

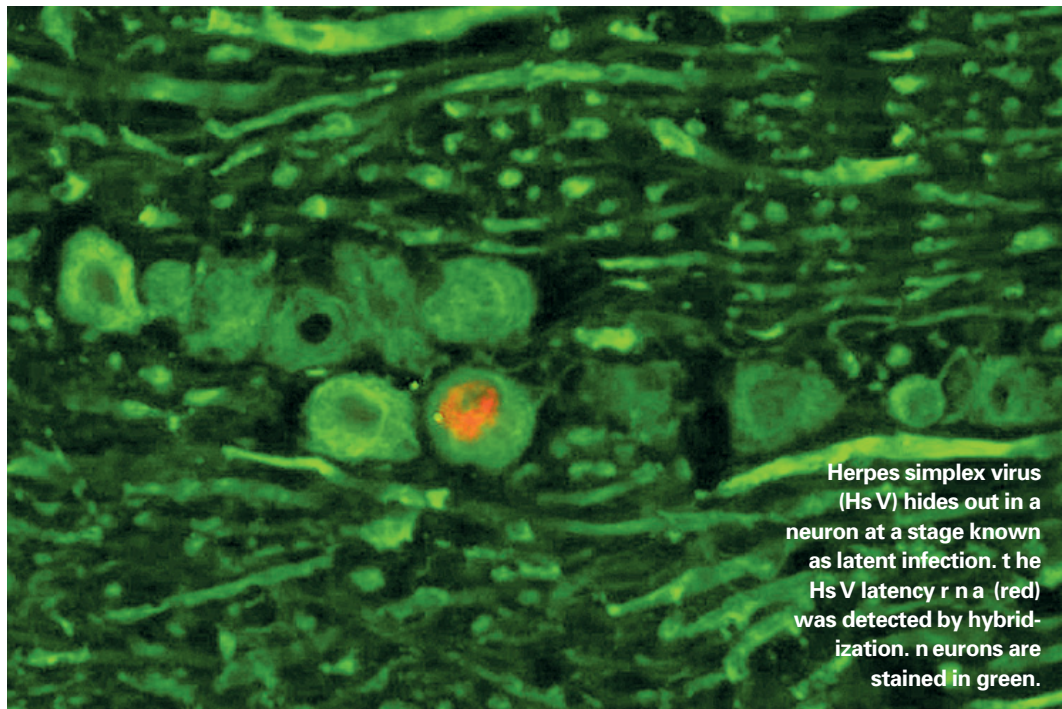
FOCUS



News from Harvard Medical, Dental and Public Health Schools
May 2011
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Herpes simplex virus (Hs V) hides out in a neuron at a stage known as latent infection. The Hs V latency RNA (red) was detected by hybridization. Neurons are stained in green.

Genital Herpes More Virulent in Africa

Researchers envision one vaccine for both strains

Strains of genital herpes in Africa are far more virulent than those in the United States, researchers at Harvard Medical School report, a striking insight into a common disease with important implications for preventing HIV transmission in a region staggered by the HIV/AIDS epidemic. The researchers arrived at this finding by testing mouse model strains of genital herpes against vaccine candidates. All vaccines were far more efficacious in abating the U.S. strain than those in Africa.

The researchers say identification of the properties of the African viruses would open the door to developing a more potent vaccine against an infection now rampant in sub-Saharan Africa. This is important, they say, because genital herpes patients are more vulnerable to HIV infection, as the open

See “Genital Herpes,” page 6



Angela Alberti

Suneng Fu (left) and Gökhan Hotamisligil

New Insight Into Obesity and Metabolic Disorders

Focus on endoplasmic reticulum reverses hallmarks of Type 2 diabetes in mice

Building on a decade of discoveries concerning obesity’s role in Type 2 diabetes and related metabolic disorders, researchers at the Harvard School of Public Health have uncovered surprising roles for lipid and calcium-processing abnormalities in the liver. By correcting these problems in a mouse model, the team reversed high blood-glucose

See “Obesity,” page 8

The science of Resiliency

Helping medical students manage stress

How do people maintain resiliency during stressful experiences? There’s no simple cure for the high rates of depression and burnout reported in recent studies of U.S. physicians, residents and medical students. But researchers who study stress and the brain say resiliency can be taught.

At the HMS Academy’s Seventh Annual Symposium on the Science of Learning on April 1, about 100 faculty members heard presentations on the topic of “Resiliency and Learning: Implications for Teaching Medical Students and Residents.”

“Understanding the neurological and psychological consequences of stress on learning and personal growth, good and bad, is critical as we work to optimize physician education,” said Richard

See “Resiliency,” page 6



Justin Ide/Harvard News Office

Jeffrey Sachs decried health inequities April 5 at the Global Health delivery symposium.

Closing the Know-do Gap

Leaders grapple with global health delivery

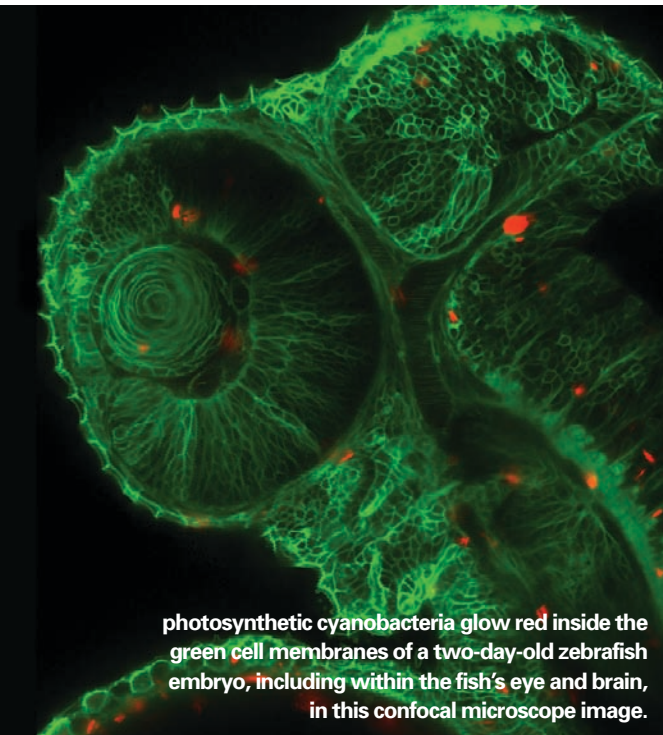
In global health, knowing the solution to a problem often isn’t enough; the challenge is using that knowledge effectively. This “know-do” gap was one of the central puzzles that drew key leaders to HMS April 4 and 5 for a symposium titled “Global Health Delivery: Challenges and Opportunities for Advancing Excellence and Equity.”

“This is a moment to critically examine where we stand in generating and delivering the ideas, interventions and leadership that will advance global health equity—and to ask how we can do better,” said Paul Farmer, Kolokotronis University Professor and chair of the HMS Department of Global Health and Social Medicine (GHSM),

See “Global Health,” page 8

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photosynthetic cyanobacteria glow red inside the green cell membranes of a two-day-old zebrafish embryo, including within the fish's eye and brain, in this confocal microscope image.

Odd Couple: Fish and Photosynthesis

Experiment in symbiosis points toward a synthetic chloroplast

Mimicking the symbiotic evolution that lets plants reap energy from sunlight, HMS researchers have injected photosynthetic bacteria into the cells of fish, which then went on to develop normally even as the solar-powered bacteria lived—for a time—inside them. The achievement not only sheds fresh light on evolution, but also lays down roots for novel cellular machines that could one day grow designer molecules such as nutrients, medicines and biofuels.

Most biologists believe that the chloroplast, the photosynthetic machinery of a plant cell, descended from a simple light-harvesting organism that evolved a symbiotic relationship with its host. In their experiment, the HMS researchers induced just such a relationship, known as endosymbiosis, inside animal cells by cultivating the photosynthetic cyanobacteria *S. elongatus* within embryonic zebrafish.

The findings, reported in an article titled “Toward a Synthetic Chloroplast,” were published April 20 in the journal *PLoS ONE*.

“We used a synthetic approach to developing photosynthetic associations with animal cells, finding that injecting *S. elongatus* into the zebrafish

embryo does not affect fish development,” wrote the researchers, led by Pamela Silver, HMS professor of systems biology. The zebrafish cells divided normally, and the cyanobacteria survived until pigments in the developing embryos began to block light.

While the Harvard researchers were conducting the experiment, a Canadian team discovered a similar phenomenon in the wild: The cells of some salamander embryos play host to algae that disappear as the embryos turn opaque.

A similar endosymbiotic relationship is believed to help explain the evolution of the mitochondrion, an organelle that, like the chloroplast, has its own genetic code.

Scientists had observed photosynthetic bacteria living endosymbiotically within invertebrate animals, including coral and sea slugs, leading Silver to wonder whether such bacteria could be introduced to other species as well.

A PhD student in Silver’s laboratory, Christina Agapakis, took up the challenge, working with master’s student Henrike Niederholtmeyer and with Ramil Noche, a research fellow in the lab of Sean Megason, HMS assistant professor of systems biology. “The biggest surprise was that the zebrafish lived just fine with the bacteria inside them,” Agapakis said.

Separately, the Silver lab has engineered strains of bacteria that produce sugar, which could in theory provide energy to a host cell, although Agapakis cautioned that the quantities were far too small to make a difference.

In future research, the HMS researchers hope to engineer relationships in which the bacteria provide essential molecules to host cells. “Our results show that it is possible to engineer photosynthetic bacteria to invade the cytoplasm of mammalian cells for further engineering and applications in synthetic biology,” the researchers wrote. “Engineered invasive but non-pathogenic or immunogenic photosynthetic bacteria have great potential as synthetic biological devices.”

The Silver lab is also exploring the potential of cyanobacteria to produce biofuels and other commodities. “We have a large-scale interest in light-harvesting microbes,” said Silver. “We want to understand how to make that process more efficient by making carbon fixation more efficient.”

—R. Alan Leo

For more information, students may contact Pamela Silver, HMS professor of systems biology, at pamela_silver@hms.harvard.edu.

Paper Chase

RECENT PUBLICATIONS FROM HMS RESEARCHERS

The index below is a selection of new studies and review articles by researchers from across the HMS community. It represents a small sample of research at focushms.com.

When to Initiate Combined Antiretroviral Therapy to Reduce Mortality and AIDS-Defining Illness in HIV-Infected Persons in Developing Countries: An Observational Study.

The HIV-CAUSAL Collaboration (12 institutions, including the Harvard School of Public Health)

Most clinical guidelines recommend that AIDS-free, HIV-infected persons with CD4 cell counts below 0.350×10^9 cells/L initiate combined antiretroviral therapy (cART), but the optimal count at which cART should be initiated remains a matter of debate. Objective: To identify the optimal CD4 cell count at which cART should be initiated. Conclusion: Initiation of cART at a threshold CD4 count of 0.500×10^9 cells/L increases AIDS-free survival. However, mortality did not vary substantially with the use of CD4 thresholds between 0.300 and 0.500×10^9 cells/L. *Annals of Internal Medicine*. 2011 April 19;154(8):509–15.

Pancreatic Cancer Requires Autophagy for Tumor Growth.

Yang S, Wang X, Contino G, Liesa M, Sahin E, Ying H, Bause A, Li Y, Stommel JM, Dell’antonio G, Mautner J, Tonon G, Haigis M, Shirihai OS, Doglioni C, Bardeesy N, Kimmelman AC. Dana-Farber Cancer Institute, HMS

Macroautophagy (autophagy) is a regulated catabolic pathway to degrade cellular organelles and macromolecules. Its role in cancer is complex and may differ depending on tumor type or context. The authors show that pancreatic cancers have a distinct dependence on autophagy. These results suggest that, unlike in other cancers where autophagy inhibition may synergize with chemotherapy or targeted agents by preventing the up-regulation of autophagy as a reactive survival mechanism, autophagy is actually required for tumorigenic growth of pancreatic cancers *de novo*, and drugs that inactivate this process may have a unique clinical utility in treating pancreatic cancers and other malignancies with a similar dependence on autophagy. As chloroquine and its derivatives are potent inhibitors of autophagy and have been used safely in human patients, these results are immediately translatable to the treatment of pancreatic cancer patients, and provide a much needed, novel vantage point of attack. *Genes & Development*. 2011 April 1;25(7):717–29. Epub 2011 Mar 15.

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Recent books written or edited by members of the HMS, HSPH and HSDM faculty or staff may be submitted to *Focus* at the address above. Books received by May 20, 2011, will be featured in the next book section.

We invite letters from our readers, which should be brief and include a signature, address and daytime phone number.

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Intrepid explorer of the extracellular Matrix

Symposium celebrates Bjorn Olsen, scientist and mentor

Friends, colleagues, former students—even competitors—celebrated the personal and professional achievements of Harvard scientist Bjorn Olsen, intrepid explorer of the extracellular matrix, at a symposium April 14 and 15 organized by Olsen's former mentees. In tribute to their teacher and guide, speakers traced their own successes in the field to the broad, sturdy foundation of Olsen's pioneering research.

"Without a doubt, he's the most brilliant man I've ever met," said Damian Medici, a Dean's Scholar at the Harvard School of Dental Medicine and an instructor of developmental biology. "He's also the kindest and most generous man I've ever known."

Scholars echoed those sentiments during the two-day event, which included a "Science Blast," a series of 31 short research reports, followed by a day of formal lectures and posters in the Joseph B. Martin Conference Center rotunda.

Olsen, who is the Hersey Professor of Cell Biology at HMS and both professor of developmental biology and dean for research at the Harvard School of Dental Medicine, arrived at Harvard in 1985 and has published more than 360 papers. The symposium, planned by former trainees Marion (Emmy) Gordon, Donald Gerecke, Kathy Svoboda and Matthew Warman, the Harriet M. Peabody Professor of Orthopedic Surgery at Children's Hospital Boston, who now head research programs in New Jersey, Texas and Massachusetts, was inspired by Olsen's recent findings connecting skeletal development and vascular biology. The event probed the complex relationships between living cells and the extracellular matrix, or ECM.

Olsen has taken the lead in sorting out the ECM's role in building and maintaining the human body from embryo to adulthood. Like mortar, the matrix binds cells together, enabling trillions to work in harmony while providing physical support and organization in higher organisms. The ECM also serves as a storehouse, transport system and source of enzymes and signaling molecules that orchestrate cellular activity.

Fundamentally, the ECM is essential to multi-cellular life: Its existence was a prerequisite for the evolution of higher organisms, and it is key to maintaining their metabolic equilibrium. Depending on the tissue or organ, the ECM contains molecules that stimulate cell growth, control cell migration or govern cell differentiation.

Numerous diseases and malformations stem from problems in the ECM and alterations in cellular interactions with the ECM. These range from tumor-like masses known as hemangiomas to deformed skeletal growth patterns and eye disorders.

Among Olsen's major achievements are an improved understanding of dwarfism, congenital vascular anomalies, osteoporosis and osteoarthritis. His lab has also uncovered complex roles played by gene transcription factors and cell-surface receptors that, for example, rearrange blood vessel networks.

FOLLOW THE LEADER

Symposium speakers noted that Olsen is good at getting people from different disciplines to talk to one another about how biological systems interact—and fail. "In the past, the muscle people and the bone people were totally uninterested in each other, but it's remarkable how well they've come together," Olsen said.

As a first-year orthodontic resident in search of a research mentor in 1986, Reginald Taylor followed a fellow resident's tip and contacted Olsen, who "taught me how to ask the right questions," said Taylor, now director of predoctoral orthodontics at Texas A&M Health Science Center Baylor College of Dentistry. "He has this depth of knowledge, but his knowledge doesn't intimidate you."

Suneel Apte, a member of the research faculty at the Cleveland Clinic, in Ohio, whose interests lie in protein regulation in the ECM, confessed that "I didn't know anything" as a postdoctoral fellow in Olsen's

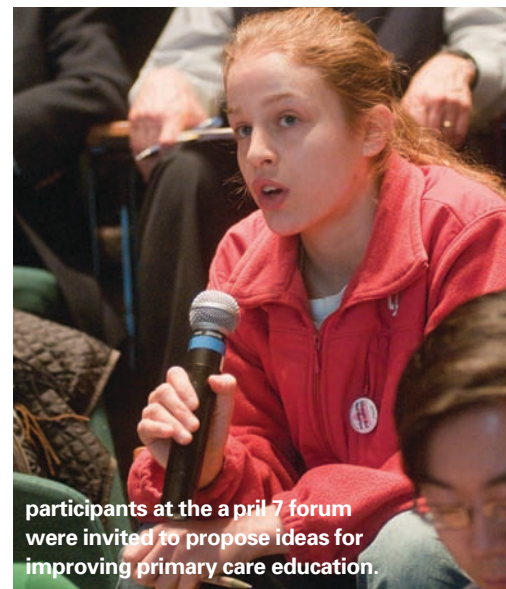
lab in 1989. At first, he said of Olsen, "I thought he was quite mad, which was very appealing." Clearly, adventures were in store. Here was a leader worth following.

Francesco Ramirez, professor of medicine and cardiology at the Mount Sinai Medical Center, in New York, said that when in 1979 he got to Rutgers Medical School, now the Robert Wood Johnson Medical School, Olsen "took away my anxiety" while helping shape his career. Ramirez now studies connective tissue diseases. His work on Marfan syndrome led to identification of the causative gene defect.

Olsen's team and collaborators recently reported on fibrodysplasia ossificans progressiva, a "rare but horrific disease," Olsen said, in which endothelial cells, which line blood vessels, transform themselves into stem-like cells that give rise to bone and cartilage cells. "Patients have bone developing in soft tissues, such as muscle, causing them to lose mobility—they are frozen in space."

The findings may open a door toward tissue repair, provided scientists can learn to control this quality of "endothelial stemness" to replace sick or dying cells. Said Olsen: "That's what I'll be working on in the next 10 years."

—Bob Cooke



participants at the April 7 forum were invited to propose ideas for improving primary care education.

Ideas Pour in for Primary Care education at HMs

The Carl W. Walter Amphitheater in the Toston Medical Education Center was a case study in infectious enthusiasm on April 7 as Harvard medical students, residents, faculty and even a few undergraduates gathered to brainstorm how the medical school's MD curriculum and residency training programs might better equip physicians for careers in primary care.

HMS Dean Jeffrey S. Flier opened the town hall-style meeting, "thrilled," he said, by the privilege of watching the new Harvard Medical School Center for Primary Care take shape. "Things are happening in this community that were unimaginable even a year ago," he said.

Flier expressed gratitude to interim co-directors David Bates, HMS professor of medicine at Brigham and Women's Hospital, Andrew Ellner, instructor in medicine at Brigham and Women's, and Russell Phillips, HMS professor of medicine at Beth Israel Deaconess Medical Center, as well as to Andrew Morris Singer, president and principal founder of Primary Care Progress, a grassroots advocacy organization that cosponsored the meeting.

Ellner introduced the Primary Care Center's new interim executive director, Jill Bassett, who is charged with establishing the infrastructure of the Center, directing its administrative activities, and fostering collaborative relationships across the School and beyond. Until last month, Bassett was chief of staff to JudyAnn Bigby, the Massachusetts secretary of Health and Human Services. Bassett, who holds a master's of science from the Harvard School of Public Health, previously served as program director at the HMS Center of Excellence in Women's Health.

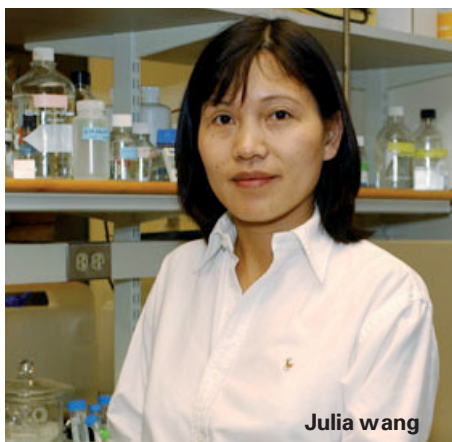
After brief presentations—including proposed skills for the primary care physician of tomorrow—Rebecca Berman, an HMS instructor in medicine at Massachusetts General Hospital, invited attendees to the microphone.

Scores of participants proposed ideas for consideration by the center's education committee, co-chaired by Berman and Sara Fazio, HMS associate professor of medicine at Beth Israel Deaconess. Suggestions ranged from the exploration of "lifestyle medicine" to innovative uses of information technology to the greater integration of HMS with community health centers.

—David Cameron



Bjorn Olsen



Julia wang

A unifying Theory of Autoimmune disease

Carbohydrate activates B cells in skin, connective tissues

Researchers led by HMS Associate Professor of Medicine Julia Wang offer a new, unifying theory on the origins of autoimmune diseases. In two related papers in the May 2011 issue of the *American Journal of Pathology*, the team outlines a process by which a carbohydrate abundant in skin and connective tissue called dermatan sulfate turns traitorous. The resulting disease may be systemic, as in lupus or rheumatoid arthritis, or localized, as in Type 1 diabetes or Graves' disease.

Only a tiny subset of molecules in the body are known to have the potential to become autoantigens, targets of an immune system that mistakes "self" as foreign. Immune B cells play a key role by producing autoantibodies to these autoantigens.

In mice, Wang, along with current and former research fellows Jongmin Lee, Ming Yan, Jung-hyun Rho and Michael Roehrl, demonstrate that dermatan sulfate plays a pivotal role in regulating a type of B cell called B-1a. Levels of both dermatan sulfate and B-1a cells are elevated when cell turnover is high, as in wound healing.

The researchers suggest that, when dead cells pile up, dermatan sulfate may help speed the clearing of these cells by the immune system. Dermatan sulfate has a downside, however. When cells with a high affinity for the molecule die, the resulting complexes can become unrecognizable as self. These complexes stimulate the proliferation of B-1a cells and the production of autoantibodies, which in turn mark healthy tissues for destruction. When autoantibodies bind to autoantigens on healthy cells, other autoimmune B cells infiltrate the tissue, and damage ensues.

In an accompanying patient study, Wang and colleagues Rho, Roehrl, Wei Zhang and Mandakolathur Murali found that the full complement of autoantigens in humans—more than 200—could be classified by their affinity for dermatan sulfate. "It is those molecules that can associate with dermatan sulfate which have a propensity to become autoantigens," Wang said.

Wang and her coauthors came to their conclusion by an unconventional route. "We did not investigate this in the traditional immunological way, using genetic approaches," Wang explained, referring to the strategy of tinkering with genes to heighten or dial back certain proteins in B cells or other autoimmune-response components.

Instead, Wang said, "we used immunological, biochemical and proteomic tactics to isolate a common denominator among autoantigens" in cell cultures, in a mouse model, and in humans. With most research focused on proteins, she said, dermatan sulfate has not been an obvious target for study.

Autoimmune diseases "are ripe for a real breakthrough," said Wang, who with colleagues has begun developing personalized molecular serum testing for patients to help diagnose autoimmune diseases at a more precise molecular level.

"Many therapies target over-reactive B cells," Wang said. "Now, with a new mechanism for B-1a cell activation in mind, scientists have a chance to disrupt the start of that dangerous process."

—Mary Bates

To learn more, students may contact Julia Wang at julia_wang@rics.bwh.harvard.edu

Lessons in Leadership

How do you lead? That's the question that drew rising stars from across the HMS medical community to the ninth conference of HMS Leadership Development for Physicians and Scientists, as 57 instructors, assistant professors and associate professors convened April 5-8 for lessons in institutional organization, finance, legal and regulatory issues, and communication. Among the highlights of the event was a panel session that convened leaders of five Boston teaching hospitals. Moderator Jean Emans, faculty director of the Office of Faculty Development at Children's Hospital Boston, invited them to share insights from their careers. Excerpts follow.



Serve

"Leadership is about serving. It's about serving the families and patients that come to us; it's about serving our faculty; it's about serving the academic mission; it's about serving all of the things that we in the medical community do to play a role for a short period of time."

— James Mandell, chief executive officer, Children's Hospital Boston, and Robert and Dana Smith Professor at HMS



Embrace Risk

"It's hard for scientists and for physicians, who are extremely data-driven, to be able to take a leap into the dark without knowing exactly what the outcome is going to be. But my 95½-year-old father taught me: If you don't take risks, you can be very, very good. But you will never be great."

— Ellen Zane, president and chief executive officer, Tufts Medical Center



Be Yourself

"The best managers I see are people comfortable in their own skin. They don't try to put on a personality in their management role that's different from who they are when they're seeing patients or at home. Adopt a management style that fits your personality. Don't try to be someone else."

—Peter Slavin, president, Massachusetts General Hospital, and professor of health care policy at HMS



Focus and Excel

"You're all extraordinarily talented, but a difficult decision at this stage of your career is where to focus. Success there is what will define you, so develop an area of excellence or expertise. Often, it's what you're passionate about. It can be research, it can be in the clinical arena, it can be teaching."

— Elizabeth Nabel, president, Brigham and Women's/Faulkner Hospitals, and professor of medicine at HMS



Check Your Ego

"It's amazing what a leader can accomplish when you don't take credit. Your mission as leader is to help other people achieve things that advance the mission of the organization, and in a sense to bask in their reflected glory. Your ego and the ego of the institution must be very much in alignment."

— Edward Benz, Jr., president and chief executive officer, Dana-Farber Cancer Institute, and Richard and Susan Smith Professor of Medicine at HMS

Photos from top: Webb Chappell/CHB; Tufts Medical Center; MGH Photo Services; NHLBI; DFCI



Back row: Jack Burke, Kim Serrecchia, Selwyn Rogers; front row: Graham McMahon, Nadège Volcy, Michael Piantignini, Margarita Alegria, Thomas Sequist, Albert Galaburda, Price Cobbs

Jeff Thiebaud

bisexual and transgender advocacy and inclusion at HMS and Brigham and Women's Hospital (BWH);

■ **Selwyn Rogers, Jr.**, associate professor of surgery and chief, Division of Trauma, Burn and Surgical Critical Care, for fostering a diverse environment within the division at BWH;

■ **Thomas Sequist**, associate professor of medicine and medical director, outreach program, BWH, for his leadership of the Four Directions Summer Research Program, which aims to address the declining representation of Native Americans in medicine;

■ **The Department of Psychiatry at Cambridge Health Alliance**, for creating an environment that supports and promotes diversity and inclusivity for faculty, trainees, students and staff; developing minority researchers who focus on health disparities; establishing programs, services and performing research that impacts the health of the local community, with particular recognition of Margarita Alegria, director of the Center for Multicultural Mental Health Research, for her mentorship and support of students, trainees and staff at all levels, and Jack Burke, chief of psychiatry, for his championing of culturally affirmative care in support of the hospital's mission "to improve the health of our communities."

■ **The Haiti Relief Committee** received the Sharon P. Clayborne Staff Diversity Award for coordinating HMS relief efforts and for their support of employees impacted by the 2010 earthquake. Members include Maria Bollinger, staff assistant, HMS; Shannon Campbell, human resources coordinator, HMS; Patrick Casky, senior research officer, Wyss Institute for Biologically Inspired Engineering; Ellen Hanson, employee coordinator, HSPH; Michael Piantignini, financial associate, HMS; Jennifer Sarbahi, former web editor, HMS; Kim Serrecchia, project manager, HMS; and Nadège Volcy, senior cost analyst, HMS.

—Valerie Wencis

Celebrating diversity

What does it mean to be an American? Psychiatrist and author Price Cobbs posed the question April 12 as he exhorted listeners to reflect upon a swiftly changing society at the 2010-2011 Howard, Dorsey, Still Lecture and Diversity Awards ceremony.

As the United States becomes more multicultural, what is happening to long-treasured images of America? And when do immigrants, legal and illegal, make the transformation into being Americans? asked Price Cobbs, CEO of Pacific Management Systems, member of the Institute of Medicine and author of *My American Life: From Rage to Entitlement*.

"While all great migrations change and enlarge the culture of the nation they enter, it is undeniable that this recent immigrant migration has greatly enlarged what we think of as American culture," said Cobbs, a founder of the African American Leadership Institute at the Anderson School of Business at

the University of California, Los Angeles. Newcomers must adapt, he said, to rules written and unstated in order to thrive; children, for example, are encouraged to be bi- or tri-lingual.

The annual Howard, Dorsey, Still Lecture was named for the first three African Americans to graduate from HMS, in 1869 and 1871, nearly 70 years after its founding. The election of Barack Obama, Cobbs noted, was for many definitive proof that America was on a new path.

Declaring the United States "a work in progress," Cobbs outlined an unfinished agenda that will entail closing wide disparities in wealth, education, health care and legal and

social justice. He exhorted listeners to promote, within the context of heightened national and cultural identity issues, self-awareness and inclusivity. "If we can identify issues, if we can make diagnoses, then we can institute treatment," he said.

CHAMPIONS OF INCLUSIVITY

In presenting the annual Harold Amos Faculty Diversity Awards, Dean for Diversity and Community Partnership Joan Reede introduced selection committee chair Winfred Williams, Jr., assistant professor of medicine at the Massachusetts General Hospital. The 2011 honorees are:

■ **Albert Galaburda**, Emily Fischer Landau Professor of Neurology, for creating a diverse environment within the Cognitive Neurology Unit at Beth Israel Deaconess Medical Center;

■ **Graham McMahon**, assistant professor of medicine, Division of Endocrinology, for lesbian, gay,

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Notable

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\$1 million Dan David Prize to **Gary Ruvkun** • Ho-Am Prize in Medicine to **Augustine M.K. Choi** • Thomas H. Lee, MD, Award for Excellence in Primary



Care to **Rebecca Cunningham** • American Association for Cancer Research (AACR)

Award for Outstanding Achievement in Cancer Research to **Nathanael Gray** • Solomon A. Berson Distinguished Lectureship in Experimental Biology (FASEB) to **Christos Mantzoros** • postdoctoral fellowship from the National Space Biomedical Research Institute to **Christopher Morris** • Henry Gray/Lippincott Williams & Wilkins

Scientific Achievement Award from the American Association of Anatomists to Bjorn Olsen • American Gastroenterological Association (AGA) Distinguished Educator



Award to **Helen Shields** • American Academy of Arts and Sciences to induct **David Corey**, **George Daley**, **Julio Frenk**, **Daniel Haber**, **Robert Kingston** • Searle Scholars are **Sandeep Datta** and **Wendy Garrett** • Paul & Daisy Soros Fellowships for New Americans to **Melis Anahtar**, **David Reshef**, **David Mou**, **Carlos Torres** and **Steve Xu**.

Genital Herpes

Continued from page 1

sores symptomatic of herpes contain a high concentration of the immune cells targeted by HIV.

The challenge lies in formulating either a single vaccine that protects against both types of genital herpes virus strains or two different vaccines. The vaccine furthest along in development—headed for clinical trials in about a year—works best against the U.S. isolates of herpes simplex 2, but it also protects laboratory animals from the African viral strains if given in fivefold-higher doses.

This research, published online on April 14 in *The Journal of Infectious Diseases*, was led by David Knipe, the Higgins Professor of Microbiology and Molecular Genetics at HMS and a vice chair of that department, and Clyde Crumpacker, a professor of medicine at HMS and physician in the Division of Infectious Diseases at Beth Israel Deaconess Medical Center. Their collaborators are former Knipe lab members Timothy Dudek of the Ragon Institute of MGH, MIT and Harvard, and Ernesto Torres-Lopez of the Universidad Autonoma de Nuevo Leon in Monterrey, Mexico.

IVe-VIRuS VACCIn e

In southern Africa, infection rates for genital herpes are exceedingly high among adults—from 80 to 90 percent in some groups compared to slightly under 20 percent in the United States.

In evolutionary terms, the herpes viruses are very old. They have become efficient parasites in humans, often persisting for decades while causing limited or no disease symptoms, although in immunocompromised people and in newborns they can be deadly.

The herpes virus that causes ordinary cold sores, herpes simplex 1, is present in about 70 percent of the U.S. population. These stealthy viruses hide in nerve cells but can emerge over and over again, prompting repeated cold sore outbreaks.

Despite decades of research, there is no commercially available vaccine for herpes. But Knipe says their prototype vaccines are being tested in animals, and one such vaccine has been licensed to the French pharmaceutical firm Sanofi Pasteur.

According to Knipe, animal tests demonstrate clearly that the strains of herpes virus in sub-Saharan Africa are more virulent than the herpes simplex 2 virus strains in the United States. That difference suggests that an effective vaccine will probably have to be given to people in Africa in larger or more frequent doses. So far, says Knipe, results of animal tests are heartening.

Part of the promise of this work lies in the strong chance that a vaccine against herpes simplex 2 would help reduce the impact of HIV/AIDS in southern Africa, Knipe said. Epidemiological studies have shown that genital herpes infection is associated with a threefold increase in the risk of HIV infection there.

“If the rate of herpes infection can be reduced, it’s conceivable that the rate of HIV infection will also come down, perhaps reducing the death rate,” said Knipe.

“This is nothing short of a smoking gun in the stunning magnitude of the HIV epidemic in Africa,” said John Mekalanos, the Adele Lehman Professor of Microbiology and Molecular Genetics at HMS and chair of the department.

“Could herpes genital lesions predispose victims to acquisition of HIV? If so, this could point to both the cause and a strategy for control of the severe HIV epidemic there. Knipe and Crumpacker’s findings should refocus efforts on genital herpes vaccines as the first step in preventing HIV transmission in Africa.”

n eXT s TePs

Knipe’s approach to vaccine development is based on using abnormal, live, mutant viruses to stimulate protective immune responses. These disabled viruses cannot multiply inside cells or cause symptomatic disease, but they do contain enough of the right proteins and molecules needed to

“This is nothing short of a smoking gun in the stunning magnitude of the HIV epidemic in Africa.”

—John Mekalanos, Adele Lehman Professor of Microbiology and Molecular Genetics at HMS and chair of the department

arouse detection by a healthy immune system. Knipe’s strategy is to trigger a strong immune response without causing disease.

“The candidate vaccine, ACAM529, is under development by Sanofi Pasteur, and under the current plan will enter phase I clinical testing in 2012,” said Jim Tartaglia, a company vice president. Phase I testing involves giving vaccine to a small group of human volunteers and watching for signs of toxicity. Trials for efficacy come later.

Although it has been difficult to create a vaccine for genital herpes, vaccines against a closely related herpes virus—varicella zoster virus, the cause of chicken pox and shingles—proved successful and are now widely used. This gives reason for optimism about a genital herpes vaccine.

The researchers caution that, previously, two well-executed trials of Acyclovir, an effective, safe, antiviral drug for herpes, did decrease the occurrence of genital herpes infections but failed to prevent transmission of HIV-1 in African study participants. With this in mind, the researchers are planning studies aimed at better characterizing strains of herpes simplex 2 in sub-Saharan Africa. With support from the Harvard Global Health Institute, Knipe’s team is expanding its relationship with scientists in South Africa and is working to gather additional isolates of herpes simplex 2.

“Using additional isolates of herpes simplex 2 virus, we will further test our hypothesis that larger doses of the current vaccine will be sufficient to provide protection,” Knipe said. “If this is not the case, we will use a new genetic backbone for the vaccine, one that better matches the genetic profile of the virus in the isolates from Africa.”

—Bob Cooke

To learn more, students may contact David Knipe at david_knipe@hms.harvard.edu.

Resiliency

Continued from page 1

Schwartzstein, director of the Academy, which works to advance medical education throughout the HMS community. Schwartzstein is the Ellen and Melvin Gordon Professor of Medical Education at Beth Israel Deaconess Medical Center.

Bruce McEwen, a professor of neuroendocrinology at the Rockefeller University, described evidence that brief episodes of acute stress can enhance memory and learning, while chronic, high levels can damage the mammalian brain.

Drawing on work with children and adults, George Everly, an associate professor of psychiatry at Johns Hopkins Bloomberg School of Public Health, plumbed the psychological roots of human resilience. Both he and McEwen cited a network of social support and faith in a higher power or purpose as key to bouncing back from trauma and intense, prolonged stress.

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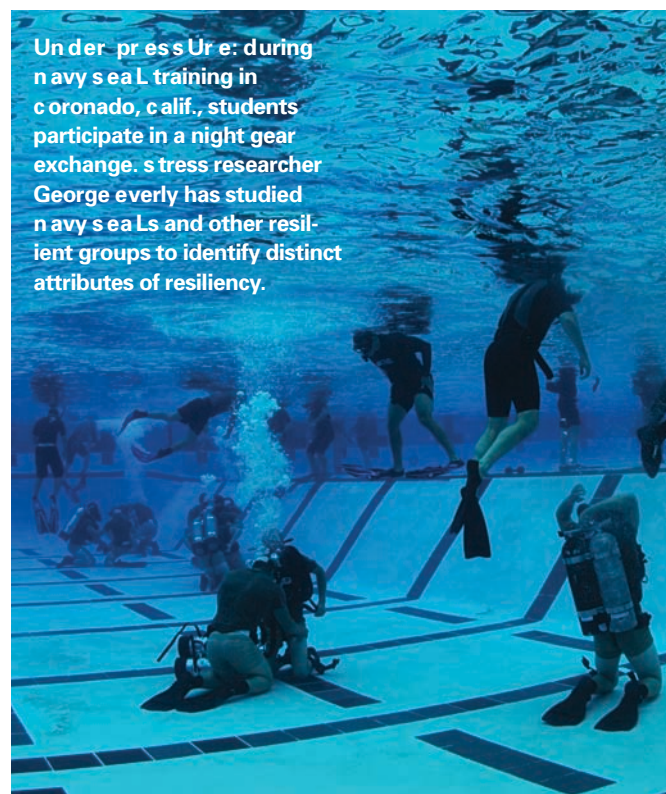
Linking the nervous and endocrine systems, biochemical mediators regulate the effects of stress, which are exacerbated by health-related behaviors such as inactivity or poor diet. Under acute stress—think “fight or flight”—the hypothalamus churns out corticotropin-releasing hormone, prompting a sharp rise in the stress hormone cortisol, which enhances immunity, memory, energy and cardiovascular function. Once the stressor has passed, the hormone DHEA, neuropeptide Y and other biochemicals rush in, restoring equilibrium and easing symptoms, such as hypertension. Acutely, these mediators, along with emotional engagement with a task, may enhance learning.

But when stress is chronic, cortisol erodes

oN THE WEB

Laurie Raymond, psychiatrist and director of the HMS office of Advising Resources, answers questions about helping students thrive at focushms.com/raymond.

Under pressUre: during navy seaL training in coronado, calif., students participate in a night gear exchange. s tress researcher George everly has studied navy seaLs and other resilient groups to identify distinct attributes of resiliency.



health. Immune suppression, hypertension, bone mineral loss, muscle wasting and metabolic disorders ensue. Within the hippocampus and amygdala, seats of memory and emotion, dendrites shrink and synapses vanish, McEwen has shown. Cognitive function declines, depression sinks in, the immune system weakens, and metabolism goes awry. In a study of medical students preparing for board exams, McEwen's collaborators found that higher levels of perceived stress predicted poor mental flexibility and reduced functional connectivity in the prefrontal cortex.

The good news: These ill effects are reversible, McEwen said. Regular exercise returns the hippocampus to normal size and improves memory, for example, while mindfulness training reduces the amygdala's volume and curbs anxiety. Many adult diseases could be prevented by reducing toxic stress in utero and in early childhood, he said.

THE Resilient Psyche

In the wake of war, natural disasters and severe abuse, 15 to 20 percent of those affected suffer from post-traumatic stress disorder. By focusing on the rest, including Navy SEALs and other stress-hardy groups, Everly has identified distinct attributes. The best predictor of immunity to stress, he said, is a social support network. Optimism (including faith in a higher cause or power), perseverance (work ethic), responsibility and integrity also count.

As for why some people sink instead of swim, Everly emphasized two factors: A lack of perspective—stemming from inadequate preparation and tenacity—and a negative attitude.

Resilience can be taught, said Everly, who also directs the Resiliency Sciences Institutes at the University of Maryland. First, let people experience success: Assign them to a successful group. Second, create a surveillance system and safety net, and provide encouragement, mentoring and training. Finally, mitigate the impact of stress by promoting “self-efficacy”—the belief that we are agents of change. Everly noted, however, that one cannot “give” self-esteem; it must be earned through personal accomplishment in the face of a challenge. Calling for a cultural shift, he said, “We must reframe mistakes as opportunities for learning.”

— Karin Kiewra



Béatrice Pautaire/Stockphoto

When the Patient Is the Teacher



Graham Ramsay

The fearless Ms. Francis cast her eyes on the future. “Give me some IV fluids so I can get home,” she commanded.

While three years of residency have taught me invaluable lessons about medical care, the most memorable have come not from fellow physicians but from my patients. Learning opportunities arise in the intimacy of the patient–doctor relationship and in the doctor's role as both participant in and witness to the patient's struggle with disease. Among my patient–teachers, three in particular have left indelible impressions.

Ms. Francis taught me that patients can be indomitably courageous. This small-framed 65-year-old with metastatic bowel cancer endured several surgeries and chemotherapy regimens over 10 years to treat her incurable disease. I met her at Dana–Farber Cancer Institute when she was admitted for infectious colitis, having presented with abdominal pain, fever and diarrhea. I remember being taken aback by the surgical scars on her abdomen, one of them still healing. Each scar represented a tumultuous hospital course in which complications meant that an invasive intervention had been her only option.

As we discussed a treatment plan, the fearless Ms. Francis cast her eyes on the future. “Give me some IV fluids so I can get home soon,” she commanded. She was defiant and full of spunk. As I walked out of her room, I wondered aloud about how such an unassuming patient could exude so much gusto and bravery, and I smiled inside.

Ms. Norton taught me that patients can be unflappably optimistic. Previously healthy, this 70-year-old woman grew short of breath while packing for a vacation with her husband. The ambulance crew found her pale and clammy. En route to the hospital, she experienced cardiac arrest, and several rounds of CPR and intravenous epinephrine were needed to recover her pulse.

Ms. Norton was intubated and admitted to intensive care. For the next two weeks, she and those who cared for her would grapple with her heart failure and kidney injury as well as pneumonia—one of the most feared complications in patients who are mechanically ventilated. When after two unsuccessful attempts she was finally extubated, cardiac catheterization revealed severe coronary artery disease and critical stenosis of a heart valve, both of which urgently required cardiac surgery.

Had I not first carefully reviewed Ms. Norton's chart, I might have thought I had the wrong patient. She was smiling. As we talked about what lay ahead for her, she was visibly nervous yet cracking jokes.

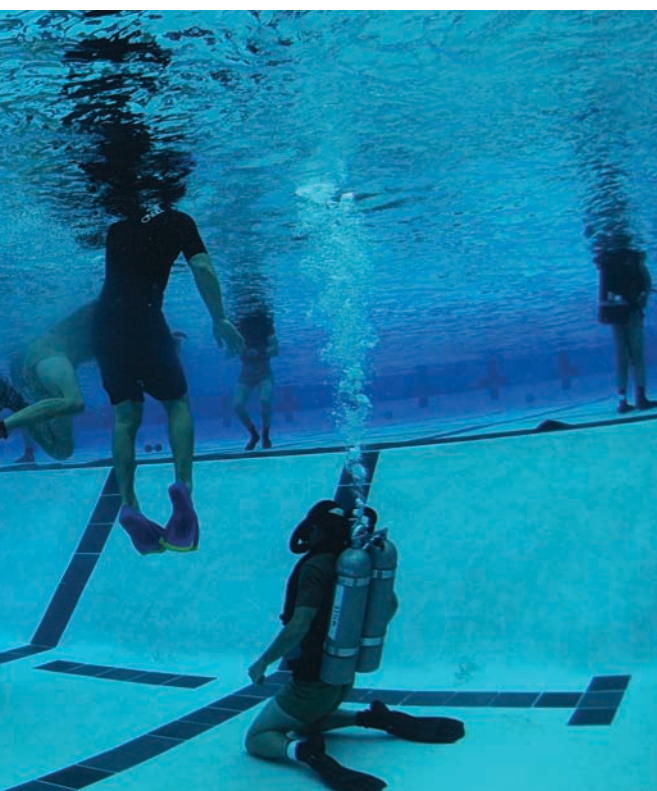
Her surgery went smoothly. After her return home, I called her. “It's like a dream,” she said. “The treatment and everything was unbelievable; I couldn't have asked for better. Thank you, Lord, I'm doing fine—I'm here today, and I'm alive another year.” I told her I admired her optimism. “That's my nature,” she said. “I can't see any other way to be. It's better to look on the positive and have a good attitude. It really helps.” I believe she is right.

Mr. Pallino taught me that patients choose how to deal with the emotional impact of their illnesses, for good or bad. This 45-year-old man hadn't left the hospital in over two months. Diagnosed with acute leukemia, he had responded only partially to aggressive chemotherapy, and recurrent fevers superimposed on a severely compromised immune system kept him tethered there.

I visited Mr. Pallino nearly every morning during my monthlong oncology rotation, and each time he struggled with depression. “It seems like nothing is going right,” he would say. Despite its partial failure, chemotherapy unleashed the full wrath of side effects, and Mr. Pallino experienced painful oral ulcers and incessant diarrhea. Low platelet counts from bone marrow eradication led to copious bleeding into his urine, necessitating transfusions and continuous irrigation of his bladder. Just before my rotation ended, he developed a cough. A chest scan revealed a fungal infection that would resist all but the most toxic treatment.

Mr. Pallino had to decide each day whether to struggle against his depression or yield to it. Usually he chose the former. “Hey, you can only do what you can do,” he'd say when his spirits lifted. “I've got to hang

See “Patient–Teacher,” page 8



Kyle D. Gahiau / U.S. Navy

Patient–Teacher

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in there and take it one day at a time.” He passed away from his disease, but he holds a place in my heart for showing me that patients must decide each day what their illness means to them—and that only they can choose how best to deal with the emotional trauma that can accompany serious illness.

These lessons are among the most important that my many patients have taught me. I am grateful, and I won’t lose sight of them as I move on to the next stage of my training.

—Joseph Ladapo, HMS ’08, is a resident in internal medicine at Beth Israel Deaconess Medical Center. The names used in this column are pseudonyms, and the opinions expressed are not necessarily those of Harvard Medical School, its

Global Health

Continued from page 1

which hosted the inaugural event for its Programs in Global Health and Social Change.

The Programs in Global Health and Social Change launched last year with a mission to advance the empirical evidence base for effective health care delivery in settings where inequitable access to health care, economic, technological, and social resources result in disease and poor health, and to link this research scholarship to medical education and practice.

The clinical focuses of the five programs correspond to major unmet burdens of disease in resource-poor settings: infectious disease, non-communicable disease, mental health, surgery and neonatal health.

“Right now, there is a remarkable amount of activity here at Harvard and across scores of universities and medical schools focused on what is loosely described as ‘global health,’” said Sadath Sayeed, director of the neonatal health program and, with colleague Vanessa Bradford Kerry, symposium co-chair. “Organizing this event, we were particularly interested in evaluating what it takes to equitably deliver excellent health care to the poorest populations, with an emphasis on the word ‘equity.’”

Keynote speaker Jeffrey Sachs, director of the Earth Institute and professor of health policy and management at Columbia University, told a rapt audience that the United States is no exception to inequity—“with the growing obesity epidemic, no access to care for the country’s poor, and a political system that is one of the most corrupt among high-income nations in the world.”

Sachs’ keynote was followed by a lively panel discussion titled, “Evidence to Policy: Translating Effective Delivery Strategies into Policy.” The panel comprised William Frist, former Senate majority leader and chairman of Hope Through Healing Hands; Rajiv Shah, administrator of the U.S. Agency for International Development; Agnes Binagwaho, permanent secretary of Rwanda’s health ministry and senior lecturer in GHSM; and John Ayanian, professor of medicine and health care policy at HMS and professor of health policy and management at Harvard School of Public Health.

Panelists offered an insider’s take on global health delivery. Frist, an HMS-trained physician

and former Republican senator from Tennessee, told the audience that while research can sway lawmakers, it must reach decision makers in a way they can understand. Key, he said, are intermediaries such as think tanks and legislative staffers—and engagement with the public.

“You’ve got to get out where real people are,” he said, before offering a bitter pill to the experts assembled in the Joseph B. Martin Conference Center: “We’re not real people in this room. You think you are, but you’re not.”

“you’ve got to get out where real people are. We’re not real people in this room.”

—Former Sen. William Frist

Binagwaho, of Rwanda’s health ministry, prescribed a path for countries that receive aid. Develop a strategy that addresses your nation’s needs and ensure that donor aid serves that plan. If not, she said, “you’ll end up serving the money.”

USAID’s Shah detailed the agency’s priorities: maternal health, vaccines, malaria, tuberculosis and HIV/AIDS. “From a macro perspective,” he said, “that’s where the ‘best buys’ are in improving the state of the world in global health.”

—R. Alan Leo

For more on Programs in Global Health and Social Change, visit ghsm.hms.harvard.edu/about/programs.

Obesity

Continued from page 1

levels, insulin resistance and other metabolic hallmarks of Type 2 diabetes.

As the related epidemics of obesity and diabetes escalate around the world, “the discovery of a faulty metabolic mechanism in fatty liver tissue opens new opportunities to consider for therapeutics,” said Gökhan Hotamisligil, the J.S. Simmons Professor of Genetics and Metabolism and chair of the Department of Genetics and Complex Diseases at HSPH. His team reported their findings in the May 2 issue of *Nature*.

The chain of molecular events by which obesity disrupts metabolism causes a domino effect of damage: high blood pressure, cholesterol abnormalities and resistance to insulin, a prelude to diabetes in which cells are unresponsive to the hormone and cannot efficiently make energy from blood sugar. In addition to diabetes, obesity has been linked to cardiovascular, liver and neurodegenerative diseases and certain cancers.

sTressed Out

The Hotamisligil lab had established chronic inflammation as a prime cause of metabolic disruption in obesity, implicating the organelle known as the endoplasmic reticulum (ER) and tracing insulin resistance and Type 2 diabetes to ER overload, or ER stress, as obesity develops. Subsequently, his group and others observed similar ER-stress-related problems in human obesity.

Until the Hotamisligil lab elucidated the ER’s role in regulating metabolism, the membranous organelle was known mainly for manufacturing and trafficking

proteins and for quality control. Why the ER fails in obesity was a mystery for the lab to solve.

HSPH Research Associate Suneng Fu, first author of the *Nature* paper, tackled that mystery by comparing the ER in fat and lean liver tissues. Instead of looking at one possible mechanism at a time, he mapped the organelle’s activities comprehensively.

Fu developed a methodology to purify the ER from lean and obese tissues, then isolated and identified each of the proteins and lipids present in the ER. HSPH collaborators Alexander Ivanov, research scientist, and Steven Watkins, visiting scientist, did the proteomic and lipidomic analyses, respectively.

The researchers anticipated that in obesity, the primary driver of ER stress was a flooding of the ER factory with protein. (Picture a conveyor belt on overdrive.) But in what Hotamisligil called a “shocking surprise,” they found that obese samples had fewer proteins and more lipids than did lean.

“Obesity was spurring a switch in the ER from synthesizing proteins to synthesizing lipids,” Hotamisligil said.

I lPId CHAn Ges

Looking closely at lipid changes in the fatty tissue, the researchers noted that two lipids critical to the structural integrity of the ER membrane, phosphatidylcholine and phosphatidylethanolamine—PC and PE—were the most altered. If the membrane were affected, they reasoned, perhaps its tubular channels, which were transporting calcium, were as well.

Hotamisligil likens the ER and its channels to a 12-cylinder Formula One race car, one that runs on calcium instead of just guzzling fuel in the form of ATP. The ER needs calcium to make and fold functional proteins. While searching the literature on channel function, the team uncovered a 25-year-old finding that a precise ratio of PC to PE was necessary for the function of proteins involved in channeling calcium. Interestingly, this ratio precisely resembled that measured by the team in the liver ER in normal, lean mice. In the fatty tissue, on the other hand, this ratio was high—perhaps explaining why, as the team noted, calcium was escaping through the ER membranes in obese liver.

To fix the leak, the researchers used two strategies. Through genetic manipulation they corrected the PC/PE ratio by blocking the effect of an enzyme, PEMT. They also used a virus to deliver to the fatty livers of lab mice a protein, SERCA, known to be responsible for pumping calcium into the ER.

Both maneuvers led to the same result: in essence, a reversal in the mice of metabolic problems. “ER stress went away, blood glucose levels fell back to normal, insulin sensitivity was restored and fatty liver was resolved,” said Hotamisligil.

In obesity, it is an increased synthesis of lipids, not of proteins, that disrupts ER function and leads to stress, the researchers concluded. Looking ahead to potential drug therapies, it might be possible to restore lipid metabolism and calcium homeostasis to normal, Hotamisligil said, adding that dietary solutions are also worth exploring.

The liver isn’t the only site wherein obesity disrupts metabolism and ignites metabolic disease by stressing the ER, Hotamisligil notes. ER stress has been observed in adipose tissue and in the pancreas and brain. In these tissues, too, he said, “we’re working to decode the ER landscape.”

—Ellen Barlow

To learn more, students may contact Gökhan Hotamisligil at ghotamis@hsph.harvard.edu.