. In a highly sophisticated version of changing a light bulb, Andrade believes he can study Wegener’s in mice by replacing a single gene in a mouse with a human gene. In almost every way, the animal will remain a plain old mouse, except for one very tiny, but very important, genetic Band-Aid. “There are an estimated 20,000 genes, and we’re going to exchange one of them in a mouse for a human gene,” he explains. “So this mouse will have 19,999 mouse genes, and one human gene.” This process is called creating a “knock-in” mouse, and it’s not to be confused with a “knock-out” mouse, in which a gene is inactivated or modified, so scientists can get a better idea of what that particular gene does.

“Why do we need a knock-in mouse? One major problem is that there are huge differences between the mouse and the human,” Andrade says. “Certain proteins or genes that have one function in a human – even though they’re located in the exact same spot on the genome, and appear to be the same – just work differently in a mouse.” He is interested in one protein in particular, called PR3. “For years, scientists have known that this protein is attacked by the immune system in Wegener’s. The big problem is that nothing more is known about this, because there are no animal models in which it can be reproduced. I strongly believe that the reason is because the mouse protein, PR3, is totally different from the human PR3. If we can get the mouse to express the Wegener’s protein, which is the major target of the disease in humans, that is going to be incredible. Then, we can try new treatments, which until now, has been impossible.”

The mouse is not cheap. Andrade estimates that just making the mouse will cost around \$70,000, not including all of the studies he plans to perform once the Wegener’s mice are available, and he wouldn’t be able to do any of this without major support from philanthropist David Lowe. “His support has been unbelievable,” Andrade says. “He has made all of this, and even more, possible. We believe this is going to work. We have a lot of scientific information telling us it’s the right thing to do,” plus a little gut intuition. “My gut is telling me it’s going to work.” ■

What I Did This Summer: Learned About People

The Aliko Initiative, a groundbreaking program, recently began at Johns Hopkins Bayview, thanks to the philanthropy of Mrs. Aliko Perroti. Its foremost goal is for doctors to have the opportunity to get to know their patients as people, and the “Aliko teachings” – designed to produce more compassionate physicians – are happening at every level of medical education.

This summer, Jennifer Cai, now a second-year medical student at Hopkins, spent much of her time working in the cardiology clinic with cardiologist Roy Ziegelstein, M.D., master clinician, and executive vice-chairman in the Department of Medicine. Ziegelstein is also co-director of the Aliko Initiative, and one of the best at teaching doctors to *care about* – not just care for – their patients. Here’s some of what this young physician-in-training learned:

BEHAVIOR IS HARD TO CHANGE

It’s easy to tell someone to stop smoking, and to be shocked when he doesn’t do it. It’s harder to understand why, and to learn that you can’t judge, because you don’t know what this man’s life is like.

“Jim” was a 53-year-old truck driver. He suffered a myocardial infarction six years ago, and came in with chest pain and shortness of breath. He was a chain smoker for 35 years, and was not willing even to consider quitting – which, at first, I couldn’t comprehend. Then, I listened to his story. Jim’s transitory lifestyle made it difficult for him to keep a normal schedule. He routinely interspersed a pot

of coffee each day with packs of cigarettes to get through his long driving shifts. The walk from the truck to his house was his only form of exercise each week. He spent half of his time in Baltimore with a relative whose house was in constant disarray, and the other half with his family, who seemed to know little about his health problems. His father died of a heart attack at age 62.

For Jim, avoiding locations that trigger the urge to smoke was tantamount to asking him to give up his livelihood; finding social support was asking him to seek the help of family members who weren’t really there to be with. Suddenly, I thought, he wasn’t being unreasonable. He was responding to what he saw as an unreasonable request.

PEOPLE HAVE COMPLICATED LIVES...

...But big problems can be broken down into smaller parts, which are easier to fix. It starts with learning to ask the right questions.

“Melissa,” a local bus driver, desperately needed to lose weight. The first question Dr. Ziegelstein asked her was, “What’s in your refrigerator?” Her answer, “Not much,” led to an important conversation about nutrition. She ate out most of the time, often at a Chinese fast food stand close to where she took her lunch breaks. She knew that cheeseburgers and pizza weren’t good for her – but she didn’t know how much sodium and fat were packed into chicken lo mein. This wake-up call was enough to jolt her to start buying and cooking her own groceries.

ASSUME NOTHING

Appearances can be deceiving.

“Dee,” a woman in her 80s, was wheeled into the room, and although she was attached to an oxygen tank and her slightly blue lips indicated cyanosis (not enough oxygen in the blood), she chatted with her late husband’s daughter, flirted with Dr. Ziegelstein, and teased herself about being a burden to society. I enjoyed talking with her so much that I felt very disoriented later, when Dr. Ziegelstein told me how sick she was. I had assumed that her energetic and bubbly nature meant that Dee was doing well. I saw how easily I could be influenced by a patient’s personality, and how those feelings might translate into my giving her a more optimistic prognosis or treatment than she deserved.

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SHOW, DON'T TELL

Learning from an expert how to explain difficult concepts.

Once, I saw Dr. Ziegelstein use the analogy of a garden sprinkler to describe the blood vessels, and how the pressure inside them relates to the heart. Another time, when "Malcolm," a very successful lawyer, asked about appetite-suppressing medications to help him lose weight, Dr. Ziegelstein asked him to picture an obese man who was unwilling to get up from the couch – but who asked his doctor to prescribe a cane. It was a "light bulb moment." Showing and not telling means boiling down a complex medical idea into simple, everyday situations, and this can be critical to helping patients understand what's going on inside their bodies.

ANXIETY AND DEPRESSION CAN KILL

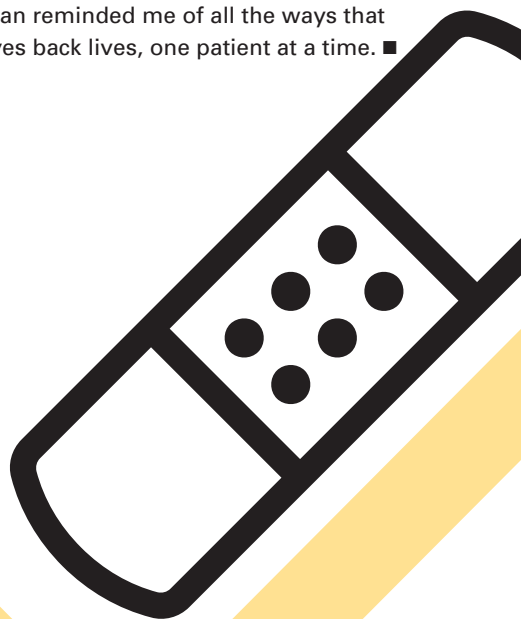
What's happening at home or work takes its toll on the body, too.

I was amazed at the number of cardiac patients who were being treated for depression or anxiety, or both. "Calvin," in particular, entered the room with palpable anger, complaining that he had been waiting for a very long time. Throughout the interview, it was evident that he and his wife were not getting along, and by the end, she was so upset that she began to cry and had to leave the room. Later, I learned that Calvin had a history of serious anger problems and was enrolled in a psychiatric study. Although it had been abundantly obvious that something was wrong, I learned how important it is to know about our patients' mental health. A simple "how do you feel today?" could help us uncover important things we need to know for comprehensive care.

THE BEST PART?

HELPING PEOPLE GET THEIR LIVES BACK

My experience in the clinic this summer reaffirmed many of the reasons I wanted to become a physician in the first place – the patient interaction, the dynamic, intellectual atmosphere among colleagues, and life-long learning. But what I found most satisfying each day was simply seeing a patient who got better. One patient in particular stands out. The first thing I noticed about "Ian" was a tattoo of a large-mouth bass – an angler's dream catch – on his bicep. He had been seeing Dr. Ziegelstein for years, but this day, he looked about 10 years younger, and proudly displayed a tan and photos from his latest fishing trip. Ian reminded me of all the ways that medicine gives back lives, one patient at a time. ■



Taking Care of His People

How does a man take care of his family? He provides for them. He watches them carefully, like a benevolent hawk, looking for problems, and then doing his best to solve them. If one of his children has trouble in school that requires outside help, he gets it. If his wife or his children or parents become sick, he goes with them to the doctor. If that man is trained as a social worker, this instinct to help is even stronger. And if that man also happens to be Greek, he has no choice. This is what he was born to do.

And this is what Stelios Spiliadis has done, except that for the last several decades, his family – beyond his beloved wife, Pauline, and two sons – has also included Baltimore’s Greektown. Bayview’s neighborhood. His work to strengthen the ties between Bayview physicians and their Greek patients – particularly, to help doctors see these patients as people, and to shed light on cultural differences – dovetails perfectly with the recent innovative work named for another Greek philanthropist, Mrs. Alike Perroti; in fact, the two share similar missions to give back to the hospital and community.

Spiliadis, a native of Patras, Greece, comes from a long line of good cooks, renowned for their hospitality. Although he came to the U.S. to study philosophy at Columbia University, earned a graduate degree in social work from the University of Maryland, and served as a community mental health worker for many years, Spiliadis also owns a



five-star restaurant, a Greek fish tavern named The Black Olive, in a 200-year-old renovated rowhouse in Fell’s Point, from which he ceaselessly works to help Baltimore’s Greek community, and the hospital in its neighborhood.

For the better part of century, since the first immigrants – most of them men, working to raise money for their sisters’ dowries back home – started coming to Baltimore in about 1905, the Greek community was so tightly knit that many could get along without much outside help. They worked for mainly Greek-speaking bosses, spent hours at Greek coffeehouses, smoking cigarettes and talking, drinking strong coffee and reading Greek newspapers, catching up on the news from back home. They ate in neighborhood taverns, bought Greek groceries at local stores, and worshipped in a Greek Orthodox cathedral much like the one they grew up in. But the children of succeeding generations went to the public school, and their parents often couldn’t help them with their homework because they didn’t know English. Spiliadis, along with a priest from the Greek Orthodox Cathedral of the Annunciation and other community leaders, started a program – the first formal intervention in this community – to help these families.

He also found a kindred spirit in Randy Barker, M.D., an internist at Bayview, who was interested in knowing more about his patients, so he could do a better job of treating their illnesses. Many of Barker’s patients were Greek. Spiliadis made a list of things Barker and the residents he helps train should know about his people, starting with a fundamental issue that had many physicians bamboozled: In Greek families, when one person gets sick, the whole family gets sick.

In Greek families, when one person gets sick, the whole family gets sick.



And the whole family goes to the doctor. “The doctor comes in, and asks, who’s sick?” In traditional Greek hierarchy, Spiliadis explains, the patriarch must be consulted first, so he describes the problem, speaking for the patient. Later, he may even send everyone else out of the room, and say to the doctor privately, “Now tell me the truth, what’s wrong? The poor doctor is in conflict between two values” – because the culture of American medicine values patient confidentiality.

Spiliadis began teaching doctors about their Greek patients, starting with a field trip around the neighborhood – to the church, the rowhouses, the coffeehouses. (Spiliadis notes that when he took residents to coffeehouses, thick with cigarette smoke, most of them bailed out fairly quickly, seeking fresh air.)

He explained about other potentially mystifying cultural quirks; such as why, when a patient who has been coughing up blood is diagnosed with lung cancer, the reaction is, “Thank God!” – because he’s so glad it wasn’t TB, which is highly stigmatized in Greece. He made sure they knew about illness Greek people are prone to, such as thalassemia. And he showed them rich Greek desserts – baklava, custards, cream-filled pastries, layered cakes, tarts – “to explain the Type 2 diabetes they were seeing.”

Spiliadis spent his work hours and free time doing this “because Randy and I were totally convinced that you couldn’t provide adequate medical care without knowing and taking into consideration the socio-cultural setting in which individual patients live.” His people. His family.

And more recently, as the path of Greek immigrants inevitably led new generations away from the old rowhouses and into the suburbs, Spiliadis has worked

with Bayview to protect the neighborhood and honor its culture. Commitment from Greg Schaefer, President of Bayview, to revitalizing this neighborhood and strengthening its ties was so strong that Schaefer served with Spiliadis on the Greektown Community Development Corporation. “He has made such a difference, not just financially, but morally – the president of a hospital coming to every meeting made all of us feel part of the hospital.”

GIVING BACK

“Out of nowhere, Greg Schaefer calls me up and says, ‘This thing has been happening at Bayview.’ The thing, Spiliadis found out, was a friendship between Bayview’s Vice President and Chief of Medicine, David B. Hellmann, M.D., and a Greek philanthropist, Mrs. Alike Perroti. Together, they were working to develop an innovative program, “focusing on influencing an approach to medical care that focuses on the entire patient. This was close to my heart,” says Spiliadis, who closed The Black Olive one night recently to host a seven-course dinner for Mrs. Perroti and community leaders, including U.S. Congressman John Sarbanes, the grandson of Greek immigrants.

“There are two Greek words that designate the most important values we have,” says Spiliadis. One is “filotimo,” a compound word that basically means “friend of honor” – a hugely meaningful concept in Greek culture. “We believe it is better to lose your eyesight than your honor. Without honor, you’re nothing.” The other word is “filoxenia,” or “hospitality to foreigners.” Mrs. Perroti honors both of these concepts, and Spiliadis honors them, too.

America, Spiliadis explains, “has been to Greece a place where need has been responded to. Immigrants came wanting new jobs. Students came wanting education. We needed, and America gave us. This is about giving back.” A third phrase, “yenothy karthia,” sums it up for him. “It means generous heart.” The Black Olive dinner will now be an annual tradition, a fundraiser to support the Alike Initiative. And the ties between Bayview and the Greek community, like grapevines, remain entwined, producing new, good fruit – a cause, indeed, for celebration. ■

When Wounds Don't Heal

The great physician William Osler, the founding professor of medicine at Johns Hopkins Hospital, once said that “the man who is well wears a crown that only the sick can see.” This is certainly true in the case of wounds. Most of us have no idea how blessed we are simply to go through our lives without having a lingering wound. To many thousands – the elderly, people with diabetes or other illnesses, such as Crohn’s disease, that affect the body’s ability to heal – we are incredibly lucky.

“Chronic wounds are a major health problem, and as our population ages, they are becoming more common,” says Gerald Lazarus, M.D., Director of the Wound Center, and chief of Dermatology. Treatment for these wounds that don’t want to heal accounts for 1 percent of the total health care expenditure in the U.S. – at least \$15 billion annually, and rising by 15 percent a year. In addition, the indirect costs are tremendous, he says. “When elderly people develop a chronic wound – from a fall, for instance – somebody’s got to shop for them and chauffeur them around. Many become isolated.” For many people with diabetes, the ulcer – a stubborn wound that can become huge, and require surgery – is a last straw that causes them to lose control of their disease, because they can’t exercise, and have trouble even moving around the house.

The Wound Center at Johns Hopkins Bayview is a remarkable resource, a hubbub of activity and research, drawing doctors and scientists from several fields, including Jonathan Zenilman, M.D., chief of Infectious Diseases; and Stephen Milner, M.D., director of Surgery at the Wound Center, and Director of the Johns Hopkins Burn Center, who also runs an inpatient program for acute, short-term wound care. William B. Greenough, M.D., a geriatrician, heads another, longer-term inpatient program, with between 25 and 30 beds for people with chronic wounds of substantial size. The Center offers expertise in podiatry, for complex ulcers of the feet; dermatology; nursing; vascular surgery; and even specialized imaging, to map the extent of wounds.

One difficulty with wounds is that they are, metaphorically, the icing on a bad cake. They tend to happen to people who have other, often complicated, health problems. Thus, treating the wound also requires getting the underlying disease under control.

WHAT'S IN THERE? TACKLING AN OLD QUESTION WITH NEW SCIENCE

Another, very serious problem with wounds is that – with their perfect culture media of blood and open tissue – they are easy gateways for nasty and potentially deadly intruders. “Almost all wounds have bacteria in them,” says Lazarus, “and how these bacteria affect wound healing is very problematic. We spend a fortune using antibiotics on patients with wounds – tons of antibiotics – but we don’t know if these antibiotics are helping the wound heal or not.”

Recently, scientists in the Wound Center began studying bacteria in new ways, asking new questions and using sophisticated technology to find some surprising answers. Their work was funded in part by a gift to the Center for Innovative Medicine from philanthropist Robert Rosenheim. “The first question is, what bacteria are in a wound,” says Lazarus. “And if you get rid of them, does it make any difference?” First, they cultured wounds the routine way, with a plain old swab. Then they used a curette, a small, spoon-shaped surgical instrument with a sharp edge, that allowed them to go deeper into the wound. “It doesn’t really hurt any more than a swab,” Lazarus notes. They took the samples to Jonathan Zenilman’s lab, and used quantitative microbiology to determine not only a

Wounds are, metaphorically, the icing on a bad cake. They tend to happen to people who have other, often complicated, health problems. Thus, treating the wound also requires getting the underlying disease under control.

bacterial “who’s who,” but how many – the various types of bacteria, and the number of organisms populating each bit of tissue. “Lo and behold, what we discovered was that the routine way of culturing wounds bore very little relation to the bacteria,” says Lazarus. “That surprised me.”

So the quantitative microbiology, carried out by Johan Melendez, was much better than the evidence provided by routine swabs. But both of those methods require a bit of horticulture – growing the bacteria in culture media. And thus, they only provided a glimmer of insight, because just a tiny percentage – about 1 percent – of bacteria can be cultured, says Lazarus. Which meant that the scientists still

CONTINUED ON PAGE 14

“Our military has done an amazing job of reducing casualties,” says Gerald Lazarus, M.D. “The ratio of people dying now is lower than ever, but the casualties are much worse.” The military’s response time to getting wounded soldiers to treatment is unprecedented. Medics are on the scene almost immediately. In 15 minutes, the wounded have gotten medical assistance, and are moved to a hospital in Iraq. Within hours, they are cleaned up, given major interventions, flown to a military hospital in Landstuhl, Germany, and some of them are at Walter Reed or the Navy hospital less than 24 hours after they are injured, carried on planes that are flying hospitals. “They bring in individuals who are devastatingly wounded, who under other circumstances would have died, and the nature of their injuries is different than in previous wars.” Instead of being shot with bullets, the soldiers are more likely injured by IEDs, or “improvised explosive devices” – booby traps, which explode on the roads. “These soldiers have horrendous blast injuries, basically in the thighs, belly, and groin.”

Lazarus and Zenilman saw some of these first-hand on the wards at Walter Reed Hospital. “It’s horrible,” Lazarus says, “but they are putting these guys back together, and dealing with wounds that previously would have been a death sentence.”

Consider, with wistful, wishful thinking, the incredible waste of human life in such massive battle as those fought at Gettysburg, or in Normandy. With the medical care today, how many of those lives could have been saved? Probably the majority, says Lazarus. It is ironic that wars, in their grim way, advance medical care “exponentially,” he adds. “The antibiotics, penicillin, the whole approach to sepsis, asepsis and bacteria, the use of prosthetic devices... Wars basically change how we practice medicine, and this one’s no different.”



knew very little about what was happening in the wounds. So they expanded their search to the molecular and genetic levels – the bacteria’s DNA.

To heck with cultures: A novel way to get a genetic picture of what’s happening in someone’s wound is a technique called PCR (polymerase chain reaction; this is also being done by Melendez), which isolates tiny fragments of DNA. The beauty of this method is that, instead of looking for tangible culprits, it simply finds their footprints. Using a method called metagenomics, “we literally take the mush that’s in the wound, and sequence the bacterial DNA from it.” How, in a sea of mush, do they know if the DNA they find belongs to bacteria, and not to the patient? Because of a material called 16-S, which is only made by bacteria. For the first time, the Bayview scientists feel, they can know exactly what’s in a wound.

HELPING SOLDIERS

This pioneering work in investigating wound bacteria has attracted the attention of the Department of Defense, which is desperate to do more to help save combat-wounded soldiers. Lazarus and Zenilman have collaborated with Lt. Col. Eric Elster, at Walter Reed Hospital, and Lt. Col. Alexander Stojadinovic, at the National Naval Medical Center. Elster and Stojadinovic have been measuring cytokines – cell signals, often related to the immune system. They found that “certain patterns said the patient was in deep trouble, and others predicted the patient would get better,” notes Lazarus. “Our role was to analyze the effects of bacteria on the healing rates. It has been a huge, ongoing collaboration.”

Could it be, the scientists wondered, that the nature of the bacteria they have identified in wounds is related to someone’s ability to heal? Very possibly. “Why is this important? Because the military casualties are really the Olympic athletes. In the Department of Medicine, most of our patients are the exact opposite – unhealthy, older people with multiple diseases. This is an opportunity to look across the spectrum of wounds and decide which aspects of this are related to age and disease, and which might be true for all wounds.”

“If you’re 80 years old and a diabetic, we can’t make the diabetes go away, and we can’t make you 34 years old again. But we can alter the bacteria that are there.”

The Bayview scientists have received funding from the Department of Defense, and have written several other grants to explore this. “The impact on patient care is staggering,” says Lazarus. “If you’re 80 years old and a diabetic, we can’t make the diabetes go away, and we can’t make you 34 years old again. But one of the things that we can do is alter the bacteria that are there.” Knowing more about wound bacteria is suggesting new molecular forms of treatment that have nothing to do with antibiotics. It may be possible to modify the bacteria – to send in more benign forms that keep more aggressive bacteria in check. More advanced testing can also identify bad bacteria that need to be treated aggressively right away.

“Bacteria come in two flavors,” explains Lazarus. One is called *planktonic*; as the name suggests, these bacteria float around through the bloodstream, and spread through tissue. This is the kind of bacteria that usually are affected by antibiotics. But some bacteria, for reasons no one understands, produce little cocoons called *biofilms*. They alight on a surface and rapidly start churning out “extracellular mucopolysaccharides” – in other words, they surround themselves with mush. Then they begin to hibernate. “In this state,” says Lazarus, “they actually become quite resistant to antibiotics. When bacteria are in biofilms, they become very difficult to treat. Yet, even in their sleepy state, these bacteria can affect the body, and the immune response. Lazarus is collaborating with scientist Mark Shirtliff at the University of Maryland to investigate these biofilm bacteria.

One goal, he adds, is to be able to isolate these strange bacteria in a wound, using DNA probes. “Is it just on the surface, or is it in the edge, and it’s progressing, and invading the patient? And how are these bacteria affecting wound healing?” The next step is to learn how to tame these bacteria, by introducing “good” bacteria, or developing unique molecules that change how these bacteria behave. “This is a very important new horizon.” ■

Academy of Clinical Excellence: One Step Closer

The first national salvo in the effort to build a national Academy of Clinical Excellence – an idea that began in the Center for Innovative Medicine – has been launched.

In our last issue of *Breakthrough* (that story and the entire issue are available on our website), it was still just a very good idea, being diligently pursued by four of Bayview's finest clinicians, with funding from Mrs. Sarah Miller (whose mother, Mrs. Anne Miller, was instrumental in starting the Center for Innovative Medicine) and her husband, Frank L. Coulson. The four clinicians – all Miller-Coulson Scholars – are Colleen Christmas, M.D., Steven Kravet, M.D., Samuel C. Durso, M.D., and Scott Wright, M.D. Their mission has been to find a way for academic medical centers and national funding agencies to define, measure, and reward clinical excellence – just as they reward scientific excellence, with grants and academic promotion.

This fall, the debate officially went national, with publication of an article and an accompanying editorial in the journal, *Mayo Clinic Proceedings*. The team spent months talking to clinically excellent physicians, as identified by eight of the country's best academic departments of medicine, and spent further months analyzing their results.

The four Bayview clinicians made rigorous efforts to bring science to the study of what is also an art – practicing good medicine, says Wright. “The Academy of Clinical Excellence is being built upon a foundation of empiric research and scholarship, rather than assumptions or conjecture.” When the Miller-Coulson Academy, named for its benefactors, becomes a reality, its planners envision that it will have a refereed board to review portfolios, give external validation, and provide national recognition of excellent academic clinicians.

“We are taking a scientific approach to its design,” says Christmas, the study's lead author, “so that the end-product will be of the highest quality, and something that could be disseminated to other academic institutions, just as one would expect of Hopkins. We are really proud of this paper,” she continues, “and are happy it is getting so much attention. The issue of overtly rewarding clinical excellence, rather than taking it for granted, has clearly struck a passionate chord.” ■

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For Osler, "the welfare of the patients who presented themselves in the clinic for diagnosis and treatment came first; next, came into consideration how undergraduate and graduate students [residents] could best be taught; and finally, came solicitude that every opportunity for contributing to the advance of our knowledge of internal medicine should be eagerly seized... Professor Osler's clinic synthesized diverse elements into a harmonious whole; it represented a new form, good in itself for its time, and yet plastic enough to admit of remoulding at later need."

Llewellys F. Barker, M.D.
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