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“The flu-like symptoms of interferon are gone. The severe fatigue is gone. Anemia, which has been a consequence of the first protease inhibitors, is no longer a major issue. And the treatment duration has been reduced to, in some cases, 12 weeks, down from 24.” – Mark Sulkowski, on promising new treatments for hepatitis C virus, p. 24.
Lost Opportunities

So many scientific breakthroughs to share with you. Such limited space.

That’s the challenge I face with each issue. For every article we include—on a protein study that has blocked progression of osteoarthritis in mice (p. 11) or a new treatment for hepatitis C virus (p. 24)—there are dozens more scientific success stories at Johns Hopkins that must go untold.

In the last few weeks alone, medical researchers here have reported on a new compound that reverses Down syndrome-like learning deficits in mice, identified a molecular marker that predicts patients most likely to benefit longest from two popular cancer drugs, and concluded that saline shots may be just as effective as steroids in relieving lower back pain for some patients. And that’s just for starters.

The pace of discovery is dizzying. Which makes recent cuts in government science funding all the more sobering. Taking inflation into account, funding for the NIH is now down to 2000 levels. Under sequestration, the NIH budget has been slashed by another 10 percent for the second half of 2013. Additional cuts loom for 2014. Support for medical education has also eroded: this past July, roughly one in 10 MD-PhD training slots was lost due to federal cuts.

Scientific breakthroughs don’t happen overnight. Our hepatitis C researchers, for instance, have been on the research trail for today’s cure since the early 1990s. In broad terms, it takes 10 to 15 years for a new drug to come to market.

So, while those of us outside the medical research lab may not experience the pain of sequestration tomorrow, we’ll undoubtedly feel the impact in five or 10 years—in the form of cures unrealized and vaccines unimagined.

Under that scenario, selecting the magazine’s story list will be easier, of course, with so many fewer breakthroughs to report on. But that’s a chilling prospect, indeed.

CLINICAL TRIALS ARE CRUCIAL

“A Cure for Sickle Cell” [Spring/Summer] could not have come at a more appropriate time—just after World Sickle Cell Day in June, and just before National Sickle Cell Disease Awareness Month in September. As a sibling of one with sickle cell disease, I have witnessed the pain crises and hospitalizations, and the interdisciplinary approach to care that is needed.

This article touches on an important issue: recruitment of African-Americans for clinical trials. If more African-Americans participated in clinical trials, the advances in medicine would benefit African-Americans. Because sickle cell disease primarily affects African-Americans, there needs to be a greater effort in recruiting African-Americans for these sickle cell clinical trials. By having increased mutual trust in the patient-provider relationship, and open lines of communication between patients and providers, one can increase the number of patients willing to participate in the studies needed to advance the cure rate for sickle cell disease.

OLUWAKEMI TOMOBI
Johns Hopkins A&S ’04
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CONSIDER THE COSTS OF SICKLE CELL

Your article on sickle cell disease shows the excellence for which the school is famous. However, you failed to segue that with the following article on genetic counseling. Sickle cell anemia, like Huntington’s chorea, could be eliminated or severely curtailed in this country with a simple lab test, identifying bearers of the sickle trait, combined with the appropriate genetic counseling.

It is all well and good to spend billions to cure this disease but think how much could be saved by eliminating it.

We have reached the point of diminishing returns in health care and that must factor in.

OWEN SEAR, MD ’62
Winter Haven, FL

AN OMISSION AND AN ERROR

As an enthusiastic reader of Johns Hopkins Medicine, I feel compelled to point out an error and an omission of personal significance in “A Cure for Sickle Cell.”

First the omission. Your article correctly points to the pioneering work done at Hopkins on hydroxyurea for sickle cell disease in the 1990s. However, the drug was also investigated for thalassemia patients...
in the same time frame at Hopkins, though to lesser success. Two of my sisters, Elizabeth Rossetti and Gloria Rossetti, bravely participated in those sadly unsuccessful trials.

Now the correction: thalassemia was misspelled multiple times in your article. In the 1990s, the NIH called thalassemia the “orphan of orphans.” I hope that with a correction in your magazine, that will be less the case.

ANGELA ROSSETTI

Disability Doesn’t Define the Person

My co-author, Sara Palmer, and I appreciated the positive review of our book Just One of the Kids: Raising a Resilient Family When One of Your Children Has a Physical Disability [Spring/Summer, p. 16].

We did, however, want to call to your attention a term that is not in use in this day and age and one about which we write in the book. Our approach—adopted universally in the disability community and professional journals—is that “crippled” is not appropriate disability etiquette. The preferred approach is person-first with disability descriptor (not “crippled”) following; for example, “Jan, a mother of three who happens to use a wheelchair.” Personally, I have never felt “crippled” but rather a person who is wife, mother, grandmother, professional, creator, and yes, by the way, someone who uses a wheelchair or scooter for locomotion.

KAY KRIEGSMAN

End Gun Violence

I applaud Dr. Adil Haider’s article about his response to the violence that he sees firsthand as a trauma surgeon [Spring/Summer, p. 47]. Rather than limiting his concerns to the surgical care of the victim, he has spoken out on the epidemic of violence in the United States and the need to create interventions for violence prevention.

Gun violence is a public health issue. It impacts our profession, but more importantly, our lives and the lives of our loved ones. I appreciate physicians who speak out, displaying their social responsibility.

LUCILLE A. MOSTELLO, MD ’70

Calling All Cardiologists … to China

After reading the letter by T. O. Cheng “An Ambassador to China” [Spring/Summer, I thought I might expand on what I have learned over the years about Chinese medicine and specifically about Chinese cardiology.

For the last seven years I have been invited to a meeting in Beijing, the GWICCC (Great Wall International Congress of Cardiology). It is chaired and run by one of the leading Chinese cardiologists, Hu Dayi. Professor Hu has championed the causes of prevention of cardiovascular disease throughout China. He is a strong advocate of controlling obesity, diabetes, lack of exercise, smoking, and blood pressure, particularly in young people. He invites several experts in cardiovascular medicine from around the world to present their information at this meeting to an audience of about 10,000 or 12,000 cardiologists from all over China.

This is the premier cardiovascular meeting in the People’s Republic of China, and I thought cardiologists at Hopkins interested in prevention might be interested in participating in this meeting. I think they might be impressed by what the Chinese are trying to do to prevent (or at least delay) cardiovascular disease.

C. RICHARD CONTI, MD ’60, MACC
Emeritus Professor of Medicine & Eminent Scholar Emeritus (Cardiology)

A Note of Gratitude

With regard to “Confronting the End” [Spring/Summer, p. 6], I am writing to note that the Johns Hopkins Metastatic Breast Cancer Couples Retreat would not be possible without the generous support of the Salisbury Family Foundation. To watch a video about this unique program of support for metastatic breast cancer patients and their significant others, visit http://bit.ly/JHBreastCancerRetreat.

LILLIE SHOCKNEY
University Distinguished Service Associate Professor of Breast Cancer

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William Crawford, MD ’79, President

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Hopkins researchers have developed new guidelines—the first in more than 35 years—to govern the amount of blood ordered for surgical patients. The recommendations, based on a lengthy study of blood use at Hopkins Hospital, can improve patient safety and potentially save the medical center more than $200,000 a year, the researchers say.

A report on the research that led up to the new guidelines, published online in the journal *Anesthesiology*, suggests millions of dollars a year nationwide could be saved in laboratory costs and wasted blood if other hospitals also reconsider how they prepare blood for surgery.

The guidelines, based on a mathematical algorithm developed and tested by the Hopkins team, ensure that blood is readied for surgeries most likely to require transfusions (such as open heart surgery and liver surgery) and that time isn’t spent preparing blood for surgeries that rarely require them—such as appendectomy, tonsillectomy, thyroidectomy, and removal of the gallbladder.

“In 1976, when the last guidelines were published, there were 60 surgical procedures on the list. Now, with the addition of laparoscopy, robotic surgery, and other minimally invasive techniques, there are 135 categories of surgical procedures,” says study leader Steven M. Frank, an associate professor of anesthesiology and critical care medicine at Hopkins. “Blood loss has declined over time as surgery has evolved, but the guidelines were never reconsidered, leading to a lot of unnecessary work to prepare blood for surgery.”

When blood is ordered for a surgical case, there are expenses associated with typing a patient’s blood and screening for various antibodies to ensure a good match is found, as well as with preparing the actual units and bringing them to the operating room, Frank says. Meanwhile, unused blood set aside for surgical patients is removed from the available pool for 24 hours, and while it can be used eventually, recent research by his team suggests that blood stored longer than three weeks begins to lose its “shelf life”—the capacity to deliver oxygen-rich cells where they may be needed most.

In some cases, Frank says, Hopkins Hospital was under-ordering blood, a condition also remedied by the new set of guidelines. Liver transplants are most likely to require the largest amount of blood, with the recommendation that 15 units be prepared and in the operating room.

While the blood-ordering guidelines developed are specific to Hopkins Hospital, they can be adapted to other hospitals, Frank notes. Also, he says, hospitals with computerized anesthesia records—roughly 50 percent of hospitals in the United States—can use the algorithm developed by the Johns Hopkins team to develop their own hospital-specific guidelines.
Blueprint for the Next Five Years
Strategic plan aims to maintain Hopkins Medicine as international leader.

After 18 months of planning involving more than 150 faculty, staff, and administrators throughout the enterprise, Hopkins Medicine leaders have unveiled a strategic plan designed to guide decisions and business strategies through FY 2018.

“It is a historic moment in the history of Johns Hopkins Medicine,” Dean/CEO Paul B. Rothman told a standing-room-only audience in a town hall meeting on June 14. “In the past few years, Johns Hopkins Medicine has had exponential growth. Our budget this coming year is $6.7 billion, and we have 41,000 employees… For the first time, this plan brings all our leaders together with a single plan that supports our vision, mission, and core values.”

The plan was created, he added, to ensure that the institution remains an international model of excellence in research, education, and patient care while confronting the challenges of health care reform and reductions in research funding.

The ambitious blueprint comprises six critical areas of focus: people, biomedical discovery, patient- and family-centered care, education, integration, and performance. Each priority has specific goals, measurements to gauge both long-term and annual performance, and strategies for achieving success.

The strategic plan begins with a commitment to invest in the talents of 41,000 people who serve the institution through its medical school, six hospitals, managed care and home care organizations, community physician groups, and its international organization.

“The strategic plan recognizes that people are really what make Johns Hopkins an outstanding institution,” says Jonathan Lewin, director of the Department of Radiology. “And the plan ends with performance, with the fact that we need to perform both financially and operationally to really be able to take our missions to our public and our constituencies.” Lewin co-chairs the planning process with John Colmers, vice president for health care transformation and strategic planning. “We fully understand and appreciate that this plan is going to be a living document,” says Colmers. “What we are doing today, particularly in an environment where the world is changing so rapidly, will require us to take a look back on a periodic basis.”

Goals include ensuring that employee compensation reflects the scope of work, quality, and leadership responsibilities; establishing the “Advancing the Frontiers of Discovery Fund” for research; engaging patients and families in shared organizational and clinical decision making; facilitating interprofessional educational programs; and developing and implementing the performance improvement initiative that will identify $150 million to $200 million in annual net operating income for Johns Hopkins Medicine. Linell Smith

Back on Top—Again
Johns Hopkins Hospital ranked #1 in the nation.

Johns Hopkins Hospital has regained the top spot in U.S. News & World Report’s annual rankings of American hospitals, placing first in five medical specialties and in the top six in 10 others.

Johns Hopkins had, until last year, been ranked #1 for 21 years in a row by the publication, when Massachusetts General Hospital took top honors. This year’s rankings mark the 22nd time in the publication’s 24-year history of surveying hospitals that Johns Hopkins has held the esteemed position.

In acknowledging their delight in again being named #1, the leadership of Johns Hopkins Medicine gave credit to the researchers, clinicians, nurses, and all of the hospital’s staff and caregivers for the remarkable standing.

“Given the competitive, rapidly changing health care environment and the realization that U.S. News evaluates more than 4,806 hospitals, we hope you share our incredible pride in achieving this top-tier ranking among the best hospitals in the United States,” wrote Dean/CEO Paul B. Rothman and Ronald R. Peterson, president of Hopkins Hospital and Health System and executive vice president of Johns Hopkins Medicine, in a joint letter of congratulations.

“Our hospital’s standings in the specialties ranked by U.S. News reflect the strong performance and historic leadership of our institution,” they added, noting that of the 16 specialties ranked by the publication, 15 at Johns Hopkins were ranked among the top six in the nation.

“The Johns Hopkins Hospital will always be the hospital ranked #1 for 21 years in a row thanks to the people of Johns Hopkins Medicine,” they said.
Setting the Course in Malaysia
A new medical school gets a new curriculum.

After two years in Malaysia, Hopkins pulmonologist Patrick Sosnay found it difficult to say goodbye to students and faculty at Perdana University Graduate School of Medicine (PUGSOM) and return to Baltimore in August. But he left knowing that medical students there are well-prepared to continue their academic journey with Hopkins’ Genes to Society (GTS) curriculum.

In a nation where most medical schools take a hierarchical and often narrowly vocational approach to medical education, the curriculum surprised and sometimes overwhelmed, says Sosnay, who was dispatched to the fledgling medical school as GTS course director in 2011. A year earlier, Johns Hopkins Medicine had signed its historic agreement to help create Malaysia’s first four-year graduate medical program, as well as to design Perdana University Hospital—a 600-bed teaching hospital—and research programs across the medical enterprise.

“Students [at Perdana] are not used to being considered colleagues of the faculty,” notes the pulmonologist. “They are also unfamiliar with the Socratic method of teaching. Especially in small groups, we want to hear what they are thinking, but they’re concerned that they’ll give a wrong answer.”

Those discomforts are exacerbated by language differences. Though students’ English sufficed for everyday conversation, for some it didn’t facilitate the kind of nuanced arguments that faculty encouraged.

Throughout his two-year tenure, Sosnay saw all of these problems diminish. But even from the start, he says, any challenges were easy to overlook because of the students themselves. Their infectious hunger for knowledge, and exhaustive pursuit of success, led him (and visiting faculty) to revel in teaching them.

“One faculty member told me, ‘Oh, my God, we’re taking your students home!’” he says.

The Malaysian students’ devotion, Sosnay observes, is a function of many factors: a cultural emphasis on the high value of education, the responsibility they feel to the government that sponsors the majority of them, and the value the students themselves place on being considered colleagues of the faculty that instruct them.

“They feel like, ‘We know everyone’s going to be looking at this and we want to make you guys, and the school, look good.’ It’s pretty humbling for me,” says Sosnay.

As course director, Sosnay oversaw the numerous visiting Hopkins faculty members who flew in to provide system-specific expertise. What 20 to 30 people might teach at Hopkins in Baltimore, only two to three teach at Perdana. As a result, he says, “everyone does a little bit more.” He fortified his own lectures by speaking on topics as varied as ethics, clinical skills, anatomy, and genetics.

Now back in Baltimore, Sosnay is looking forward to becoming re-entrenched in his research on adult cystic fibrosis. He’s kept up-to-date during two years of Friday night, cross-continental conference calls that connected Italian, Canadian, and U.S. researchers.

Sosnay will most miss his colleagues (students and faculty) and friends. But he’s also not short on praise for the place he called home for two years. “I brought my parents out from Wisconsin—the extent of their previous international travel was Cancun and Niagara Falls,” he says. “I think it was neat for them to see how comfortable it is in Malaysia.”

“STUDENTS [AT PERDANA] ARE NOT USED TO BEING CONSIDERED COLLEAGUES OF THE FACULTY,” NOTES SOSNAY. “THEY ARE ALSO UNFAMILIAR WITH THE SOCRATIC METHOD OF TEACHING.”
How often are you on campus these days and what does your work entail?
I'm usually here two days a week, and I do a lot by phone. Interestingly, I'm meeting with quite a few people who are looking for career advice. They are wondering, What should I do next in my career? And it's not just the docs but administrators too, or lawyers, or people who might have some opportunities: Should I stay, should I go? What's the advantage? All those nuts and bolts kinds of questions. They just want some help sizing up the opportunities.

What’s your involvement with the Armstrong Institute for Patient Safety and Quality?
I’m active on the board, and I’m also serving as honorary chair of the planning committee for the Forum on Emerging Topics in Patient Safety that we will host September 23–25. We’re bringing together leaders from health care and other industries around the country, as well as experts from the World Health Organization, NASA, and Consumer Reports’ Health Ratings Center to discuss the most important issues in patient safety today.

You’re also on the board of the Brain Science Institute. Any new developments there?
I attend many meetings lately where we are trying to put together a sustaining funding source for the Brain Science Institute. It’s important work.

When you “retired,” turned off the lights and went home, was that change immediate or did it take some time before you fully realized you were in charge of your own schedule again?
A lot of people gave me the advice not to take on too many responsibilities, so I didn’t. I sit on a total of four boards. That work comes in quarters so their agendas all occur at the same time of year. My work with the University of Virginia board consumed much more time than I expected. I’m on the board of visitors for the entire university. I’m also the chairman of the trustees that oversee the medical center, so I do weekly phone calls with them. I’m on the investment committee as well. UVA has a very large $5.4 billion endowment, considering it’s a public institution. The first members of their board of visitors included Thomas Jefferson, James Madison, and James Monroe, so it’s quite a legacy to live up to.

Are there unique challenges on the UVA board?
Yes, it’s emblematic of what higher education is going through these days. How can you continue to raise tuition year after year, two to three times the CPI? Is that a sustainable business model? Are we training the students for the right needs for the future? I did not vote for a tuition increase this year. A 1.8 percent increase, which was inflation, seemed reasonable, but I wouldn’t vote for a 3.9 percent increase. It does not make sense. If you continue to increase your revenue in this way, you will avoid facing hard choices.

I see undergraduate education exactly where medicine was 15 years ago. Up until then, we just kept raising prices. And now where are we? The hospital gets no increase this year. Medicare gets 1.8 percent and funding for Medicare will continue to decrease. The Accountable Care Act will continue to drive prices down so you can end up in a situation where instead of us going in the direction we should go, we’re being influenced by others to make some improper choices. The same thing will happen in undergraduate education to the kids in the middle. They can’t afford these huge tuitions.

Has anything from your earlier career in anesthesiology bubbled back to the surface?
I’m still active on the national level with the Foundation for Anesthesiology Education and Research. I received one of their early grants, as did Ron Miller who was the chief anesthesiologist at the University of California, San Francisco. Together, we were pretty instrumental in getting the American Society of Anesthesiologists to offer $1 million annually for small grants to fund young investigators. This has turned into a way for people to get their first grant. These are small grants—not an NIH-size grant. Just enough to get the hook in so people will be able to go and do other things. I think it’s important for the field.

If you could give President Obama one piece of advice on health care, what would that be?
Well, the thing he didn’t do that he might have done, should have done, but didn’t politically do, is to change Medicare from fee-for-service to population health.

Everything is keyed off of Medicare—everything. This includes reimbursements and regulations. The Blues follow what Medicare does; Medicaid follows Medicare. There are some pilot projects and we have some of those, but if you stay on fee-for-service you’re never going to get the costs under control and you’re not going to improve quality. Interview by Michael Keating
From Leeches to Lasik

Semba’s new work catalogs William H. Wilmer’s “spectacular” collection of ophthalmology books.

Deep in a subbasement of the Wilmer-Woods Building is a small library that houses what Richard Semba calls “the most important specialty book collection of its kind in the world.” Semba, the W. Richard Green Professor of Ophthalmology at the Wilmer Eye Institute, is referring to the rare book collection of William Holland Wilmer, the founder and first director of the eponymous institute and a passionate bibliophile. Wilmer collected books that traced the scientific discoveries leading to our modern-day understanding of vision and the treatment and prevention of eye diseases. In 1936, shortly before his death, he bequeathed his collection to the Institute.

“There are other collections of rare books on ophthalmology, but Wilmer’s is spectacular,” says Semba. In 1999, in an effort to share Wilmer’s literary treasure trove with the public, Semba—along with Kristine Smets, “one of the best rare-book catalogers in the world”—began curating the collection. The result of their labors, A Perfect Vision: Catalogue of the William Holland Wilmer Rare Book Collection, was published in July, and contains detailed, technical descriptions of each of the more than 400 texts in the collection.

The swath of topics covered by Wilmer’s collection and the stories behind them open up a world of behind-the-scenes Renaissance drama. For example, Christoph Scheiner, a Jesuit priest and astronomer, observed sunspots in 1611. His book on sunspots, Rosa Ursina sive Sol, published in 1620, greatly angered Galileo, who claimed he discovered sunspots. There are also books dedicated solely to the optic nerve, the making of eyeglasses, the beginnings of Braille, and the (correct) theory (by Johannes Kepler) that the retina—and not the lens—receives and transmits visual stimuli. There’s even a guide on how to make an appointment with a famous German ophthalmologist who treated patients for free.

The rarest book in the collection is a treatise on color, written by a Portuguese diplomat and published in Malta in 1787. “I was only able to locate two other copies; they’re in Portugal and they’re in very bad condition. Wilmer’s is in very fine condition,” says Semba, a bibliophile and book collector in his own right.

Importantly, Wilmer’s collection contains what’s known in the rare book world as “incunabula.” “Incunabula are books printed before the year 1501,” says Semba. “Wilmer had 13, which is incredible. If you have these, it’s like saying you own Old Master paintings.” The oldest book in Wilmer’s collection—an “incunabulum”—is Peter of Limoge’s De Oculi Morali, published prior to 1476, and a shining example of Johannes Gutenberg’s invention of movable type, invented about two decades prior.

“It’s really humbling to go through these books, because you realize that some of these books are by some of the greatest scientists that ever lived,” says Semba. Erin Montgomery
from the Stanford University Medical Alumni Association. Nathans has also been named a Gilman Scholar—a distinction recognizing the best of the best at Johns Hopkins University.

Jeffrey Palmer, professor and director of the Department of Physical Medicine and Rehabilitation, has been named editor-in-chief of the new, online-only journal Current Physical Medicine and Rehabilitation Reports.

Peter Pronovost, professor of surgery, and of anesthesiology and critical care medicine, and director of the Armstrong Institute for Patient Safety and Quality, has been named a Gilman Scholar, a distinction recognizing the best of the best at Johns Hopkins University.

Peter Rabins, professor of psychiatry and behavioral sciences and co-director of the Division of Geriatric Psychiatry and Neuropsychiatry, has received the American Psychiatric Association’s 2013 Jack Weinberg Memorial Award for Geriatric Psychiatry.

Geraldine Seydoux, professor of molecular biology and genetics, has been elected to the American Academy of Arts and Sciences. Seydoux, a 2001 recipient of a MacArthur Foundation “genius” award, is renowned for her research into the complex development of an embryo to adulthood, based on her studies of this process in the roundworm C. elegans.

Patricia Thomas, professor of medicine, associate dean for curriculum, and associate director of the Osler Housestaff training program, and April Fitzgerald, instructor of medicine, have been honored by the Society of General Internal Medicine. Thomas received the 2013 Career Achievement in Medical Education Award and Fitzgerald won the Association of Chiefs and Leaders in General Internal Medicine’s leadership award.

Dean F. Wong, professor of radiology, psychiatry, neuroscience, environmental health sciences, and business, has received the Society of Nuclear Medicine and Molecular Imaging’s 2013 Paul C. Aebolsted Award for his three decades of contributions to the application of basic science to nuclear medicine.

Jonathan Zenilman, professor of medicine, and of obstetrics and gynecology and chief of the Infectious Diseases Division, has been named the 2013 recipient of the Distinguished Career Award from the American Sexually Transmitted Diseases Association.

12 Million Nucleotides Strong

Building the first synthetic yeast genome requires strength in numbers.

In July, Jef Boeke, professor of molecular biology and genetics in the Institute for Basic Biomedical Sciences, traveled to London for an international meeting on a project near and dear to his heart: the building of the first synthetic yeast genome. “Rumor has it microbrew beer samples will be available—as [they] should be for a yeast meeting. See you in London?” was the lighthearted message on the home page of the Second International Synthetic Yeast Genome Consortium Meeting, known as Sc2.0.

Turns out that yeast is more than just a necessary ingredient for beer- and bread-making. It has the potential to be “designed” to produce drugs or new types of fuel. But why yeast? “Yeasts are organized much like mammalian cells,” explains Boeke, who launched the yeast genome project more than five years ago. “Unlike bacteria, which have circular strands of DNA, both yeast and mammalian cells have linear strands of DNA and nuclei.” Yeast’s similarities to mammalian cells could make it the key to ushering in the next generation of gene therapy and disease cures in humans.

In recognition of his pioneering synthetic biology work, Boeke was inducted into the National Academy of Sciences last spring, one of 84 new members elected in 2013. Best known for revealing how mobile yeast and human transposons, or “jumping genes,” move around the genome, Boeke has been asked to serve on the National Academy’s Forum on Synthetic Biology.

Constructing a yeast genome—made up of 16 chromosomes containing 6,000 genes and 12 million nucleotides long—requires a lot of teamwork. More than 100 scientists from around the world, including China and the United Kingdom, are helping to build it. Many of these scientists met at Sc2.0 to discuss their progress. “About 50 percent of the DNA is synthesized, and about 20 percent of it is in the yeast and functioning,” Boeke reported upon his return from the conference, noting that he and his team—including key Hopkins collaborators Joel Bader and Srinivasan Chandrasegaran—plan to finish construction by 2017.

Hopkins undergraduates, professors, and even a few exceptional high school students have also joined in the effort, through Boeke’s Build-A-Genome course, going into its sixth year at Johns Hopkins University this fall. After boot camp, each student is given the keys to the lab and assigned 10,000 base pairs or more of the genome to synthesize. As segments of the genome are assembled, the researchers install them in yeast cells in place of the pieces of native DNA. “It’s like editing a book, instead of writing it from scratch,” Boeke explains. “We’re taking what nature gave us and fine-tuning it.”
Doctors have come a long way in treating brain aneurysms over the past several decades, says Hopkins neurosurgeon Alex Coon.

Surgeons are now able to avoid the risks associated with open surgery by using a process known as “coiling,” which involves threading a long, thin platinum wire from an artery in the groin all the way up to the aneurysm in the brain. There, the wire is “coiled”—packed into the aneurysm so that it fills the pouch. If all goes well, the coiled platinum induces a clotting response, which closes off the aneurysm.

Coiling has greatly advanced aneurysm treatment, Coon says. “It’s superior to open surgery in terms of duration of the procedure, not needing to open the skull, and recovery times,” he explains. “But the downside is that there’s a high recurrence rate.”

In about 10 to 30 percent of cases, he says, the clot dissolves and the aneurysm reappears. The risk is even greater for very large aneurysms, which have recurrence rates of up to 50 percent.

However, a new procedure offered at Johns Hopkins could prevent recurrence for all sizes of aneurysms. It involves placing a very flexible, thick mesh stent in the blood vessel. These stents, which resemble miniature Slinky toys, prop open the blood vessel and divert flow away from the aneurysm. Over time, Coon explains, reduced flow to the aneurysm causes it to clot off and eventually close on its own.

Although the procedure can take weeks or months to work, far longer than the nearly instant results from coiling, the stent offers the possibility of permanently removing the aneurysm. “This device offers a cure, with no recurrence,” Coon says.

Over the short time that this stent, known as the Pipeline Embolization Device, has been offered in the United States, Johns Hopkins has been one of the leaders in performing this surgery, Coon says. He and his colleagues have placed more than 150 of the stents in patients and traveled around the country teaching the technique to other physicians.

Coon was recently joined by a new colleague, Geoffrey Colby, who trained at Johns Hopkins for his neurosurgery residency as well as a fellowship in techniques that allow problems in the brain to be treated through instruments fed through blood vessels elsewhere in the body. “Having a larger team,” Coon says, “will make this therapy even more accessible for our patients.”

Christen Brownlee

Although the procedure can take weeks or months to work, the stent offers the possibility of permanently removing the aneurysm. “This device offers a cure, with no recurrence,” says Coon.
Osteoarthritis Progression Halted in Mice
Finding holds potential for avoiding joint replacement surgery.

Hopkins scientists have turned their view of osteoarthritis inside out. Literally. Instead of seeing the painful degenerative disease as a problem primarily of the cartilage that cushions joints, they now have evidence that the bone underneath the cartilage is also a key player and exacerbates the damage. In a proof-of-concept experiment, they found that blocking the action of a critical bone regulation protein [TGF-beta 1] in mice halts progression of the disease.

The prevailing theory on the development of OA focuses on joint cartilage, suggesting that unstable mechanical pressure on the joints leads to more and more harm to the cartilage—and pain to the patient—until the only treatment option left is total knee or hip replacement. The new theory, reported May 19 in *Nature Medicine*, suggests that initial harm to the cartilage causes the bone underneath it to behave improperly by building surplus bone. The extra bone stretches the cartilage above and speeds its decline.

“If there is something wrong with the leg of your chair and you try to fix it by replacing the cushion, you haven’t solved the problem,” says Xu Cao, director of the Center for Musculoskeletal Research in the Department of Orthopaedic Surgery. “We think that the problem in OA is not just the cartilage ‘cushion’ but the bone underneath,” he adds.

“Our results are potentially really good news for patients with OA,” says Cao. “We are already working to develop a clinical trial to test the efficacy of locally applied TGF-beta 1 antibodies in human patients at early stages of OA.” If successful, their nonsurgical treatment could make osteoarthritis—and the pain and debilitation it causes—halt in its tracks, he says. Cathy Kolf

When Exercise Can Be Deadly

Healthy people who carry a genetic mutation for the life-threatening heart disorder known as ARVD/C are at much higher risk of developing symptoms if they participate in endurance sports and frequent exercise, according to a new Hopkins study. The good news, according to the study, published in the July 17 *Journal of the American College of Cardiology*: Carriers who significantly cut back on their exercise regimen may reduce their risk or delay the onset of symptoms.

An inherited disorder, ARVD/C is one of the most common causes of sudden death in athletes and young, apparently healthy adults. Its prevalence is estimated at one in 5,000 people.

Getting Aggressive

Although prior studies of prostate cancer have found it safe to delay treatment and monitor some presumably slow-growing or low-risk cancers, such “active surveillance” does not appear to be a good idea for black men, according to a new Hopkins study.

Researchers found that African-Americans diagnosed with very low-risk prostate cancers are much more likely than white men to actually have aggressive disease that goes unrecognized with current diagnostic approaches.

“This study offers the most conclusive evidence to date that broad application of active surveillance recommendations may not be suitable for African-Americans,” says Hopkins urologist and study co-author Edward M. Schaeffer. “It turns out,” he adds, “that black men have a much higher chance of having a more aggressive tumor developing in a location that is not easily sampled by a standard prostate biopsy.” The study appeared in the *Journal of Clinical Oncology*. 
Medical Rounds

A New Weapon Against Leukemia

Promising drug clears cancer from bone marrow in hardest to treat cases.

Dorothy Schilder considers herself pretty healthy. The McLean, Va., resident exercises regularly and follows a Mediterranean diet. So when she noticed a few nagging problems in the fall of 2011—a sinus infection, bruises, a rash on her face—she chalked them up to just being worn down.

After her mother, a nurse, urged her to get blood work, she went straight from an exercise class to her doctor’s office, only to be told that what she thought was a mild health issue was in fact acute myeloid leukemia (AML). Her doctor booked her right away with an oncologist, who quickly got her into a chemotherapy program. Although treatment appeared to be working, says Schilder, 49, “I had this feeling something wasn’t going right.” When she relapsed a few months later, she was referred to Johns Hopkins Kimmel Cancer Center.

Shortly thereafter she encountered oncologist Mark Levis, who was directing a multicenter phase II clinical trial of a drug he helped develop called quizartinib that blocks a gene called FLT3-ITD. In healthy people, FLT3 produces an enzyme signaling bone marrow stem cells to divide and replenish, but in a quarter of AML patients, the disease mutates FLT3 so it stays on permanently, causing rapid growth of leukemia cells and making the condition harder to treat.

Survival for patients like Schilder, with relapsed FLT3-ITD AML who have failed to respond to conventional treatment, is “near zero,” Levis says.

“A FLT3-ITD mutation tells us that, typically, patients will need very intensive chemotherapy just to achieve a remission, and then the disease will regrow quickly,” Levis says, “so we have learned to try to perform a bone marrow transplant soon after we get the patient into remission, before the cancer relapses.”

The new drug, available in oral form, is so potent that it typically starts working in just two days, though it may take up to 60 days to reduce the AML cells to a very low or undetectable level in the bone marrow.

Schilder enrolled in the trial, and did so well that she qualified for a bone marrow transplant, performed last November. Other trial participants fared well, too. Leukemia was completely cleared from the bone marrow in more than a third of the 137 participants, many of whom also moved on to potentially curative bone marrow transplants despite failing prior therapies.

“It caught us by surprise how well [the drug] works,” Levis says.

Levis presented results of the phase II study at the American Society of Hematology meeting, and is working with colleagues at the Eastern Cooperative Oncology Group to plan a phase III trial. Long-term survival from the therapy is still unknown, but some patients have survived two years after treatment with no disease recurrence.

As for Schilder, who for now remains on another cancer-fighting drug called sorafenib, “the odds were very much against her, but they’re not anymore,” Levis says.

 Says Schilder, “I’m just so blessed and grateful, and I’m anxiously awaiting [FDA] approval of the drug.”

Karen Blum

Don’t Worry, Be Healthy

A happier temperament could reduce chance of heart attack.

People with cheerful temperaments are significantly less likely to suffer a heart attack or sudden cardiac death, new Hopkins research suggests.

Previous research has shown that depressed and anxious people are more likely to have heart attacks and to die from them than those whose dispositions are sunnier. But the new study shows that a general sense of well-being—feeling cheerful, relaxed, energetic, and satisfied with life—actually reduces the chances of a heart attack.

“A happier temperament has an actual effect on disease and you may be healthier as a result,” says study leader Lisa R. Yanek.

Yanek cautioned that cheerful personalities are likely part of the temperament we are born with, not something we can easily change. While some have suggested that happy people are also more likely to take better care of themselves and have more energy to do so, Yanek says her research shows that those with higher levels of well-being still had many risk factors for coronary disease but had fewer serious heart events.

The mechanisms behind the protective effect of positive well-being remain unclear, Yanek notes, but her research offers insights into the interactions between mind and body, and could yield clues to those mechanisms in the future.

Stephanie Desmon
Thousands of children and adults who were once in liver failure are alive today because of live donor liver transplantation (LDLT). Yet in recent years, interest in LDLT as a viable alternative to cadaveric donation has waned. In part, that’s likely because of the emergence, in 2002, of a prioritized national model scoring system for wait-listed liver recipients. Those patients with higher MELD (model for end-stage liver disease) scores based on the urgency of their condition—bilirubin and creatinine levels and prothrombin time—can receive cadaveric livers sooner. Even so, the average wait time for a cadaveric liver donation in the United States is 149 days for adults and 86 days for children.

But for those whose MELD scores haven’t risen high enough, a healthy, appropriately matched live donor can shorten the recipient’s wait time significantly, says Ahmet Gurakar, medical director of liver transplantation at Hopkins Hospital.

Though LDLT surgery is technically more complex, he says, “our experienced team does a rigorous workup, and only after the donor has been deemed a good match surgically and psychologically will we consider doing the operation.” Still, ever since a highly publicized donor death in New York in 2002, perceived high risk of mortality to living liver donors persists.

So is it really safe for potential donors to donate part of their livers? In skilled hands and with standardized protocols the answer is yes, says Gurakar. According to a widely cited 2012 study published in Gastroenterology by transplant experts at Hopkins Hospital, including Nabil Dagher, the mortality of live liver donors does not differ from that of healthy, matched controls during a mean of 7.6 years.

“From the moment a potential donor is identified, our program is exceptionally attuned to that person’s safety,” says Dagher, live liver donor surgical director at Hopkins. Each case is discussed among a team that includes a hepatologist, surgeon, transplant coordinators, living donor advocate, social worker, psychologist, and nutritionist. In all, the process takes between three and four weeks. The age cutoff for adult donors is 60.

After the surgery, it takes about three months for the donor’s liver to regenerate. Roughly 30 percent of the liver is taken from an adult for a child recipient; about 60 percent is resected in adult-to-adult donation. “The liver is a wonderful organ,” says Dagher. “Once a portion of it has been resected, it immediately starts to regenerate and stays in tune with the metabolic needs of the body.”

Johns Hopkins has been performing LDLTs since 1992, and the program recently has been reinvigorated with the addition of Gurakar, Dagher, and Ayman Koteish, live liver donor medical director. Since January 2012, the team has already performed four successful LDLTs—three adult to child; one adult to adult. Most recently here, a firefighter donated part of his liver to his infant daughter. He was back to work in two months, says Gurakar, and he and his daughter are doing well.

That’s the amount that could be saved immediately in the U.S. if ER physicians stopped the routine and excessive use of head CT scans to search for stroke in dizzy patients, according to a report by Hopkins researchers that appeared in the July issue of Academic Emergency Medicine.

“We need our emergency physicians to be able to confidently identify patients with benign ear conditions who can be safely treated and sent home, without imaging,” said Hopkins study leader David Newman-Toker. “Accurately and efficiently separating inner-ear patients from the other dizzy patients who probably have strokes will save lives and money.”

On the Web:
To find out more about living donor transplantation, watch a Q&A with Nabil Dagher at: http://www.hopkinsmedicine.org/transplant/programs/liver/living_donor/
I didn’t grow up playing with a stethoscope, or dreaming of being a medical student. I headed to college to pursue my interest in language and travel. The intrigue of authoritarian dictatorships and economic development in Latin America captured my interest first in college and eventually as a doctoral student.

Sometimes life has twists in store for us, however. Somewhere between Juan Peron’s Argentina and the Mexican Debt Crisis, I realized I wanted to incorporate a more tangible human component into my everyday life. The idea of entering medicine came to me piecemeal through shadowing and speaking to those in the medical field. But when it came to committing to the medical path and completing premed requirements, I had to strike a careful balance between my work as a PhD student and the basic science courses necessary to prepare for medical school.

It’s a story familiar to many non-traditional students in medicine. When inspiration from a previous career leads us to medicine, how can we navigate the road that more traditional premed students have doggedly been following since their first year in college?

The cornerstone of preparation for medical school in recent years has been completion of an undergraduate program and specific courses from the basic sciences. Students must then complete the Medical College Admissions Test, or MCAT—a test that helps differentiate between applicants with near-perfect grades, college leadership positions, and shadowing experience.

In 2015, the Association of American Medical Colleges (AAMC) will be introducing a substantially different MCAT. In addition to the chemistry, biology, and physics questions on the current exam, the new MCAT will test material taught in introductory psychology, sociology, and biochemistry. The purpose of the new emphasis on social and behavioral sciences, according to AAMC President and CEO Darell G. Kirch, is the recognition that “being a good doctor is not just about understanding science … it is also about understanding people.”

At its core, the initiative to recruit broadly trained students shows insight into the more humanistic and less tangible aspects of medicine, offering opportunities for students trained across the liberal arts to showcase strengths that lie outside premedical science courses.

Nonetheless, adding introductory psychology is only one very specific method of assessment.

When I decided to pursue medicine in my mid-20s, I had never taken a single psychology, sociology, or biochemistry course. I started the long medical career trajectory later than most students knowing that I could finish the premedical course work in two years. Had I been required to take courses or pass an assessment in the additional subjects of psychology and sociology, it would have added another year and thousands more dollars to my career path—and I might have given up before I started.

In this way, the new MCAT puts a particularly difficult burden on exactly the students the AAMC hopes to attract—those who have a broad range of interests and who spent their college careers, and perhaps a few years after college, pursuing important passions. Students who worked in the Peace Corps or Teach for America and majored in music or language or even political science will be a few critical steps further away from careers in medicine.

My own experience is not unique.

Indeed, more than half of my classmates in the Class of 2016 here at Hopkins took at least one year off between college and medical school, and many transitioned from different careers entirely. Often their career paths allowed little room for additional courses either as a college student or while in the workforce.

The new MCAT represents an important shift, and the AAMC should be credited for its insight. But introductory sociology isn’t the only place that students get perspective on the world; it’s simply one of the easiest skills to measure. The medical school interview has long served as a useful way to gauge the personal characteristics and values of applicants. What will be demonstrated on the new MCAT that would not have been demonstrated in an interview?

While the value of psychology and sociology training for future medical students is indisputable, so too is the reality that additional training could deter talented applicants. *
Eugenics “is no longer a sticky, noisome residue to be scrubbed off the skin of human genetics before it can go medical,” writes Comfort.
The cover of Hidden Beauty includes a stunning photograph of multicolored items resembling burnished charms. They are unquestionably beautiful—yet they’re actually gallstones, excruciatingly painful crystalline deposits removed from the gallbladders of patients.

“As caretakers, researchers, and photographers working in a busy academic setting, every day we are faced with images that are awe inspiring for their beauty and for the terror they may represent to our patients suffering from disease,” writes Christine Iacobuzio-Donahue, professor of pathology, oncology, and surgery, and co-author of Hidden Beauty with Norman Barker, associate professor of pathology and art as applied to medicine. “The idea that disease with all its negative ramifications can still have aspects of beauty intrigued me,” Iacobuzio-Donahue writes. “After all, the human body truly is a thing of beauty and wonder!”

Barker, who has spent 30 years helping physicians and scientists visualize their research, had a similar epiphany early in his career. He writes that as a young medical photographer just out of art school, he was “asked by a pathologist to photograph a bloody kidney specimen in the autopsy room. The physician told me to make sure that it’s ‘beautiful’ because it was being used for publication in a prestigious medical journal. I can remember thinking to myself; this doctor is crazy, how am I going to make this sickly red specimen look beautiful? Of course I did the best I could and the image was published, but I learned a lot from that experience. There truly is beauty in everything, although sometimes it might be in the eye of the beholder.”

Enlisting 60 colleagues—50 of them from Hopkins—Barker and Iacobuzio-Donahue have compiled an astonishing assortment of images. These include photos encompassing every aspect of the human body, from the head and neck to the chest, abdomen, pelvis, and connective tissues, as well as pictures of infections, inflammations, and research efforts. Each is accompanied by a concise explanation of what the image depicts and its importance. Also included are some magnificent drawings by Max Broedel (1870–1941), founder of the Department of Art as Applied to Medicine. NAG

Hidden Beauty: Exploring the Aesthetics of Medical Science
Norman Barker, MS; Christine Iacobuzio-Donahue, MD, PhD (Schiffer, 2013)

More Books

Living with Itch: A Patient’s Guide
Gil Yosipovitch, MD; Shawn G. Kwatra, MD (Johns Hopkins, 2013)

Just reading the word itch can make many people want to scratch.

Whether referred to by its medical designation, pruritus, or the layperson’s more common term, itch, this often-chronic, sometimes maddening, frequently painful, and virtually universal affliction affects millions of people and has done so since time immemorial.

Yet despite being the principal symptom of most skin diseases, as well as linked to many systemic conditions such as liver disease, renal failure, hematologic abnormalities, and autoimmune and endocrine disorders, itch was until the mid-1990s what often is referred to as an “orphan disease”—neglected, rarely researched, and absent a widely effective treatment, such as aspirin is for pain.

Into this void stepped Gil Yosipovitch, founder of the International Forum for the Study of Itch and head of the Department of Dermatology at Temple University, and co-author Shawn Kwatra, who spent a year as a dermatology resident at Johns Hopkins.

Together, Yosipovitch and Kwatra have produced a clearly written, extremely useful, and admirably compact book (just 140 pages) that in 15 brief chapters covers everything from the definitions and mechanisms of itch, to the types of itch from which people suffer, to what treatments are available for the wide array of torments it inflicts—from eczema (atopic dermatitis) to hives (urticaria), psoriasis, and other conditions.

Also featured are moving testimonials from individuals who have endured intractable itch themselves or watched family members or others suffer from it, as well as a list of resources, such as the names of associations for people with specific skin conditions, and a helpful glossary.

No “simple remedy” exists for treating chronic itch, Yosipovitch and Kwatra write, but “there are many things people can do right now” to alleviate their suffering. The authors offer advice on how to prevent some forms of itch without medications, as well as describe topical and systemic treatments for itch. Some of the measures may sound like folk remedies—among them sleeping in wet pajamas underneath a dry pair—but there is solid scientific evidence on why they can work. For the topical and systemic treatments, the authors also provide itemizations of possible side effects. NAG
Today, millions of individuals owe their arrival on Earth to clinical in vitro fertilization (IVF)—but few are aware of the pivotal role Johns Hopkins played in the initiation of this important medical advance nearly a half century ago.

I was there and participated in it. I’m happy now to provide the inside story of how Johns Hopkins became the birthplace of the breakthrough that ultimately led to what later became known popularly (but completely erroneously) as “test tube” babies.

The story begins in 1963, when a young British physiologist, Bob Edwards—who would become the Nobel Prize-winning Sir Robert Edwards—joined the Department of Physiology at Cambridge as a Ford Foundation research fellow. Bob would continue his association with that department until his retirement, rising to the rank of full professor in a position created especially for him. (Bob passed away last April at the age of 87.)

Bob had become intrigued by a report from reproductive biologist M.C. Chang of the Worcester Foundation of Experimental Biology in Shrewsbury, Mass., who had successfully fertilized a rabbit egg in vitro. Building on earlier work by French reproductive biologist Charles Thibault, Chang observed the presence of two pronuclei. (One pronucleus contains the genetic message of the father and one contains the genetic message of the mother.) He showed this to be proof positive of fertilization. He reported that an alternate proof of in vitro fertilization could be seen that would not require transfer of the zygote and the birth of rabbit pups. Instead, if one found two pronuclei and also saw the tail of a sperm embedded in the cytoplasm (the jelly-like substance that fills the cell), this would suffice as incontestable proof of fertilization.

This latter criterion—the need to see the tail of a sperm in the cytoplasm—ended up being of great significance in the work that Bob Edwards would do at Hopkins.

Chang had undertaken additional research. He reported that an alternate proof of in vitro fertilization could be seen that would not require transfer of the zygote and the birth of rabbit pups. Instead, if one found two pronuclei and also saw the tail of a sperm embedded in the cytoplasm (the jelly-like substance that fills the cell), this would suffice as incontestable proof of fertilization.

Soon after Bob arrived at Cambridge in 1963, he was prompted by Chang’s report that IVF could be accomplished in a rabbit to try attempting it in a mouse. He also became obsessed with the notion that IVF could be—and should be—applied to humans. For that, he would need human oocytes.

He contacted every obstetrical and gynecological specialist in the Cambridge area and was disappointed to discover that he could find no one who thought that it was feasible to supply him with human oocytes.

He expanded his search and had a response from Molly Rose, a London obstetrician who had delivered two of Bob’s daughters while he was at Mill Hill near London. She did supply a few human oocytes to Bob—albeit
only one at a time and at infrequent intervals. Furthermore, Bob had to travel from Cambridge to London, pick up the oocyte, return to Cambridge and expose the oocytes to human sperm. He did this five times and had no indication in any of the oocytes that fertilization took place.

Bob’s wife, Ruth, shared his frustration with obtaining so few specimens and suggested that he contact Victor McKusick ’46, then chief of Genetics at the Johns Hopkins School of Medicine, and ask whether it would be possible for him to obtain human oocytes if he came to Hopkins. Bob wrote to Victor, who on receiving the letter referred it to me.

I then was a member of the Department of Gynecology and chief of Hopkins’ Crytogenetics Laboratory and replied through Victor that I thought it was entirely possible that a supply of human oocytes could be obtained at Hopkins. This was because at that time a therapy for polycystic ovarian disease (PCO), a relatively common endocrine disorder, was wedge resection of the ovaries. We were doing one or two of these wedges per week, and it seemed perfectly feasible to give Bob a portion of the wedge.

A normal ovary weighs about 8 grams, the polycystic ovary averages about 30 grams, and the wedges usually weighed about 10 grams. It seemed to me that if we could give Bob half of a wedge, he would have about 5 grams of ovarian tissue. The remaining half was required for pathological examination.

This, in fact, was the protocol adopted—after much discussion—when Bob arrived in Baltimore in July 1965 and joined Hopkins as a fellow. He was able to tease eight to 12 oocytes from the one half of each removed wedge. Although most of the oocytes came from the patients with PCO, a few whole ovaries became available from patients who required ovary removal for a variety of reasons.

Bob would place the liberated oocytes in culture medium and allow them to mature overnight (i.e., go to Meiosis II, at which stage fertilization is possible). Indeed, human oocytes did “spontaneously” mature. The “spontaneous” maturation phenomenon in the human oocytes was the subject of the first paper from Bob’s work at Hopkins.

In addition to the maturation of the oocyte to M II, Bob was very keen that we figure out a way to capacitate—or enable—the sperm to do its job.

Chang and Australian Collin Russell “Bunny” Austin had independently discovered—using the rabbit—that freshly ejaculated sperm were not capable of fertilizing a mature rabbit egg. They showed that if these sperm stayed in the fallopian tube of the rabbit from eight to 10 hours, they acquired the capacity to achieve fertilization.

Bob and I and others in our group had many discussions on how to accomplish capacitation in our experimental model. Bob came up with the notion that we try placing small pieces of the human female genital tract in the culture tube. My role was to furnish such samples.

It was necessary to have a negative control so we used 36 oocytes for this purpose. The sperm were washed with saline by what we now call a “swim-up.” Then we placed the sperm in the culture tube with the liberated eggs.

In retrospect, the results are interesting. After 24 hours in culture, 17 of the 36 oocytes did not mature. They still had a germinal vesicle, or an enlarged nucleus that had not completed its division. Seven degenerated. Twenty-six did mature to M II and therefore were ready for fertilization, but were unfertilized. However, three others had two beautiful pronuclei and one had four pronuclei. Great efforts were made to find sperm tails. None could be found.

There was much discussion about these pronuclei. If they were not real pronuclei, what were they? Since it was thought that it was impossible for a saline wash to capacitate the sperm, the matter was closed by a shrug of the shoulders. In retrospect, we now know that a saline wash will capacitate human sperm. (This assumes that capacitation in the human is really required; there still is some uncertainty about that point.)

What we thought was a negative control turned out to be a positive control.

Of course, we didn’t know it at the time, so we continued our experiments.

Decades after they collaborated in the lab at Hopkins, Howard W. Jones (left) and Sir Robert Edwards enjoyed a jovial reunion.
We tried sperm that had penetrated human cervical mucus at mid-menstrual cycle, thinking that this possibly could cause capacitation. Seven M II oocytes were exposed to such sperm but no fertilization could be observed—that is, we had no cells with two pronuclei.

There became available a human fallopian tube removed on the 17th day of a menstrual cycle. Scrapings from this tube were put in the culture medium. Of 20 oocytes, 15 went to M II and of these, two had two pronuclei—but no sperm tails.

We also undertook a series of experiments aimed at achieving capacitation of the human sperm using the rabbit. In these efforts, we placed sperm in the rabbit’s uterus for various lengths of time and then recovered them by irrigation. Some 118 oocytes were used in the rabbit experiments. There were three oocytes that may have had vanishing pronuclei, but it was not possible to confirm this by fixation and microscopic examination.

After Bob’s time was up in Baltimore he returned to Cambridge, but we continued our research at Hopkins. When five macaque monkeys became available, we placed a total of 67 mature oocytes with human sperm in the fimbria of the monkeys (with the help of Ted Baramki). This was what we now call a GIFT procedure. At intervals of 12 to 18 hours after the injection of the gametes, a hysterectomy and bilateral salpingectomy was done and an attempt was made to flush the specimens. In all, only two unfertilized oocytes were recovered. What the monkeys do with human gametes remains a mystery.

The experiments that I have just described were published in the September 1966 issue of the American Journal of Obstetrics and Gynecology under the title “Preliminary Attempts to Fertilize Human Oocytes Matured In Vitro.” We called our results “preliminary attempts” because we didn’t realize that the pronuclei alone were sufficient evidence of a successful in vitro fertilization.

As it turns out, we did not need to see a sperm tail in the cytoplasm. We had succeeded in achieving the first in vitro fertilization of a human egg—but we didn’t know it.

Back in Cambridge, Bob must have sensed that our work at Hopkins was crucial to what he sought to accomplish. In his 1980 book, A Matter of Life: The Story of a Medical Breakthrough, Bob says that he left Baltimore “exultant,” and refers to his experiences at Hopkins as “decisive.”

Bob persisted, and finally, with gynecologist and obstetrician Patrick Steptoe, he succeeded in overseeing the normal birth of the world’s first-ever IVF baby, Louise Joy Brown, in the United Kingdom on July 28, 1978. Three years later, with my late wife Georgeanna Seegar Jones ’36, we succeeded at our Jones Institute of Reproductive Medicine at Eastern Virginia Medical School in ushering into the world the United States’ first IVF baby, Elizabeth Carr, on December 28, 1981.

Bob’s work finally was recognized in 2010 when he was awarded a Nobel Prize in medicine. Those of us who knew the details of the studies initiated at Johns Hopkins in 1965 were disappointed that it took the Nobel Committee so long to bestow this award, which was well-deserved and should have been given to Bob much earlier.

After Bob received the Nobel Prize, a plaque commemorating his work in Baltimore was placed in Hopkins’ Department of Obstetrics and Gynecology. IVF was born because of its inception—one could say its fertilization—with 268 human eggs at Hopkins.


Howard Jones, wife Georgeanna Seegar Jones, and Edward Wallach reminisced about the rich accomplishments of Obstetrics and Gynecology at Hopkins during the 1987 Biennial Reunion.

Photo by Peter C. Howard
Safe Keeping

Preserved and frozen in time, the blood and tissue samples stored in Hopkins’ biorepositories hold myriad clues to curing disease.

By Judith F. Minkove
Illustration by Michael Glenwood
Last spring, when 16-year-old Angela Sanborn began to feel pain shoot through her groin, doctors attributed it to muscle strains from her regular gym workouts. But as the pain intensified and her leg swelled and turned purple, the Florida teenager was sent to All Children’s Hospital in St. Petersburg, a member of the Johns Hopkins Health System. Doctors there detected and successfully treated a blood clot, aka deep vein thrombosis, which extended from the deep veins of Angela’s calf to the inferior vena cava in her abdomen.

A few weeks later, when she returned to All Children’s for a follow-up visit, Sanborn discovered that her experience could wind up helping others. By providing blood and fluid samples for future biomarker studies, she might aid researchers in unlocking clues about the most effective ways to treat deep vein thrombosis. Neil Goldenberg, her doctor and director of research at All Children’s, couldn’t have been more pleased by Sanborn’s offer to serve as a donor.

Ushering in a new era of personalized medicine, biomarker research focuses on matching the unique genetic characteristics present in blood, saliva, urine, cells, and tissue with the best available treatments. Johns Hopkins Medicine is at the forefront of these efforts, accumulating samples from patients who want to help further research.

Sanborn was the first patient to volunteer for one of Goldenberg’s large studies that span All Children’s in St. Petersburg and Hopkins Hospital in East Baltimore. His studies include investigations not only on thrombosis but on a host of other childhood diseases, and her donation is among the first specimens stored in All Children’s new, state-of-the-art biorepository.

Across the nation, hospitals are building such storage facilities to coral millions of biosamples, maintain uniform storage standards in cryofreezers, and sustain the samples’ integrity so they will remain viable for decades, notes Margaret “Sue” Penno, who has directed the Genetic Resources biorepository at Hopkins Hospital for the past 25 years. Currently she is also serving as interim director of All Children’s Hospital’s repository.

THINK OF A BIOREPOSITORY as a perpetually secure safe, one that’s stocked with patients’ blood, tissue, DNA, and RNA—important genetic information preserved, following strict industry standards. Penno is the bank’s maximum security guard, protecting the precious gifts of generous research subjects.

“The goal,” she says, “is always focused on the patient—to put a sample away securely for a time when we know more, so [patients] might benefit from future research.”

At Johns Hopkins, the quest to collect and store samples in a secure place began in 1989. Now Hopkins researchers are able to tap into hundreds of thousands of samples for cohort studies involving groups of people with common characteristics—who suffer from illnesses ranging from sickle cell disease to colon cancer. The biorepository on Blalock 10, which offers rapid retrieval from 12 large-capacity freezers, currently supports approximately 250 IRB-approved Johns Hopkins investigations and several dozen outside investigators.

Penno, a seasoned research scientist inspired by genetics legend Victor McKusick ’46, has spent the past three decades investigating how cells move, clump together, and divide in her studies of tumor cell metastasis and other pathologies. In the quarter-century since the biorepository opened on Blalock, Penno has tapped into the specimens for her own research, while
Think of a biorepository as a perpetually secure safe, one that’s stocked with patients’ blood, tissue, DNA, and RNA—important genetic information preserved, following strict industry standards.

also gaining insight into the science of specimen storage. Over the past four years, she and others on the Dean’s Biospecimen Task Force have been calculating how best to safeguard every aspect of biospecimen storage at Johns Hopkins.

Penno says her task is “like running a 24/7 day care center.” And just as each child is individual, various specimens require different temperatures and types of freezers, made safe by elaborate software and alarm systems. There’s a plan in place to keep samples safe from hurricanes, power outages, fires, or floods, such as occurred last fall at the Cancer Research Building in the aftermath of Hurricane Sandy.

This year, the Genetic Resources Core Facility (GRCF) Biorepository in Blalock was among the first to be recognized as a College of American Pathologists-accredited facility, offering superior services in cryopreservation, cryostorage, bioshipping, and bioprocessing, Penno and Melissa Olson, the facility’s new director, are working hard to achieve the highest possible standards. “We are proud to join the 20 or so laboratories worldwide that have received this accreditation,” says Olson. “It defines our commitment to offering the highest-quality standards for investigators.”

While pleased with the new accreditation honor for the Hopkins Hospital facility, Penno is also impressed with the progress on All Children’s biorepository—and with its research pipeline: 23 cohort studies are currently underway in neonatology, oncology, cardiology/cardiovascular surgery, and neuroscience. In one oncology study, for example, researchers are preserving specimens from tumors to examine the proteins in the DNA or RNA and test drugs that might prove effective.

Goldenberg, who directs All Children’s clinical and translational research as well as Hopkins Medicine’s pediatric thrombosis program, calls this a “momentous time” in the development of biorepositories. Pooling resources, he explains, helps researchers address a number of questions in the most efficient way and find key predictors of outcomes.

Penno currently travels to the Florida hospital every two weeks to chart the development of the new repository, a gleaming facility that uses robots to store samples, providing one more layer of protection against human contamination. All Children’s, Penno believes, is poised to become a premier pediatric academic program as it continues to recruit high-caliber scientists.

For Penno, one of the highlights of her regular trips to Florida is just riding the pediatric elevators. “As someone who never treats patients, I think it’s cool to see all these little kids. You never forget what you’re working toward,” she says.

Donations like Angela Sanborn’s, she adds, will drive research and help solve mysteries. “I think you can feel confident that there’s hope.” She pauses, then reiterates, “…so much hope.”

Sue Penno and Neil Goldenberg show off All Children’s new biorepository, which houses two automated (robotic) sample management systems (SAM). Each SAM holds 30,000 samples and can collect 15,000 tubes stored at various locations in the SAM and reconfigure them into one box in an hour.
Life is poised to get dramatically better for millions with hepatitis C, thanks to new treatments that promise a more effective cure, without the debilitating side effects.

By David Glenn
Photos by Christopher Myers
The new therapies are arriving at a crucial time, says Mark Sulkowski. “We’re just now getting into the peak of the impact of hepatitis C in the United States.”
One day in late 1995, David Frick began to suffer severe abdominal pain. A few months earlier, he had completed a PhD in biology at Johns Hopkins, and now he was doing a postdoctoral research fellowship on the Homewood campus, studying bacterial enzymes. When the pain hit, his first assumption was that it was appendicitis. He’d go under the knife, be away from his lab bench for a week or so, and then life would return to normal.

Or so he thought. A few days later, the diagnosis arrived: Frick had hepatitis C. He had probably acquired the virus from a contaminated blood product shortly after he was born, when he received transfusions to treat a rare disorder. After 20-odd years of silent destruction, the virus had caused extensive cirrhosis in his liver. He would need a transplant.

Two years later in Boston, where he was doing a postdoc at Harvard, Frick’s liver went into severe failure, and he received his transplant. It was a grueling experience, with long weeks in a hospital bed. “But the transplant year wasn’t the worst year of my life,” Frick says today. “The worst year of my life was the following year, when I went through the treatment for hepatitis C.”

After his transplant Frick needed to try to eradicate the virus from his body, so that hepatitis C wouldn’t ruin his second liver. That meant taking what was, in the late 1990s, the cutting-edge therapy for hepatitis C: 48 weeks of injections with interferon-alfa, a synthetic version of one of the body’s common antiviral proteins. Interferon-alfa carries brutal side effects: fevers, sweats, chills, depression, fatigue. “It felt like I had the flu for nearly an entire year,” Frick says. “I’m glad I did it—I’ve been perfectly fine ever since. But that was very, very tough.”

Frick, who now studies the hepatitis C virus (HCV) at the University of Wisconsin-Milwaukee, vowed to devote the rest of his career to hepatitis C until a more effective and tolerable cure was discovered. That moment appears finally to have arrived—thanks in part to decades of effort by Johns Hopkins researchers.

In the last three years, several new classes of drugs have emerged that directly target enzymes specific to the hepatitis C virus. As early as December 2013, the FDA might approve the first-ever interferon-free therapy for certain hepatitis C patients. Within a few years, says Mark Sulkowski, medical director of the Viral Hepatitis Clinic at Johns Hopkins, the standard treatment for hepatitis C might be just 12 weeks long—-or even eight—and involve no interferon. Even better, the new medications appear to be effective for almost everyone, whereas roughly 50 percent of patients have failed to respond to interferon-alfa.

“These have truly been breakthroughs,” says Sulkowski. “The treatment stands to become dramatically simpler, more effective, and easier to tolerate.” Sulkowski has waited a long time to see these victories. For nearly two decades, he has directed clinical trials of hepatitis C medications at Hopkins. While most of those drugs have been brewed in pharmaceutical companies’ private labs, Hopkins researchers have played a central role in testing their safety and efficacy, especially among vulnerable populations such as people co-infected with HIV and HCV.

The new therapies are arriving at a crucial moment, Sulkowski adds. “We’re just now getting into the peak of the impact of hepatitis C in the United States,” he says. Millions of baby boomers are believed to have been exposed to the virus via intravenous drug use, tattooing, and contaminated blood transfusions between 1965 and 1990. (Blood products have been screened for the virus since 1992, so transfusion is no longer a danger.) Because it takes decades for the virus to do its silent damage to the liver, the national rates of cirrhosis and liver cancer have only recently begun to spike upward. Each year since 2007, hepatitis C has been estimated to kill more Americans than HIV; liver cancer is one of the few types of cancer with a rising mortality rate.

“People say, [the virus] has a very slow progression rate,” Sulkowski says. “And that’s true. It takes decades to progress. But the peak infections in the U.S. occurred 30 or 40 years ago. So, now we’ve reached the time when many people are progressing. This is a major issue right now.”

When David Frick received his blood transfusions as an infant in the late 1960s, hepatitis C was an unknown concept. The year 1974 saw the first scientific publication about transfusion-related liver infections that were not caused by the familiar hepatitis A or hepatitis B viruses. But it took another decade and a half until the viral pathogen behind what was then known as “non-A-non-B hepatitis” was finally found. In April 1989, a pair of papers in *Science* announced the discovery and basic structure of the hepatitis C virus.

A year later, a young physician named David L. Thomas began a fellowship in infectious
Thomas, perhaps more than any other single scientist, helped alert the world to the severity of the hepatitis C problem. “We knew that it was a transfusion issue,” he says. “So it was natural to ask whether the virus could also be transmitted through other blood vectors.”

Sadly, the answer turned out to be yes. Throughout the 1990s, Thomas worked with Hopkins colleagues at the schools of Medicine and Public Health to document the alarmingly high rates of hepatitis C infection among IV drug users in Baltimore and other sites around the world. The team also studied sexual transmission (which turned out not to be a major vector), transmission during childbirth, and needle stick injuries among Johns Hopkins Hospital employees.

Those early needle stick studies became a vital source of information about the virus’s life cycle: Because Thomas and his colleagues knew almost the exact time of transmission, they could draw blood samples from the employees daily to learn how the virus evaded the human immune system during the acute phase of infection.

The studies also allowed Hopkins researchers to examine the mechanisms that allow a lucky minority of people—roughly 20 to 30 percent—to clear the virus from their systems without developing chronic infections. That line of research, which was led by Chloe Thio, an associate professor of medicine, and Priya Duggal, a geneticist at the Bloomberg School of Public Health, has helped lay the groundwork for potential vaccines.

After several years of study, a basic epidemiological portrait emerged. After exposure to the virus, between 70 and 80 percent of patients develop chronic infections. (More than 150 million people internationally, including 12 million in the United States, are now estimated to have chronic hepatitis C.) Of those chronic infections, between 15 and 30 percent will eventually cause liver cirrhosis, though that process can take as long as 30 years. And among hepatitis C patients who progress to cirrhosis, between 1 and 3 percent each year will develop liver cancer.

“The most alarming thing is that roughly half of the people with chronic hepatitis C in the United States have not been diagnosed,” says Scott Holmberg, chief of the epidemiology and surveillance branch of the viral hepatitis center at the Centers for Disease Control, which recently recommended that all Americans born between 1945 and 1965 be screened for the virus. “And among those who have been diagnosed, only a relatively small proportion have been treated, in part because the treatments have been so difficult to take.”

That will soon change. While his Hopkins colleagues have analyzed the virus and traced the vectors of public infection, Sulkowski has spent years leading clinical trials of potential new treatments. He has seen firsthand the side effects that made David Frick’s year of treatment so miserable. But in the last two years, Sulkowski’s team has led trials of drugs that appear to radically change the nature of treatment for hepatitis C.

“The cornerstone of hepatitis C treatment since the late 1990s has been interferon-alfa and ribavirin, a regimen that carries severe side effects,” Sulkowski says. “So what we have had, in effect, is a treatment that’s effective for many people, but toxic. And the special challenge is that hepatitis C is an asym-
Attacking the Swarm

While researchers and clinicians have great hopes for the new classes of drugs for hepatitis C, no drugs, no matter how powerful or well tolerated, will ever truly conquer the disease. That will require a vaccine.

In April 2012, Hopkins researchers began to enroll participants in the first-ever Phase I/II clinical trial of a hepatitis C vaccine. If it proves successful, it will mark the culmination of more than 20 years of research on the virus that causes the illness.

“The hepatitis C virus is very diverse, even more diverse than HIV or influenza,” says Andrea Cox, an associate professor of medicine, who is leading the trial after more than a decade of research on the virus’s behavior. “Even within a single individual, the hepatitis C virus circulates as what’s called a ‘quasi-species.’ You can think of it as a swarm of viruses that are related but not identical.”

HCV’s genetic diversity has made vaccine development an enormous challenge. The vaccine under trial—developed by the Italian drug company Okairos—has tried to solve the problem with sheer firepower. The vaccine is designed to generate an immune response that is so robust that it will not much matter which genetic HCV variants the patient encounters in the future. Scientists have done this by enveloping harmless fragments of the HCV virus within other viruses that cause virtually no illness. Although the viruses in the vaccine cause nothing worse than a common cold, they inspire extremely powerful immune responses, in part because they do not normally circulate in humans. The recipient’s immune system then “remembers” both the virus and the fragmentary-HCV antigens that were smuggled inside the virus. If HCV ever enters the recipient’s body again—even if it’s a different genetic variant than the one in the vaccine—the immune system will have enough of an edge that it can prevent the establishment of a chronic hepatitis C infection.

At least, that is the hope. The ongoing double-blind, placebo-controlled trial, which is sponsored by the NIH, will help determine whether the vaccine actually does prevent chronic hepatitis C infection. The participants are being enrolled from an ongoing longitudinal study of Baltimore residents who have recently become injection-drug users. It is estimated that up to half of injection-drug users acquire HCV within a year of starting to inject drugs, so this is a population at high risk.

“A very important part of the trial, which complicates it, is that we’re doing everything we can to prevent participants from becoming infected,” Cox says. “We’re offering them drug counseling. We’re offering them referrals to needle exchange and drug treatment programs. Two of our staff members have decades of experience helping people get off drugs. All participants are extensively counseled about minimizing the hazards of drug use.” The infection rates observed in this trial will probably be significantly lower than among injection-drug users with weaker access to health services.

Regardless of the outcome of this trial, Cox intends to keep pressing for an effective vaccine. “It’s very difficult to believe that we’re ever going to get the disease fully under control on a global scale through drug treatments,” she says. “It could be much more effective to immunize people as children, so they’re protected long before they ever encounter HCV.”

—DG
they appear to be far better tolerated than the traditional therapies. Sofosbuvir was submitted to the FDA for approval this summer, with a decision expected in December.

“The flu-like symptoms of interferon are gone,” Sulkowski says. “The severe fatigue is gone. Anemia, which has been a consequence of the first protease inhibitors, is no longer a major issue. And the treatment duration has been reduced to, in some cases, 12 weeks, down from 24.”

Because the medications in the pipeline appear so promising, many physicians are urging their patients to defer treatment unless they already show signs of significant liver fibrosis. “I’m encouraging my patients to wait until the new medications come on line,” Thomas says.

“I wouldn’t take any of the old stuff,” says Lynda Dee, a Baltimore attorney who tested positive for hepatitis C several years ago. From firsthand observation of friends and acquaintances, she drew her own conclusion: “Interferon-alfa and ribavirin are a nightmare.”

Since early tests showed that her liver had not been severely damaged, Dee decided to wait for better treatments to emerge. When she learned last year about the opportunity to participate in a clinical trial of the new antiviral drugs, she chose to sign on. “There’s always a lot of angst associated with something like that,” she says. “But it seems to have worked beautifully.”

Andrew Cameron, who directs the liver transplant program at Hopkins, also sees great promise in the new medications. Among hepatitis C patients whose livers have already deteriorated so badly that they require transplantation, the traditional therapies have usually done poorly, both before and after transplant, Cameron says. People with end-stage liver disease are especially intolerant of interferon’s side effects.

“If we can use easy-to-tolerate drugs to clear the virus or reduce the viral load before surgery, that will make a huge difference,” Cameron says. Among other things, it will broaden the range of livers available to hepatitis C patients. Traditionally, these patients have been restricted to livers from donors younger than 50 or 55, because (for reasons not well understood) the hepatitis C virus tends to roar back and quickly destroy livers from older donors. Since roughly half the transplant pool is from donors older than 55, this has been a major burden for hepatitis C patients. “We might soon be able to open up the entire range of donors to hepatitis C cases,” Cameron says. “That’s very, very exciting.”

Alongside their excitement, hepatitis researchers like Sulkowski also raise four notes of caution about the new wave of medications. One is that the drugs have not been thoroughly tested so far on some of the most medically vulnerable populations, including people who carry both HIV and HCV and those with advanced liver disease. (Clinical trials in that group are presently under way, and Sulkowski says that the early findings are promising.)

A second concern: It’s not known yet whether viral resistance will emerge as these drugs are used in real-world settings. “That’s a question that I don’t think we have much data for yet,” says Susanna Naggie, a Duke University scientist who earned her MD at Hopkins in 2002. “But the early signs are that it probably will matter. Some recent data suggested that of the people who have failed treatment on [the protease inhibitors approved in 2011], half of them have protease-related mutations in the virus.”

The solution, Naggie says, will probably be to use combinations of drugs from different classes, as is done in HIV therapy.

Third, scientists hope that the apparent success of the new drugs will not slow down funding of vaccine development for hepatitis C. Andrea Cox, an associate professor at Hopkins, is currently conducting a clinical trial of a potential vaccine [see sidebar].

Finally, researchers foresee difficult conflicts ahead about how many people should be offered the new medications, which are expected to carry a price tag of tens of thousands of dollars, at least initially. Should the drugs be given to the millions of people who are HCV-positive, or only to those who have already suffered actual liver damage? Should some patients be asked to wait until the drugs get cheaper? “I don’t know of any precedent for this kind of thing in the history of medicine,” says Hopkins virologist Stuart Ray. “This won’t be an easy ethical decision.” Recall that only 15 to 30 percent of chronic hepatitis C infections are estimated to result in full-blown liver cirrhosis. If you’re an HCV-positive individual, you might understandably feel that it’s worth $70,000 to reduce that risk to zero. But will private insurance companies and Medicare agree?

Even with all of those cautions in mind, these scientists seem palpably joyous about the imminent transformation of hepatitis C therapy. “It was completely unimaginable a decade ago, or even two years ago, that we would have these kinds of treatment advances,” Sulkowski says. “Soon we’ll be able to tell patients that they’ll only have to take one pill, once or twice a day, for 12 weeks.”

### Hepatitis C Treatment

<table>
<thead>
<tr>
<th>Standard Treatment</th>
<th>Current Clinical Trials</th>
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<tr>
<td>24–48 weeks of interferon-alfa and ribavirin</td>
<td>8–12 weeks of pills. No interferon-alfa</td>
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<tr>
<td>Fevers, sweats, chills, depression, fatigue</td>
<td>Few significant side effects</td>
</tr>
<tr>
<td>50% of patients fail to respond to treatment</td>
<td>Effective for almost everyone</td>
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### Clinical trials

- **Standard Treatment**
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  - 8–12 weeks of pills
  - No interferon-alfa

- **Current Clinical Trials**
  - Few significant side effects
  - Effective for almost everyone

*Numbers and percentages are approximations.**
Too few doctors are prepared to help guide women through menopause. Wen Shen and her compatriots are intent on changing that.

Lifting the Fog

By Jim Duffy
Photos by Howard Korn
These women were in their 50s, and they were complaining of the hot flashes, night sweats, moodiness, memory lapses, vaginal irritation, and other symptoms that can accompany the onset of menopause. The severity of their problems was all over the map, with relatively minor annoyances on one end of the spectrum and full-scale life crises on the other—serious enough to put careers and marriages at risk.

“In my residency at Hopkins, the patients we saw in the clinics were mostly young women, so we were dealing with pregnancies, birth control, and sexually transmitted diseases,” Shen says. “Now all of a sudden I found myself seeing patients who wanted me to do something about these menopause symptoms, and I just didn’t know what to do. It was a helpless feeling.”

So Shen set out to find answers that would help her avoid unnecessary delays and potential missteps in helping her new patients. Without the Internet back then to guide her, she scrounged around for textbooks and journal articles in bookstores and libraries.

What she found astonished her: “The reference materials out there had very little information about the things my patients were struggling with, and very little information about how I might help them,” she says.

Flash-forward 18 years to 2005, when Shen took a new career turn. With her three children now headed into young adulthood, she decided to return to academia and mix more research and teaching into her clinical work. She came back to Hopkins as an assistant professor of gynecology and obstetrics.

“Right away I found out that we still weren’t teaching residents at Hopkins about menopause,” she says. “It was almost funny, how right away I became the menopause queen around here. Whenever residents found themselves with a menopausal patient in our clinics, they’d page me.”

They were full of questions: What tests should we order? Are there other possible causes for these symptoms? If a patient complains of “mental fog” and memory lapses, can that be due to menopause—or is it just aging … or something else? When is hormone therapy recommended? What other treatments are out there, and which should we try first?

The opportunities for OB/GYN residents to see menopausal patients were still as rare as they had been during Shen’s time in the program. Mindy Christianson, who completed her residency in 2010, chalks that up to the demographics and health needs of the community in and around the East Baltimore campus.

“I didn’t have much exposure to menopause patients, and so coming out of my residency here, I just didn’t feel comfortable taking care of them,” says Shen.

Wen Shen finished her residency in obstetrics and gynecology at Hopkins in 1987, she jumped straight into private practice in the resort town of Southampton, N.Y. She quickly found that her Hopkins training hadn’t prepared her for the problems many of her new patients were facing.

“[Doctors] tended to send a whole lot of women home with Valium and Xanax back then. And so we ended up with a lot of women being drug dependent in their later lives.”

—Wen Shen
Christianson, who recently joined the OB/GYN faculty after completing a clinical fellowship in the department in Reproductive Endocrinology and Infertility. “The more I thought about it, the more I found myself wondering, ‘If I’m training at Hopkins and I feel uncomfortable in this area, what’s it like for residents in the rest of the country?’”

In short order, Shen ran out of patience with the situation. “It became more and more obvious that this was no way to teach our residents,” she says. “That’s how I got the idea in my head: ‘Somebody’s got to do something about this, and I guess that somebody is going to be me.’”

**VIEWED OVER THE COURSE** of a woman’s lifetime, menopause is more of a gradual transition than a discrete event. It can start anytime between 40 and 60, with the average age of onset being 51, and it unfolds over the course of a four- to five-year stretch as a woman’s ovaries slowly but surely stop producing eggs.

Once menopause ends—the official definition is 12 months after a woman’s final menses—the body will produce lower levels of estrogen and progesterone, a development that over the long haul can have a wide range of health effects on bone metabolism, cardiovascular functioning, breast health, and more.

During menopause, however, the levels of those hormones actually go both up and down, following something of a roller-coaster pattern. These fluctuations help spark the most common symptoms of menopause, which vary wildly in number and intensity among different individuals.

“Patients in menopause have unique complaints and issues,” Christianson says, “and the doctors we’re training here really need to be ready for that when they step out into their own practices. The size of the population of people living through menopause and then in their post-menopause years is huge right now. And with the baby boom generation getting older, it’s getting huger every year.”

The U.S. Census Bureau estimates that there will be between 50 and 60 million menopausal and post-menopausal women in the country by the year 2020—an increase of between 5 and 15 million since 2000. With the average life expectancy of these women now up to 85 years, a sizable number of individuals will spend a considerable portion of their adult lives in menopause and post-menopause.

**Signs and Symptoms**

The number and severity of symptoms that accompany menopause vary widely. The most common complaints physicians hear from menopausal patients include:

**Hot flashes** affect 85 percent of women in menopause. Lasting between one and five minutes apiece, these flashes cause upper body sweating and may be followed by chills. They also cause night sweats that can disrupt sleeping patterns.

**Sleep disturbances** affect nearly 40 percent of women in menopause. These are usually related to night sweats.

**Psychological issues** arise in 10 to 30 percent of menopausal women. These often unfold in a domino-like sequence in which fluctuating hormone levels cause night sweats and sleep disturbances that in turn result in moodiness, daytime drowsiness, memory lapses, and difficulties concentrating.

**Vulvovaginal symptoms** include dryness, irritation, burning, itchiness, and pain in the vaginal area, as well as increases in swelling (vaginitis) and thinning of the vaginal walls (vaginal atrophy). These symptoms can also disrupt a woman’s sex life. Between 30 and 50 percent of women experience one or more of these symptoms, with problems becoming more frequent in the later years of menopause.

**Other complaints** from menopausal women can include urinary issues, weight gain, hair and skin changes, and generalized aches and pains, but at this point there is no compelling evidence that these issues are directly related to menopause.
will be spending fully one-third of their lives during or after menopause.

Both Christianson and Shen stress early on in conversations about the topic that menopause is both a perfectly natural process and one that many women go through without suffering significant health issues. Shen points to a 1998 Gallup poll that asked postmenopausal women to choose the point in life when they felt happiest and most fulfilled.

“More than half (51 percent) chose the years between 50 and 65, the ages that include menopause,” Shen says. By comparison, just 10 percent of the women surveyed chose their 20s, 17 percent chose their 30s, and 16 percent chose their 40s.

But somewhere between 10 and 15 percent of women endure menopause-related symptoms that Shen rates as “severe.” These are the patients who can arrive at their doctor’s office in desperate straits. They can’t get any sleep, their mood is always sour, their workplace performance is slipping, and their relationships are going south.

“By the time they show up, they’re feeling scared and desperate,” Shen says. “They’re saying, ‘Look, I just screamed at my boss.’ Or, ‘My husband is going to leave me if I don’t stop behaving like this.’ They know what’s happening, they can see it clearly, but they can’t seem to stop it on their own.”

Such extreme moodiness can also be accompanied by the somewhat mysterious phenomenon known as “mental fog.”

“For highly functioning professionals, that’s actually one of their major issues,” Shen says. “In the middle of giving a high-powered presentation, they find themselves”—here she snaps her fingers, then slaps her forehead—“Wait, I was going to say something, but it just slipped my mind.”

“Things like that are happening more often than these women are comfortable with,” Shen continues. “They’re not coming up with numbers and names, and this is happening at an age when people are at the peak of their careers. They just can’t afford to seem less than totally sharp.”

**ONCE SHE DECIDED** to remake menopause education in residency, Shen signed on for the nine-month-long curriculum development course offered each year by the School of Medicine. It meets once a week on the Bayview campus, guiding participants step by step through the creation of their curricula.

“What that did was give me a firm foundation not just in establishing a curriculum, but establishing it in a way where you can measure things and show that it makes a significant difference,” Shen says. “It was a fabulous experience, actually.”

She also stopped in at about this time to see Jessica Bienstock, the residency program director in the Department of Gynecology and Obstetrics. Shen wanted to understand how difficult it might be to add new material in an era of tightened work-hour restrictions for residents.

Bienstock offered nothing but encouragement. Not only was she looking at the demographic trends showing more and more women headed into menopause, she was also looking at results of the annual in-training exams residents take through the Council on Resident Education in Obstetrics and Gynecology (CREOG).

“Our residents were not doing particularly well on the menopause questions,” Bienstock says. “So we’d already been thinking about that, and we’d been thinking as well about the fact that our residents don’t see a lot of menopause patients. I was very happy to hear about Dr. Shen’s plans.”

“The Gang of Four” is Shen’s playful name for the team she assembled to get the ball rolling. Wanting input from colleagues who understand the lifestyles and learning preferences of contemporary residents, she recruited two young physicians—Christianson and Jennifer Ducie—who were either still in the residency program or just finished with it. Shen’s faculty colleague Kristiina Altman helped lead the project as well.

Their first step was to gain a better understanding of the lay of the land nationwide. They sent Web-based surveys to the 258 residency-training directors listed in the CREOG database, asking them to share the survey with residents. Eventually, they received 510 responses from residents.

“We expected to find that there would be a huge need for teaching residents around the country more about menopause, and that’s what we found,” Christianson says. “In fact, it was a little worse than we expected.”

Survey results were published this past spring in the online journal *Menopause*. Overall, the study indicated that fewer than one in five residents receives any formal training in menopause, while seven in 10 residents say they would like to receive such training.

“The residents who responded basically admit
that their knowledge and clinical management skills of menopause medicine are inadequate,” says Christianson, the study’s lead author.

**TODAY, MENOPAUSE** medicine is a more nuanced and cautious affair than it used to be. Early on in her practice in New York, Shen found her way to the North American Menopause Society (NAMS), which was then a fledgling professional society just getting started on the work of helping physicians deliver better information and improved care to their menopausal patients. (The society will celebrate its 25th birthday next year.)

“The first thing I learned from NAMS was that there was a real need for research in this area,” Shen says. “But physicians at the time were basically handing out hormone therapy like candy to every menopausal and postmenopausal woman who walked through the door.”

Gynecology was still dominated by male physicians then, and that may have contributed to some level of disconnect between doctors and patients when it comes to understanding just how much the effects of menopause can vary from individual to individual.

“They tended to send a whole lot of women home with Valium and Xanax back then, too,” Shen adds. “And so we ended up with a lot of women being drug dependent in their later lives.”

Shen links the evolution of the field in no small part to broader changes in American society. By the time the baby boomer generation started to arrive at middle age, many social taboos around the topic of menopause had disappeared.

“People my age, we have moms who just didn’t talk about menopause,” Shen says. “It was regarded as an embarrassing subject. Also, more of our moms tended to not work outside the home, and that meant issues surrounding workplace functioning weren’t as important.”

“This topic of hormone therapy especially can be overwhelming and daunting at first. I don’t see how residents who don’t have any experience with it or training in it could possibly feel comfortable in this area.” —Mindy Christianson
Modern-day clinical treatments for menopause symptoms generally fall into one of three broad categories, with “common sense” being the first line of defense.

Consider the example of a menopausal patient who’s having trouble sleeping. Her physician might first test out some simple “sleep hygiene” improvements—avoiding caffeine and alcohol in the evenings, darkening the room, and having a warm drink before turning in. Basic lifestyle changes can also help, especially regular, weight-bearing exercises.

These first steps are unlikely to solve the most serious cases. “Night sweats can have women up and down over and over again during the night,” Shen says. “I’ve had patients who are changing the sheets on their bed three or four times a night, and it’s like that night after night after night.”

Next, the physician might try a pharmacological solution. Antidepressants can help reduce night sweats, with Paroxetine (65 percent reduction) and Venlafaxine (57 percent) performing best. But the choice of which antidepressant can be complicated, with the mix of side effects varying quite a bit from drug to drug.

The last treatment to consider is hormone therapy, which seeks to stabilize hormone levels in the patient’s body. This remains the most effective treatment for hot flashes, night sweats, and vaginal atrophy, but its use necessitates a careful, case-by-case balancing of risks and benefits (see below).

In Christianson’s experience, as physicians get deeper into the treatment options, they need to sort through increasingly complex issues with their patients.

“This topic of hormone therapy especially can be overwhelming and daunting at first,” Christianson says. “I don’t see how residents who don’t have any experience with it or training in it could possibly feel comfortable in this area.”

Another challenge for young physicians is recognizing when and how the physiological changes of menopause can have long-term implications for patients. Estrogen deficiency due to menopause can contribute to the risk of osteoporosis, for example, especially in women who go through the transition early, starting before age 45. Similar complexities can arise during and after menopause in the areas of cardiovascular disease and breast health.

Sexual activity is something else physicians should discuss with menopausal patients, especially those who are divorced, separated, or single. As the vaginal walls get thinner during menopause, it makes it easier for sexually transmitted diseases to

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**Hormone Therapy: “Lowest Dose, Shortest Time”**

In considering menopause treatments, physicians and patients alike are still grappling with results from the Women’s Health Initiative (WHI) study.

Launched in 40 centers around the country in 1992, WHI sought to test the hypothesis that long-term hormone replacement therapy (HRT) after menopause would help prevent heart disease, osteoporosis, and some cancers later in life. That hypothesis failed, and most of the study was shut down in the early 2000s amid evidence that the risks involved with long-term HRT—more strokes, pulmonary embolisms, breast cancers, and heart disease—outweighed the benefits.

Understandably, this heavily publicized result raised public fears about using hormone therapy in menopause medicine. But Hopkins gynecologist Wen Shen points out that the study never directly addressed the way this therapy is used in her field.

The WHI study was looking at administering hormone therapy over the long haul of decades; in menopause medicine, it’s a short-term affair. Similarly, she notes, WHI’s aim was to prevent disease over a long period rather than to focus on relieving current symptoms.

Finally, study participants in WHI were 65 years old on average at the start of the study, so there were very few menopausal women in the pool.

“Today, we give hormone therapy only to the more serious cases, where there are significant quality-of-life issues, and we do so with lowest dosages over the shortest possible time,” Shen says. “In menopause medicine today, hormone therapy is about the short-term management of symptoms and improving quality of life. Hopefully, we’ll be able to investigate the long-term benefits of hormone therapy for high-risk patients. But this is another project for the future.” —JD
take hold. In fact, menopausal and postmenopausal women now rank as the fastest growing population of new HIV infections.

“The most important thing we’ve learned in this field is that we need to evaluate every individual case in particular,” Shen says. “There is no single answer out there that can apply to every woman who’s going through menopause.”

THE MENOPAUSE CURRICULUM made its debut two years ago as a series of four lectures. It has grown step by step since then, and this year’s new residents will have eight lectures. For the first time, they’ll also travel out to Green Spring Station in north suburban Baltimore to see patients at Shen’s menopause clinic.

This gradual rollout enabled Shen and her colleagues to pay attention to the goal of creating a program in which senior residents become an integral part of the teaching process, serving as mentors and even delivering some lectures.

While it’s still too early to come to any firm conclusions about the success of the curriculum, Christianson describes the early results as “very promising.” On pre- and post-curriculum tests, the residents’ scores have jumped from 57 percent before the lectures to 80 percent after.

In surveys prior to the curriculum, nearly 85 percent of residents said they felt either “barely comfortable” or “not at all comfortable” about caring for menopausal patients. After the lectures, 71 percent of residents described themselves as either “comfortable” or “very comfortable.”

Shen has also been active on other fronts in promoting menopause education. In recent years she served first as vice chair and then chair of the professional education committee at the North American Menopause Society.

“I made a lot of noise during a lot of meetings,” she says with a laugh. “I thought it was just ridiculous that as the professional group for menopause, we didn’t have a curriculum to teach residents.”

Her push succeeded. NAMS worked with the Association of Professors of Gynecology and Obstetrics (APGO) to create a Web-based curriculum that’s available for a fee. However, the Hopkins researchers’ survey data indicate that today’s residents much prefer training delivered in supervised clinics, lectures, and case presentations to Web-based independent study.

And that bit of frustration is how Shen found herself talking now and again with patients about her goal of expanding access to the new Hopkins curriculum to residents around the country. “Then this wonderful patient of mine decided to give me this wonderful check,” she says. “It was just fabulous of her, and she has continued every year since then to support this effort.”

The surprise donation helped finance a program to videotape the curriculum lectures and offer them on CDs. Off to the corner of Shen’s office are two large oblong cardboard boxes full of the disks.

“There used to be four of those boxes,” she says. “I took the other two to the most recent APGO meeting, and 500 people came up to take a CD.”

Shen says she has come away from the project deeply impressed with the commitment and capabilities of today’s residents. “They are so facile at navigating the new world of information,” she says. “If we can just pose the right questions and point them in the right directions, they’re off and running, and that’s all they need.” *
Biennial Meeting and Reunion Weekend 2013

The 2013 Biennial Meeting and Reunion Weekend was a great success! From June 6 to 9, the Johns Hopkins Medical and Surgical Association and the School of Medicine welcomed to the East Baltimore campus hundreds of its family members: alumni, students, and current and former faculty, fellows, and house staff. Many attendees enjoyed seeing the Armstrong Medical Education Building, the Charlotte R. Bloomberg Children’s Center, and the Sheikh Zayed Tower for the first time. Throughout the weekend, attendees participated in educational programs, learned about the future of Johns Hopkins Medicine, celebrated achievements, honored colleagues and friends, and enjoyed catching up and reminiscing at the All Classes Reunion Dinner. Of the many successes that were celebrated, here are just some of the highlights:

- 5 portrait dedications
- 23 award recipients honored
- 15 departmental academic programs hosted
- More than 800 guests registered
- More than 300 alumni and guests attended the All Classes Reunion Dinner
- More than $8 million collectively donated

The Biennial Meeting and Reunion Weekend always provides an opportunity for reflection and reminiscing. It’s a time for reconnecting with classmates and colleagues, celebrating the reunion of each class as well as the reunion of the School’s alumni family, and expressing Hopkins pride.

Please mark your calendars now: The Biennial Meeting and Reunion Weekend returns June 4–7, 2015!
Left to right: Jack Zimmerman, Med '53; Doris Zimmerman, Nursing '53; Lois Kaiser; Maria Crea-Smith, Med '53; George Kaiser, Med '53; Richard Welch, Med '53; Betty Welch; Nancy Herman; Emery Herman, Med '53; and Grace Hopkins, widow of F. Thomas Hopkins, Med '53.


Class of 1972: Mike Katz, Steve Neville, and Erik Hewlett.

Left to right: Albert Polito, MD, Krieger '85, and wife, Redonda Miller, Med '92; Brett Simon, Med '84 and wife, Elizabeth Martinez, Med '92; Reid Thompson, Med '89, and wife, Lorriane Ware, Med '92; John Hwang, Med '92; Roger Perez, Med '92.


George Dover, Faculty; and Class of 1987: Rebecca Wells, Marie Bellantoni, Kevin Johnson, Susan Vitalis, and Charles Anderson Jr.
Front and Center

Lorsch steps up to lead the largest scientific funding agency in the world.

Shortly after Jon Lorsch (faculty, biophysics and biophysical chemistry, 1999–2013) was named director of the National Institute of General Medical Sciences (NIGMS), he was flabbergasted by how many congratulatory emails he received.

He shouldn’t have been. NIGMS appropriately is known as “the center of the center” of the National Institutes of Health—this nation’s, and the world’s, largest source of funding for medical research. With an annual budget of $2.4 billion, the NIGMS is the primary federal funder for basic research in cell biology, biophysics, genetics, developmental biology, pharmacology, physiology, biological chemistry, biomedical technology, bioinformatics, and computational biology.

Lorsch, 44, earned his PhD in biochemistry at Harvard, working first with the legendary enzymologist Jeremy Knowles and then with biologist Jack Szostak. Szostak shared the 2009 Nobel Prize with Hopkins’ Carol Greider and Elizabeth Blackburn of the University of California, San Francisco, for their discoveries about the role played by the enzyme telomerase, which helps preserve the ends of a cell’s chromosomes when it divides.

At Hopkins, Lorsch and his laboratory’s researchers have made significant discoveries in their studies of the mechanism by which molecular machines locate the beginning of the protein-coding region of an RNA molecule, called “translation initiation.” His group, in close collaboration with the National Institute of Child Health and Human Development, created a fully reconstituted yeast translation initiation system and used it to dissect the molecular mechanisms of each stage of the process. Lorsch will bring a small lab with him to NIH and continue to collaborate on this work with intramural researchers, he says.

Outside of the lab, Lorsch has been an eloquent advocate for science education reform in graduate and medical curricula. During his years at Hopkins he served as director of admissions for the graduate program in molecular biophysics, and headed the Scientific Foundations of Medicine class for first-year medical students, and the research elective for medical students. He also chaired the MA/PhD committee that oversees graduate education in the School of Medicine.

His experiences at Hopkins will undoubtedly inform related efforts at the NIH, where diversity in “scientific subjects, settings, and researchers” will be a theme, Lorsch says.
Connecting the Dots
Coordination is key to Cullins’ role at Planned Parenthood.

As vice president for external medical affairs at the Planned Parenthood Federation of America, Vanessa E. Cullins ’83 is at the center of a rapidly changing health care environment. Her mission, she says, is to make sure the communications, public policy, and medical services components of the national organization understand each other and are working together to best provide health services, education, and advocacy.

“These various functions sit in different divisions and within those divisions you have multiple departments. What I try to do is connect the dots to coordinate things,” says Cullins, who was awarded a Distinguished Medical Alumna Award at the 2013 Johns Hopkins Medical and Surgical Association Biennial Meeting.

Planned Parenthood, founded in 1916, is the health care provider of choice for millions of women, with more than 800 health clinics operated by 74 independent affiliates. Its services, focused around reproductive health, include cancer screenings, testing and treatment for sexually transmitted diseases, and assistance with contraception. While some women visit Planned Parenthood just a few times in their lives, others rely on the organization as their primary provider, Cullins notes.

The Affordable Care Act (ACA) is expected to increase by approximately 30 million the number of people with health insurance, she says, burdening a health system that is already struggling with a workforce shortage. “We’re here to help. We have the ability to provide primary care services for reproductive-age women”—freeing capacity in the system to care for men and children. Cullins notes that the ACA is changing the “conceptual framework” of medical care, requiring that organizations work together, with a primary care provider as the “medical home.” Planned Parenthood can be that home, she believes.

Emergency contraception is another issue on the front burner for Cullins. In May, the Food and Drug Administration made morning-after contraceptives available over the counter, with no age restriction. The decision, which she hailed as good news, means she must work to make sure all parts of Planned Parenthood understand what it means.

“Not only do all our medical folks need information about that, educators need education about that, our public policy people, and our consumers in general need to have that information,” she says.

Cullins earned her undergraduate degree at Spelman College, and has an MPH from Hopkins’ Bloomberg School of Public Health and an MBA from the Wharton School of the University of Pennsylvania. After completing her medical training at Hopkins (internship, residency, and fellowship), she joined the OB/GYN faculty at Hopkins, and also served as acting director of Baltimore City’s Bureau of Primary Care and Reproductive Health. She joined Planned Parenthood in 2001.

Planned Parenthood is poised to be a primary care “medical home” for women, says Cullins.

1973
Marc C. Hochberg, of Baltimore, has received the 2012 Distinguished Clinical Investigator Award from the American College of Rheumatology, the 2013 Lifetime Achievement Award from the Osteoarthritis Research Society International, and the 2013 Arthur Modell President’s Award from the Arthritis Foundation. Hochberg is a professor of medicine and epidemiology and preventive medicine at the University of Maryland School of Medicine and head of rheumatology and clinical immunology in its Department of Medicine.

1976
Stephen J. McPhee, of San Francisco, professor emeritus of medicine at the University of California, San Francisco, has had an endowed chair named in his honor by the Division of Internal Medicine in which he has been a pivotal leader for three decades.

1982
Edward J. Farmlett, of Laconia, N.H., has been inducted as a fellow in the American College of Radiology. Farmlett works for Lakes Region Radiology PA in Laconia and is a member of the New Hampshire Radiology Society, the Radiological Society of North America, and the American Roentgen Ray Society.

1983
Steven M. Holland, of Bethesda, Md., has been elected as a 2013 Academy fellow in the American Academy for Microbiology in recognition of his significant contributions to the field. Pomerantz was one of the first to elucidate the molecular mechanism of HIV persistence.
Putting Patients First

Bach is committed to improving patient outcomes while controlling medical costs.

Empowering patients and finding ways to control skyrocketing medical costs are focal points for Peter Bach (HS, 1992–95; fellow, pulmonary and critical care medicine, 1997–98), who directs the Center for Health Policy and Outcomes at the Sloan-Kettering Cancer Center in New York.

Bach, who is a full member with tenure at both the Cornell Medical School and at Memorial Sloan-Kettering, lately has been examining the important question of who would most benefit from CT screening for lung cancer, the leading cause of cancer deaths in the United States.

“By the time we diagnose most people with lung cancer today, the disease is in advanced stages, cannot be removed through surgery, and is difficult to cure,” Bach notes. While CT scanning can be a valuable diagnostic tool, it is expensive and carries health risks. “[So] we are trying to develop policy-oriented models of who should be screened,” he says.

He and his colleagues developed statistical prediction models that pinpointed a population of heavy smokers (estimated at 8 million Americans) who would see a 20 percent reduction in lung cancer death with regular screenings. Those who don’t fall into this group have a much lower chance of developing lung cancer, so screening might do more harm than good. Based on these findings, which appeared in the May 20 Journal of the American Medical Association, the American College of Chest Physicians and the American Society for Clinical Oncology have published new screening guidelines.

The larger issue, Bach believes, is giving patients the information they need to make rational choices. “The days of doctors telling patients what to do, even when it’s not really clear for that patient that the risks are worth the benefits, are hopefully over,” says Bach, whose popular health blog in the New York Times earned avid followers.

It was at Johns Hopkins, where Bach was a member of the Osler Medicine house staff and later a fellow in pulmonary and critical care medicine, that Bach says he learned that taking care of the patient is the most important thing. “I still, to the irritation of my colleagues, refer to Hopkins as the place I learned to be a doctor,” he says. KN

“The days of doctors telling patients what to do, even when it’s not really clear for that patient that the risks are worth the benefits, are hopefully over.”
Faculty, Fellows, House Staff

Clarence “Buck” Brown III (HS and fellow, medicine, 1966–72), of Orlando, Fla., retired in 2012 as president/CEO of MD Anderson Cancer Center Orlando. He was leader of the facility since it opened 20 years ago. Brown is now vice president of the Orlando Health Foundation and will continue to support its oncology programs.

Randolph H. Howes (HS, surgery, 1971–77; fellow, plastic surgery, 1975–77), of Kentwood, La., has been named the first international recipient of the American College for Advancement in Medicine’s Dr. Charles Farr Award for achieving excellence in oxidation medicine.

Jerome A. Paulson (HS, pediatrics, 1974–76), professor of pediatrics at the George Washington University School of Medicine, professor of environment and occupational health at GW’s school of public health, and medical director of the Washington, D.C.-based Children’s National Medical Center, recently went to Dar es Salaam, Tanzania, to meet with the leadership of the Pediatric Association of Tanzania. The aim of the meeting was to develop a long-range plan to increase that nation’s capacity for assessing, managing, and preventing environmental health threats to its children. Paulson also is director for national and global affairs of the Child Health Advocacy Institute and director of the Mid-Atlantic Center for Children’s Health and the Environment.

Gordon L. Klein (HS, pediatrics, 1977–78), of Dickinson, Texas, a pediatric gastroenterologist at Scott & White Memorial Hospital in Temple, Texas, will edit Bone Drugs in Pediatrics: Efficacy and Challenges, a book to be published by Springer, a New York-based science, technology, and medicine publisher.

Mark A.C. Hoeplinger (HS, otolaryngology, 1979–82), of West Seneca, N.Y., has been inducted into the Signum Fidei Society of the St. Joseph’s Collegiate Institute’s Alumni Association in Buffalo, N.Y. Hoeplinger founded the Western New York Ear, Nose, and Throat practice in 1987. He has been named a deacon in the Orthodox Catholic Church of America in recognition of his frequent mission trips to perform ear surgery and provide hearing aids to the poor in such countries as Peru, Guatemala, and Uganda.

Peter N. Schlegel (HS and faculty, urology, 1985–89), of Larchmont, N.Y., is now serving as medical board president of the New York Presbyterian Hospital, where he is also urologist-in-chief. Schlegel currently works at the Weill Medical College of Cornell University as professor and chairman of urology, as well as professor of reproductive medicine.

Andrea L. Cox, of Baltimore, was inducted into the American Society for Clinical Investigation last April for her work in treating people infected with the hepatitis C virus. Cox is an associate professor of medicine and oncology and a co-director of the Medical Scientist Training Program in the Hopkins School of Medicine.

Austin G. Ratner, of Brooklyn, N.Y., was profiled last May in a *New York Times* article that featured his novel, *In the Land of the Living*, and other literary works. He has received several awards for his writing, including the 2011 Sami Rohr Prize for Jewish Literature for his first novel, *The Jump Artist*.

Kevin B. Jones, of Salt Lake City, an orthopedic surgeon and scientist at the Huntsman Cancer Institute and Primary Children’s Medical Center at the University of Utah, has published *What Doctors Cannot Tell You: Clarity, Confidence and Uncertainty in Medicine*.

Melissa S. Camp, of Baltimore, returned to the Johns Hopkins Department of Surgery after fellowship training in breast surgical oncology at Massachusetts General Hospital in Boston. She is part of a highly specialized team at the Hopkins Breast Center that ensures compassionate patient care and personalized surgical treatment.

Douglas E. Ramsey, of Wausau, Wis., a musculoskeletal radiologist, was recently named chairman of the Radiology Department at Aspirus Wausau Hospital, where he also serves as director of CT imaging.
IN memoriam

School of Medicine

Herbert Elias Sloan Jr. ’40, of Ann Arbor, Mich., who influenced generations of cardiothoracic surgeons during his long career, died on May 17, 2013. He was 98. A pioneer in thoracic and cardiovascular surgery, he performed Michigan’s first successful open-heart surgery in 1956; and in 1960, he became the first to perform such a procedure on infants there. On the University of Michigan medical school faculty since 1949, he headed thoracic surgery from 1970 to 1985.

Robert D. Sloan ’43 [February], of Medford, Ore., the first chairman and professor of the University of Mississippi Medical Center’s Department of Radiology when it was founded in 1955, died on April 3, 2013. He was 95.

John McGee ’44, of Sun City West, Ariz., a U.S. Navy veteran of World War II and the Korean War who practiced surgery in Marin County, Calif., for 40 years, died on March 29, 2013. He was 93. McGee’s wife of 69 years, classmate Marjorie LaMont McGee ’44, whose career included service as a physician for the Public Health Department, died a few months later, on June 11, at the age of 93.

Mohsen Ziai ’52, of Great Falls, Va., whose career in pediatrics included influential work spanning two nations, died of pneumonia at his home on March 27, 2013. He was 85. He returned to his native Iran after completing his medical education, but came back to Hopkins in 1965 as an associate professor and director of the pediatric ambulatory service. In 1969 he again went home to Iran to become dean of the medical faculty at the University of Tehran. He returned to the U.S. in 1977 as a professor of pediatrics at the University of Rochester and chair of pediatrics at Rochester General Hospital in New York. He later taught pediatrics at Georgetown University in Wash-

Chemo and Stem Cell Pioneer

Colvin set the course for cancer therapeutics.

During a three-decade Hopkins career, O. Michael Colvin conducted landmark research on how high-dose chemotherapy works—as well as on its toxicity—that continues to have a fundamental impact on cancer therapeutics in general, and bone marrow transplantation specifically.

Because of Colvin’s pioneering investigations, the Hopkins cancer center became the site of the nation’s first cancer pharmacology program; and his work with such Hopkins colleagues as John Hilton, Richard Jones, and Saul Sharkis led to the development of a stem cell isolation probe that remains a commonly used marker for identifying stem cells.

Colvin, who began his Hopkins career as an intern in 1961, also served as associate dean for research from 1988 to 1990. He left in 1995 to become head of Duke University’s Comprehensive Cancer Center, which experienced significant growth during his seven-year tenure as its director. He retired in 2008 as a professor emeritus of medicine and died on March 16 at the age of 76.

As director for 20 years of what became Hopkins’ internationally famous Division of Pharmacology and Experimental Therapeutics, Colvin deciphered the mechanism of action of cyclophosphamide, one of the first and still one of the most commonly used anti-cancer drugs—indeed, the first rationally designed “targeted therapy” medication, long before that term was coined. Cyclophosphamide also remains one of the most important drugs in the treatment of autoimmune diseases and still is the most commonly used drug in bone marrow transplantation.

Colvin’s research on cyclophosphamide’s stem cell-sparing activities when used to destroy tumor cells also helped spawn current stem cell therapies, noted William Nelson ’87, current director of Hopkins’ Sidney Kimmel Comprehensive Cancer Center.

In response to Colvin’s pioneering research, Hopkins’ cancer center experts soon “began developing and testing novel new drugs and quickly earned an NCI grant to begin Phase I clinical trials” of them, Nelson said.

Co-editor of the journal Molecular Cancer Therapeutics, Colvin was a prolific investigator, publishing hundreds of articles in peer-reviewed journals, as well as book chapters and abstracts. He also held five patents based on his findings. A year after he stepped down as head of Duke’s cancer center, Colvin received the university’s 2003 R. Wayne Rundles, MD Award for excellence in cancer research.

Known as a compassionate advocate for all cancer patients, he and his wife of 53 years, the former Arline Macey Lockerbie, were honored in 2004 with a Light of Hope Award from the Duke Cancer Patient Support Program.

Neil A. Grauer
Multifaceted Dynamo

Brancati was a widely beloved and admired figure.

An internationally acclaimed expert on the epidemiology and prevention of type 2 diabetes, Frederick Brancati's talents sparkled not only in the laboratory but through his role as a much-beloved mentor.

On top of that, he had an irrepressible sense of humor. “He could have been a stand-up comedian,” observed Michael Klag, dean of the Bloomberg School of Public Health, whom Brancati succeeded as chief of the Division of General Internal Medicine in 2004. “Luckily for Hopkins and the health of populations everywhere, he decided to do clinical research and become a mentor par excellence.”

Brancati died on May 14 following a three-year battle against amyotrophic lateral sclerosis (ALS). He was 53.

“Fred was a truly remarkable person,” said Lawrence Appel, director of the Welch Center for Prevention, Epidemiology, and Clinical Research, a joint program of the schools of Medicine and Public Health. “To his colleagues, he was a brilliant scientist with a dazzling sense of humor. For the 200-plus faculty and staff in the Division of General Medicine, he was an extremely supportive and effective leader. For his students and trainees, he was a superb mentor. In all roles, he was warm and compassionate. He deeply cared about people.”

Brancati’s research had a profound impact on the understanding of type 2 diabetes’ clinical epidemiology and its complications. With extraordinary creativity, he used observational and experimental methodologies to address a broad array of issues related to the origin, prevention, treatment, and consequences of this chronic disease—forever changing how clinicians and researchers view it.

An honors graduate of Harvard and Columbia University’s school of medicine, Brancati arrived at Hopkins in 1989 as a general internal medicine postdoctoral fellow. He then earned a master’s degree in clinical epidemiology from the Bloomberg School. Joining the Medicine faculty in 1992, he became a full professor in 2003 and was named director of the General Internal Medicine Division in 2005. Under his leadership, the division grew to include 80 full-time faculty, 150 part-time faculty, and 17 postdoctoral fellows. Its share of federal research grants from the NIH and other agencies grew from $12 million per year to $30 million annually.

Brancati’s wife of 33 years, Elizabeth Jaffee, co-director of the Cancer Immunology Program and the Immunology and Hematopoiesis Division, had been his high school sweetheart. She told The Sun, “I was going through Fred’s wallet and he had kept our prom tickets. He was my best friend.”

Mark Noël Martz ’70, of Whithington and established the pediatric residency program at what is now Inova Children’s Hospital in Fairfax County, Va. In 2000, he became chairman of pediatrics at Suburban Hospital in Bethesda, Md., now part of Johns Hopkins Medicine.

John C. Smith II ’54, of Minneapolis, a former director of pathology and nuclear medicine at the Trinity Medical Center in Minot, N.D., and coroner of Ward County, N.D., whose training in forensic science led to his appearing as an expert witness in numerous high-profile state and federal trials, died on March 14, 2013, of leukemia. He was 83.

Salvatore J. Cantolino ’61, of Bradenton, Fla., an ophthalmologist who was chief of staff for Manatee Memorial Hospital and a founding physician of the University of South Florida’s School of Medicine, died on March 9, 2013. He was 77. In addition to being a clinical professor of ophthalmology at USF, he served on the board of trustees of the USF Eye Institute.

Stephen J. Ryan ’65, of San Marino, Calif., who served from 1974 to 1995 as the first full-time head of the University of Southern California’s Department of Ophthalmology and its Doheny Eye Institute, as well as dean of the university’s Keck School of Medicine from 1991 to 2004, died on April 29, 2013, of cancer. He was 74.

An internationally renowned expert in retinal diseases and ocular trauma, he was an enthusiastic mentor to young physicians. A member of the board of trustees of Johns Hopkins Medicine, he also was a former president of the Association of University Professors of Ophthalmology and of the Macula Society, as well as founding president of the Alliance for Eye and Vision Research.

Mark Noël Martz ’70, of Whithington and established the pediatric residency program at what is now Inova Children’s Hospital in Fairfax County, Va. In 2000, he became chairman of pediatrics at Suburban Hospital in Bethesda, Md., now part of Johns Hopkins Medicine.
An avid traveller, Paul S. Lietman, PhD ’69, always kept bags packed in case an overseas professional mission beckoned, as one often did.

Lietman, a specialist in bacterial and viral infections and world-renowned for pioneering antiviral treatments—including drugs for patients infected with herpes simplex virus and HIV—was the longtime chief of the Division of Clinical Pharmacology. He spent more than three decades as an influential teacher and mentor for Hopkins medical students and scientists, both in Baltimore and abroad.

After making what turned out to be his last overseas trip to London last March, Lietman died at his Baltimore home on April 20 of congestive heart failure. He was 79.

Serving from 1972 to 2001 as head of the clinical pharmacy division, which is part of the Department of Medicine and the Department of Pharmacology and Molecular Sciences, Lietman also held an appointment in the Department of Pediatrics. His skills behind the lectern earned him the unusual distinction of receiving faculty awards from medical students in both the basic sciences and clinical fields. He held the Wellcome Professorship of Clinical Pharmacology from 1980 to 1998 and was instrumental in the creation of a number of innovative research groups and initiatives.

“He was a gifted educator and was beloved by generations of Hopkins Medical students,” said Myron “Mike” Weisfeldt ’65, chairman of the Department of Medicine.

When Hopkins launched its Johns Hopkins Singapore research and medical care operation in 1998, Lietman was named the founding director of research and education there. From scratch, he created eight basic research laboratories and five other projects. As director of academic relations for Johns Hopkins Medicine International, he led the successful effort to resurrect a historic academic relationship between Hopkins and the medical faculty of the American University of Beirut in Lebanon. He also led the efforts to establish collaboration between Hopkins and the Children’s Hospital of Fudan University in Shanghai and the University of Trinidad and Tobago in Trinidad and Tobago.

But for brief stints at the Hospital for Sick Children on Great Ormond Street in London, and at the National Institutes of Health, he spent most of his 51-year career at Hopkins, retiring in 2010.

To perpetuate Lietman’s legacy, the Division of Clinical Pharmacology has established the Paul S. Lietman Fellowship in Clinical Pharmacology. It will support postdoctoral fellows interested in clinical pharmacology. NAG
from medical school in Germany after the war, he worked as a merchant marine physician before immigrating to Baltimore for his residency. While at Children’s Hospital in Washington, he concluded that major depressive disorders seen in adults also could be found in children. He coined the phrase “masked depression,” conducted two decades of research at the NIH that confirmed his ideas, and co-authored two well-known books, Why Isn’t Johnny Crying: Coping with Depression in Children and Growing Up Sad: Childhood Depression and Its Treatment.

Peter Sterling Mueller Sr. (HS, psychiatry, 1963–66), of Princeton, N.J., a groundbreaking psychiatric researcher, died on March 29, 2013. He was 82. Collaborating with researchers at the National Institute of Mental Health, Mueller confirmed his theory that seasonal light variations caused mood swings, leading to the naming of seasonal affective disorder and seasonal energy syndrome. He also published extensively on the role of fatty acid metabolism and insulin resistance in psychiatric disease, as well as the role of lipid and glucose metabolism in neurodegenerative disorders. In addition, he was instrumental in the creation of the Department of Psychiatry at the College of Medicine and Dentistry in New Jersey.

The School of Medicine also has received word of the following deaths:

Jean Morrow Tune ’50
(Art as Applied to Medicine) on March 19, 2013

Gerald Maurice Little ’54 on April 30, 2013

Thomas R. Bell ’59 on Feb. 18, 2013

Former Faculty, House Staff

Allan R. McClary

Jean M. Marshall
(faculty, physiology, 1951–60) on April 14, 2013

John Richard Strawsburg
(HS, medicine, 1953–54) on April 9, 2013

Jane Donohue Battaglia
(HS, neonatology, 1958; anesthesiology, 1961; faculty, medicine, 1961–65) on March 5, 2013

William Doyle Calley
(faculty, pediatrics, 1965–76) on Feb. 27, 2013

James Harold Heroy III
Investing in People

Our five-year strategic plan zeroes in on our most valuable resource: people.

BY DEAN/CEO PAUL B. ROTHMAN

Imagine this. You sit down with your department director for a performance review. But instead of getting an appraisal of your own work, you comment on your manager’s job skills, pointing out where he or she excels and where you see room for improvement. This might sound ill-advised, but here at Johns Hopkins Medicine (JHM), we believe that leadership benefits when feedback flows both ways. For that reason, over the next few years, we will be rolling out so-called “360-degree reviews” for employees at some levels. It’s just one of many initiatives to come out of our strategic plan—the roadmap that will guide our business decisions for the next five years.

If you read the plan (http://www.hopkinsmedicine.org/strategic_plan/), you will see that the first area of focus is an investment in JHM’s most valuable resource: our people. It may sound clichéd to say that our 41,000 employees are what make Hopkins great, but it’s one of those worn-out lines that cannot be avoided because it is simply true. If we want Hopkins Medicine to remain a world health care leader in the face of constricting budgets, mounting competition, and a heightened emphasis on quality and affordability, we need to chart a course that will help our employees thrive.

You may be thinking: An investment in people sounds promising, but what does it actually mean? Here are a few examples of what we are doing, in the words of the strategic plan, to “attract, engage, retain, and develop the world’s best people.”

First, we are ramping up opportunities for professional development. Johns Hopkins has always attracted the best and brightest scientific minds, but we also need to arm faculty members with the business savvy to be successful in the workplace. The voluntary Junior Faculty Leadership Skills Program aims to do just that by bringing in experts from around the university to teach professional skills such as public speaking, negotiation, and conflict management. (As a bonus, this nine-month program hits on another component of the strategic plan: By creating close ties among members of different departments, it fosters interdisciplinary collaboration.)

Along with providing job-skills training, we need to promote mentorship and outline clear pathways for advancement, especially for minority employees. Diversity is paramount in the health professions. Patients report higher trust levels when they see a physician of the same race, and studies have shown that students trained at diverse schools are more comfortable treating patients from a wide range of backgrounds. We are committed to boosting the number of underrepresented minorities on campus, and we have laid out specific benchmarks for the gender and racial makeup of our leadership.

We’re testing other ways to keep our staff satisfied and engaged through wellness programs and community involvement. One ambitious proposal laid out in the strategic plan is to expand Healthy@Hopkins to the entire JHM workforce. This initiative promotes healthy lifestyles by rewarding employees—think: bonuses—for good habits relating to nutrition, fitness, care management, and tobacco cessation. The goal is to bring down health care costs by creating a culture of health within the Hopkins community, an endeavor we hope to replicate in the larger regions JHM serves. The plan also calls for a measurable increase in community service through undertakings like our Henrietta Lacks school visits. This program brings Hopkins scientists and bioethicists into Baltimore schools to expose students to real-world lab work and, hopefully, stimulate interest in careers in science. Government and Community Affairs has built a website to aggregate these volunteer programs to make it easier for all to participate.

Most importantly, we must identify incentives—financial and otherwise—to show that employees’ contributions are valued. One quality that sets Hopkins apart from the average workplace is the level of dedication to the collective mission. Medicine is a caring profession, and here, the ethos of helpfulness extends beyond the clinic, permeating every office on campus. From the time I turn up N. Broadway in the morning, I encounter people who outperform their job descriptions. Kathy Grimes, an attendant in the Rutland Garage, asks about your family members by name and waves you through the gate with a smile. Our IT specialist in the Administration office, Don Harrison, reliably answers our panicked calls in the late afternoon when he’s off-duty. Our workdays can be frenetic, but we need to take time to say thank you for these extra efforts. Promoting a culture of gratitude is a vital part of the strategic plan, even if it’s not a quantitative metric.

Over the next decade, we will encounter unprecedented challenges in the health care landscape. It’s natural to feel apprehensive about this uncertain future, but thanks to the caliber of people at Johns Hopkins and the plans we have in place to support your work, I am confident we are positioned to lead the way through these uncharted climes. *
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