FOCUS

News from Harvard Medical, Dental and Public Health Schools

March 2011 ▶ focushms.com

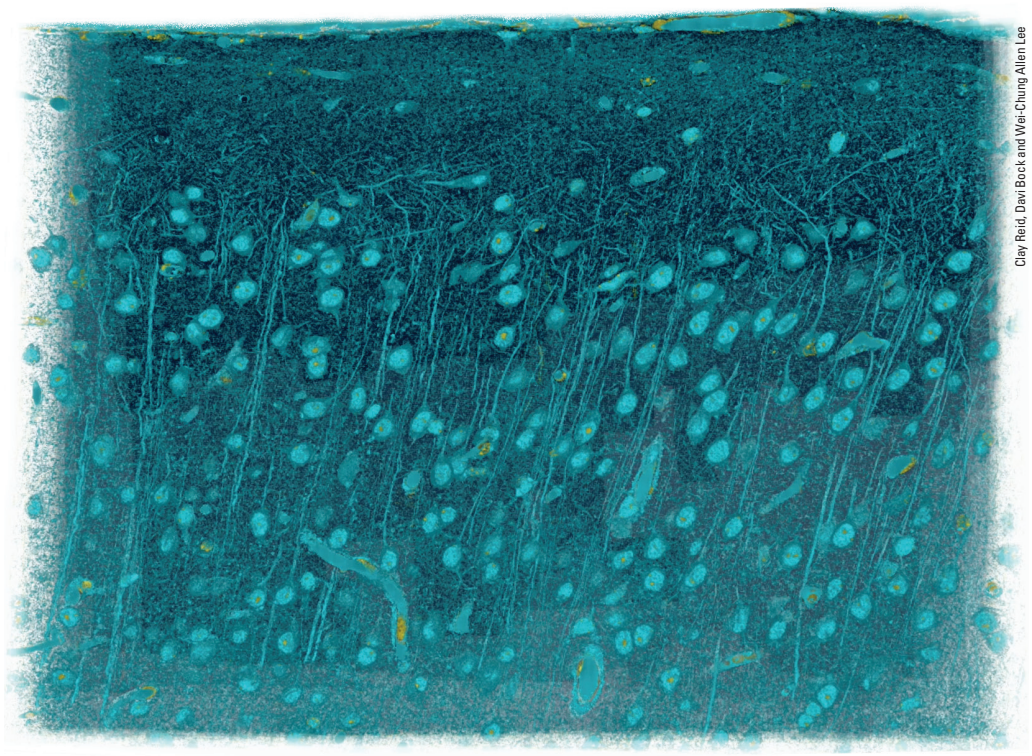
Pioneers

HMS psychiatrist Alvin Poussaint and Bill Cosby shared honors at Tufts for excellence in children's media.
See COMMUNITY, page 4

Web-Crawling the Brain

Neurobiologists map individual neurons to unravel the brain's circuitry

A single brain circuit contains millions of individual connections and is profoundly difficult to analyze. By mapping both the function and the connections of one part of a cortical circuit, researchers in the Department of Neurobiology at HMS have demonstrated a new way to study neural circuits, creating a powerful means to explore how the brain works. *See story, page 6*



Clay Reid, Davi Bock and Wei-Chung Allen Lee

Electron micrographs of thin sections of tissue from the cerebral cortex were aligned to reveal neural connections in three dimensions in a false-color composite rendering.

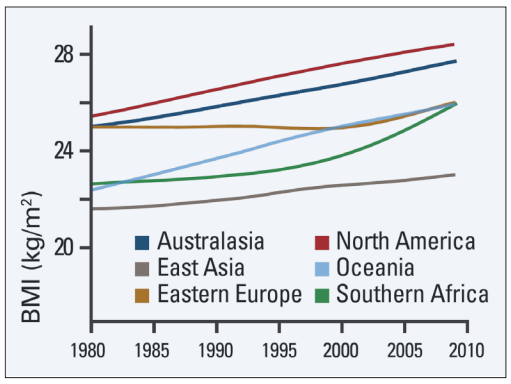
The Weight of the World

HSPH researchers help raise warning on skyrocketing rates of global obesity

Worldwide, 1 in 3 adults is overweight, and 1 in 9 is obese, according to a study in *The Lancet* on Feb. 12 that draws on an unprecedented volume of international data spanning the period from 1980 to 2008. These statistics bode ill for human health, experts say, triggering potentially catastrophic levels of chronic diseases, including Type 2 diabetes, cardiovascular diseases and cancers.

The study, led by Majid Ezzati, formerly an associate professor of international health at the Harvard School of Public Health (HSPH) and now chair in Global Environmental Health at Imperial College London, paints a stark picture: Obesity affects half a billion adults worldwide, a doubling of prevalence within 28 years. International monitoring groups such as the World Health Organization estimate that each year 3 million deaths can be attributed to obesity-related illnesses, including heart disease and stroke, musculoskeletal disorders, Type 2 diabetes and cancers of the breast, endometrium, gall bladder, kidney, colon and esophagus. So swiftly have waistlines expanded that some experts argue that, in high-income nations, gains in pounds could threaten gains in life expectancy.

Study researchers—including Goodarz Danaei, a research fellow in epidemiology at HSPH, and an international team of clinicians and researchers known as the Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating



Trends in mean BMI for men, 1980–2008

See "Obesity," page 8

Stephanie Mitchell/Harvard News Staff

The Genome at Year 10

Researchers marvel at the still-emerging blueprint of us

OK, we're part Neanderthal, and not that much different from chimpanzees after all. We also know that some drugs won't work on my cancer, even though they might work on yours.

And, if you want to find out what your DNA has been saying behind your back, the price of having your personal genome decoded is dropping like a stone.

The map of the human genome, completed in 2001, has wowed scientists in the years since, even if the scale of its impact has not matched some of the early predictions surrounding the project.

To mark the 10th anniversary of the publication of the map of the human genome, Harvard President Drew Gilpin Faust hosts a panel discussion on the project in Sanders Theatre.

Eric Lander, a leader of the Human Genome Project, said Feb. 22 that he has been surprised at the pace of advances stemming from the project, which has been likened to "biology's moon shot."

"This has gone so much faster than I ever imagined," said Lander, president and director of the Broad Institute of MIT and Harvard and professor of systems biology at

See "Genome Anniversary," page 6

INSIDE

When a Bad Cut-and-Paste Is Good

New research from the lab of Robin Reed, HMS professor of cell biology, sheds light on cellular gene-processing machinery known as the spliceosome and its role in cancer, and advances a promising front in the search for new cancer drugs.

In 2007, researchers reported that the anticancer drug, E7107 (E7) targeted a component of the spliceosome, a dynamic complex of proteins and RNA in a cell's nucleus that splices pre-messenger RNA (pre-mRNA), the transcribed form of DNA. How E7 induced anticancer activity when bound to the component, SF3b, remained unclear. In a study published in the March 1 issue of *Genes & Development*, Reed and her research team, Eric Folco and Kaitlyn Coil, reported that E7 binds SF3b and impairs spliceosomes. The findings not only implicate spliceosomes in cancer and other human diseases, but also suggest that using drugs such as E7 to selectively modulate spliceosome activity in cancer cells may have therapeutic potential.


Robin Reed

In most human genes, intervening sequences called introns interrupt functional exons. During the extensive cut-and-paste process of RNA splicing, introns are clipped and exons are stitched together by a gigantic spliceosome containing several RNA molecules and more than 100 proteins to produce mRNA for gene expression. The SF3b factor tightly anchors the pre-mRNA to spliceosomes.

Reed showed that E7 hampers splicing by loosening the critical RNA–RNA association between a "branch point sequence" in the pre-mRNA and a U2 snRNA in the SF3b/U2-snRNP complex. Reed and team assert that SF3b remodels U2 snRNP to facilitate these RNA–RNA interactions, and that E7 inhibits remodeling.

As reported in a companion paper by Juan Valcárcel at Centre de Regulació Genòmica in Spain, another anticancer drug called spliceostatin A also impairs splicing. Reed's and Valcárcel's studies raise intriguing questions—including why E7 targets tumor cells when splicing occurs in both normal and tumor cells. High-resolution structures of SF3b bound to E7 may provide answers and aid in the design of second-generation anticancer drugs.

— Raji Edayathumangalam

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 papers highlighted online at **focushms.com**.

THE RNA EXOSOME TARGETS THE AID CYTIDINE DEAMINASE TO BOTH STRANDS OF TRANSCRIBED DUPLEX DNA SUBSTRATES
Basu U, Meng FL, Keim C, Grinstein V, Pefanis E, Eccleston J, Zhang T, Myers D, Wasserman CR, Wesemann DR, Januszyk K, Gregory RI, Deng H, Lima CD, Alt FW. Howard Hughes Medical Institute, Immune Disease Institute, Children's Hospital Boston, Harvard Medical School, Columbia University

Relevance: Activation-induced cytidine deaminase (AID) initiates immunoglobulin (Ig) heavy-chain class switch recombination and Ig variable region somatic hypermutation in B lymphocytes. However, the mechanism of AID access to the template DNA strand, particularly when hybridized to a nascent RNA transcript, has been an enigma. We now implicate the RNA exosome, a cellular RNA-processing/degradation complex, in targeting AID to both DNA strands. Our findings reveal a role for noncoding RNA surveillance machinery in generating antibody diversity. *Cell.* 2011 Feb. 4;144(3):353-63.

THE UNFOLDED PROTEIN RESPONSE MEDIATES ADAPTATION TO EXERCISE IN SKELETAL MUSCLE THROUGH A PGC-1α/ATF6α COMPLEX
Wu J, Ruas JL, Estall JL, Rasbach KA, Choi JH, Ye L, Boström P, Tyra HM, Crawford RW, Campbell KP, Rutkowski DT, Kaufman RJ, Spiegelman BM. Dana-Farber Cancer Institute, Harvard Medical School

Relevance: The molecular mechanisms for adaptation to exercise training are not fully understood. Here we show that the unfolded protein response (UPR), an adaptive response pathway that maintains endoplasmic reticulum homeostasis upon luminal stress, is activated in skeletal muscle during exercise and adapts skeletal muscle to exercise training. These findings suggest that modulation of the UPR through transcriptional co-activator PGC1α represents an alternative avenue to improve skeletal muscle function and achieve metabolic benefits. *Cell Metabolism.* 2011 Feb 2;13(2):160-9.

DISCOVERY AND GENOTYPING OF GENOME STRUCTURAL POLYMORPHISM BY SEQUENCING ON A POPULATION SCALE
Handsaker RE, Korn JM, Nemesh J, McCarroll SA. Harvard Medical School, Broad Institute

Relevance: Accurate and complete analysis of genome variation in large populations will be required to understand the role of genome variation in complex disease. We present an analytical framework for characterizing genome deletion polymorphism in populations using sequence data that are distributed across hundreds or thousands of genomes. Our approach uses population-level concepts to reinterpret the technical features of sequence data that often reflect structural variation. These methods offer a way to relate genome structural polymorphism to complex disease in populations. *Nature Genetics.* 2011 Mar;43(3):269-76.

SMAD4-DEPENDENT BARRIER CONSTRAINS PROSTATE CANCER GROWTH AND METASTATIC PROGRESSION
Ding Z, Wu CJ, Chu GC, Xiao Y, Ho D, Zhang J, Perry SR, Labrot ES, Wu X, Lis R, Hoshida Y, Hiller D, Hu B, Jiang S, Zheng H, Stegh AH, Scott KL, Signoretti S, Bardeesy N, Wang YA, Hill DE, Golub TR, Stampfer MJ, Wong WH, Loda M, Mucci L, Chin L, DePinho RA. Dana-Farber Cancer Institute

Relevance: Effective clinical management of prostate cancer (PCA) has been challenged by significant intratumoral heterogeneity on the genomic and pathological levels and limited understanding of the genetic elements governing disease progression. Mouse model-informed progression analysis, together with genetic, functional and translational studies, establishes SMAD4 as a key regulator of PCA progression in mice and humans. *Nature.* 2011 Feb 10;470(7333):269-73.

ABERRANT OVEREXPRESSION OF SATELLITE REPEATS IN PANCREATIC AND OTHER EPITHELIAL CANCERS
Ting DT, Lipson D, Paul S, Brannigan BW, Akhavanfard S, Coffman EJ, Contino G, Deshpande V, Iafrate AJ, Letovsky S, Rivera MN, Bardeesy N, Maheswaran S, Haber DA. Massachusetts General Hospital Cancer Center, Harvard Medical School

Relevance: Satellite repeats in heterochromatin are transcribed into noncoding RNAs that have been linked to gene silencing and maintenance of chromosomal integrity. Using digital gene expression analysis, we showed that these transcripts are greatly overexpressed in mouse and human epithelial cancers. The overexpression of satellite transcripts in cancer may reflect global alterations in heterochromatin silencing and could potentially be useful as a biomarker for cancer detection. *Science.* 2011 Feb. 4;331(6017):593-6.

CORRECTION: The subject of a page 3 photo was misidentified in the January/February 2011 print edition. The student researcher was Justin Zaghi, who led an effort to prevent neural tube defects in Nicaragua by advocating for the fortification of rice with folic acid. We regret the error.

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Conflict disclosures and funding sources appear online.

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 March 18, 2011, will be featured in the next book section.

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

In February 2001, Science *and* Nature *published two papers that provided the first detailed look at a nearly complete sequence of the human genome. On the 10th anniversary of this breakthrough,* Focus *invited HMS research leaders to weigh in on the mapping of the human genome.*

HMS PODCAST

David Altshuler reflects on how the Human Genome Project has changed the landscape of biomedical research at focushms.com.

Where Has the Human Genome Project Made The Most Surprising Impact?

David Altshuler

The greatest impact of the Human Genome Project has been in illuminating previously unsuspected biological processes and contributors to disease.

For example, I was taught that the typical "gene" consisted of a protein-coding region and a small amount of nearby regulatory DNA. The rest was "junk." Today we know that the majority of the functional DNA in the human genome falls outside of this narrow depiction of a gene. A great task for the next generation is to untangle the biological functions and disease relevance of noncoding DNA sequences.


Len Rubenstein

I learned about "genetic" diseases, but in most cases the specific genes and pathophysiological mechanisms were unknown—a black box. Today, using the unbiased approach of genetic mapping in families and populations, we know of genes and mutations for thousands of rare familial diseases, and increasingly for common, complex diseases. In the vast majority of cases, the specific genes mapped by genomic methods were previously unsuspected as playing a role.

Some have expressed disappointment that, 10 years after the sequencing of the human genome, medicine remains a highly imperfect science, without magic bullets for disease. My own view is that progress in medicine is held back by the fundamental and largely unexplored complexity of human biology and disease. By providing comprehensive tools that expand our thinking beyond the "usual suspects," genomics has built a foundation for and accelerated the ultimate arrival of more effective prevention and treatment for disease.

No doubt, progress will still take a long time. But how long would it have taken without the genome project?

David Altshuler is professor of genetics and of medicine at Harvard Medical School and a physician at Massachusetts General Hospital. He is also a founding member, deputy director and chief academic officer of the Broad Institute of MIT and Harvard.

Raju Kucherlapati

We are in the golden age of human genetics and genomics. The sequencing of the human genome not only provided the blueprint for human life but the work in the past 10 years has provided great information about the genetic diversity in human populations and individuals. The past decade also has seen a dramatic reduction in the cost of DNA sequencing and many other ancillary technologies. The combination of technology developments and biological and medical discoveries is enabling us to assess risk, provide accurate diagnosis and—for those individuals who are already diagnosed with a disease—prognosis, and in many instances use genetic and genomic information to determine the most optimal treatment for the patients. These aspects can together be called personalized medicine. If I had to identify two of the most surprising areas of impact, I would say first the dramatic reduction in the cost of sequencing, and second the adoption of the use of genetic and genomic information in clinical settings.

Sequencing individual human genomes is now offered in commercial settings for $10,000 or less. This cost is anticipated to go down further in the next few years. This development has significant impact on developing better risk assessment and diagnostic tools that are being widely embraced by commercial entities and the medical and patient communities.

One of the most surprising aspects of personalized medicine is the acceptance of the importance of genetics in making treatment decisions, as evidenced by the current involvement of many pharmacy benefit managers, such as Medco, and drug store chains, such as CVS Caremark, Walgreens and Walmart. Together these organizations serve tens of millions of individuals, and they could have a high impact on how genetic information is used by the general population.

Raju Kucherlapati is the Paul C. Cabot Professor of Genetics at Harvard Medical School and a professor of medicine at Brigham and Women's Hospital.

Matthew Meyerson

The Human Genome Project (HGP) has exerted an unexpected impact on cancer therapy. Now it is possible to discover and diagnose the major genome alterations that cause cancer and to select patients for genome-targeted therapies where available. One dramatic example has been the development of the first targeted therapy for metastatic melanoma, a deadly and poorly treatable disease. One year after the HGP announcement, a group of scientists in Cambridge, England, identified mutations in the *BRAF* gene for a protein kinase in about 60 percent of melanomas. This past year in clinical trials led by Keith Flaherty at Massachusetts General Hospital, the first B-Raf kinase inhibitor drug was shown to be effective for the treatment of melanomas bearing *BRAF* mutations.


Graham Ramsay

A similar dramatic transformation has occurred in the treatment of non-small cell lung cancer. Here, genomic knowledge enabled researchers at both Mass General and the Dana-Farber Cancer Institute to identify mutations in the *EGFR* gene for a different protein kinase. Treatment with *EGFR* inhibitors has dramatically benefited patients whose lung cancers harbor *EGFR* mutations, opening the door to a floodgate of new targeted therapies for genomically defined subpopulations of lung cancer patients.

Because of these developments, the diagnosis of cancer for the selection of therapy is beginning to move from the location and appearance of the tumor to detection of the genome aberrations that may be targets for therapy.

Matthew Meyerson is a professor of pathology at Harvard Medical School, co-director of the Center for Cancer Genome Discovery at Dana-Farber Cancer Institute and a senior associate member of the Broad Institute of MIT and Harvard.

IDEA LAB
Join the conversation
focushms.com/idealab

What do YOU think? Join this month's discussion about the surprises wrought by the Human Genome Project through the HMS Idea Lab, a virtual laboratory for sharing thoughts and opinions on research, academic medicine, medical education and more.

Paula Johnson

Jeff Thiebauth

Health Access Called Unfinished Work of Civil Rights

Advancing 'the most basic of human rights'

Declaring health "the unfinished work" of the civil rights movement, Paula Johnson, an HMS alumna and associate professor of medicine, called on society to embrace that agenda in the 2011 Alvin F. Poussaint, MD Visiting Lecture.

In her talk on Feb. 8, "Achieving Health in the U.S.: Lessons from the Civil Rights Movement," Johnson posed challenging questions. "What is our broader vision," she asked. "One that goes beyond a discussion of health care to a unifying movement that builds communities of healthier people? Who are the leaders in the movement, and do we have a role?"

"Health, the right to health care and to live a healthy life are the most basic of human rights," said Johnson, executive director of the Connors Center for Women's Health and Gender Biology and chief of the Division of Women's Health at Brigham and Women's Hospital. She warned that the next generation of Americans may be the first at risk of worse health than their parents.

Five lessons from the civil rights era, she said, could be applied to a movement to broaden access to health:

- Change takes time. Seek opportunities to accelerate change.
- A compelling vision and effective leadership are critical at all levels.
- Although laws are necessary, change rarely comes through legislation alone.
- Individuals' needs are important, but genuine reform requires a societal approach.
- Innovation must intersect with health care delivery and public health.

Bridging the gap between the delivery of care and public health is essential, Johnson said, citing examples of success. To treat and prevent asthma, the program Breathe Easy at Home connects public health and health care organizations with city agencies. Its services range from conducting home inspections to providing information about asthma and its environmental triggers.

Illustrating the power of a grassroots effort, Johnson looked to breast cancer activists who, in the 1970s, began a national conversation concerning a disease cloaked in silence and shame. "When you no longer tolerate the status quo, you can create change," Johnson said.

Johnson pointed to the lecture's namesake, Alvin Poussaint, HMS professor of psychiatry and faculty associate dean for student affairs. "Dr. Poussaint made the decision to lead from where he stood, on that bridge from racial strife to a better America," Johnson said. "The greatest tribute we can pay him today is to embrace our task with an equal measure of courage."

Invited to the podium by HMS Dean for Diversity and Community Partnership Joan Reede, Poussaint offered his hard-won perspective.

"The only way you're going to create change is by making noise," he said. Thanking Johnson for a shot of inspiration, he said, "I'm ready to go out and do much more."

Addressing HMS students, Reede issued a call to action. "Harvard is poised to take a leadership role in this," she said. "It's up to you to push us."

— Valerie Wencis

ON THE WEB

To view Johnson's lecture, visit **www.mfdp.med.harvard.edu/pastevents.html.** To watch Poussaint's Feb. 14 discussion of his role and observations in the civil rights movement, titled "The Long Haul: The Obstacles that Remain," visit **hms.harvard.edu/community/talksattwelve/index.shtml.**

Alonso Nichols/Copyright 2011 Trustees of Tufts College

HMS psychiatrist Alvin Poussaint acknowledges applause from the audience as entertainer Bill Cosby looks on during the fifth annual "Abby Award" ceremony hosted by the Eliot-Pearson Department of Child Development at Tufts University on Feb. 25. The Abbys award excellence in children's media, honoring commitment to innovation, diversity, non-violence and developmentally appropriate media.

Poussaint and Cosby, Partners Again

HMS psychiatrist, educator and social commentator Alvin Poussaint, HMS faculty associate dean for student affairs, has been honored for his work in support of children and families at Tufts University with the Eliot-Pearson Award for Excellence in Children's Media. His co-recipient at the Feb. 25 event was his former collaborator, the entertainer, educator and author Bill Cosby.

The so-called Abby award, co-sponsored by Tufts' Communications and Media Studies (CMS) Program and the Eliot-Pearson Department of Child Development, is given biennially to individuals, organizations or companies with a commitment to innovation, diversity, nonviolence and developmentally appropriate media. Nominees "work to create media that are free of gender, racial and ethnic stereotypes and that make a real difference in the lives of children," said CMS Director Julie Dobrow.

"I was very honored to receive such an award from this distinguished program at Tufts," Poussaint said.

An expert on race relations, families and parenting, Poussaint has long lent his voice to the prevention of child exploitation in the media. He was a production consultant to "The Cosby Show," in which Bill Cosby both starred and produced. Now a senior adviser for the Campaign for a Commercial-Free Childhood, Poussaint previously served as the media center director for the Judge Baker Children's Center, an HMS affiliate.

— Valerie Wencis

FOCUS ONLINE

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Bruce Wahl/BIDMC

Pier Paolo Pandolfi

Pezcoller-AACR Award Honors Cancer Geneticist

Pier Paolo Pandolfi, the George C. Reisman Professor of Medicine, has won the Pezcoller Foundation-American Association for Cancer Research (AACR) International Award for Cancer Research. The $100,000 prize, announced Jan. 12, recognizes his outstanding work in the field of cancer genetics as well as in developing mouse models for cancer research and co-clinical testing of novel therapeutics.

Pandolfi has made important contributions to the understanding of the molecular mechanisms and genetics underlying the pathogenesis of leukemias, lymphomas and solid tumors. A professor of medicine and pathology, he is also director of research at the Beth Israel Deaconess Cancer Center, director of the cancer genetics program, and chief of the division of genetics.

According to AACR chief executive officer Margaret Foti, Pandolfi's work has had a significant impact on understanding the basis of acute promyelocytic leukemia (APL), now considered curable. "His laboratory's mouse models for various subtypes of APL have shown efficacy when utilizing different drug combinations," she said. "Clearly, this innovative research is leading to progress in the treatment of other types of cancer."

The Pezcoller award, now in its 14th year, is presented to an individual of international renown who has made a major scientific discovery in basic or translational cancer research. Pandolfi will deliver a lecture, "The Non-Coding Revolution: A Coding-Independent Function of Gene and Pseudogene mRNAs Regulates Tumor Biology," at the AACR's 102nd Annual Meeting on April 4 in Orlando, Fla.

Call for Ethics Fellows

The Harvard Medical School Division of Medical Ethics seeks applications from physicians, nurses, lawyers, social workers and others in academic fields related to medicine or health who have a serious interest in medical ethics and who wish to further their knowledge of the history, philosophical underpinnings and contemporary practice of bioethics. Fellows attend a weekly three-hour seminar to explore a wide range of issues, including ethical theory, clinical ethics, research ethics and related topics in public health. The application deadline for 2011-2012 fellowships is April 8. For additional information, contact Helena Martins in the Division of Medical Ethics at 617-432-3041 or helena_martins@hms.harvard.edu.

Windows of Opportunity Open for Junior Faculty

2011 Faculty Fellows awarded time to flex research muscle

Daunting are the demands on junior faculty, from research and clinical care to teaching and family. In an ongoing effort to assist HMS junior faculty in career development and to help emerging talent climb the professorial ladder, the Office for Diversity and Community Partnership (DCP) in February conferred fellowships upon five rising stars.

The two-year, $100,000 fellowships come at a pivotal point in the recipients' career development, freeing them from clinical and teaching obligations to pursue research.

Competition is stiff for the fellowships, which are awarded by the Harvard Catalyst Program for Faculty Development and Diversity (PFDD) and the DCP in collaboration with HMS, its affiliated institutions and the Harvard University Office of the Provost. In 2011, the five Faculty Fellows, as they are known, were selected from among 46 applicants by a committee of faculty and CEOs from HMS-affiliated institutions.

At a celebratory breakfast in February, Dean Jeffrey S. Flier extolled the recipients' "promising lives and careers" before a gathering of department chairs, mentors and former fellows.

"These fellowships," Flier said, "are a testament to the collaborative spirit of our community—and to its commitment to nurturing tomorrow's leaders in medicine and science."

Fellows conduct mentored research projects and participate in career development activities. They present their findings at the DCP-sponsored Minority Health Policy Annual Meeting through poster and oral presentations.

Jeff Thiebauth

Dean Jeffrey S. Flier (from left) with the 2011 fellows: Patricia Sylla, Sarosh Rana, Aaron Styer, Mary Townsend, and Sudha Biddinger.

2011 Faculty Fellows

Following are the 2011 fellows and their research projects. The first is a PFDD Fellow; all others are DCP Fellows.

Patricia Sylla of the Department of Surgery at Massachusetts General Hospital will evaluate the safety and efficacy of transanal endoscopic rectosigmoid resection for rectal cancer, a type of Natural Orifice Translumenal Endoscopic Surgery (NOTES).

Sudha Biddinger of the Division of Endocrinology at Children's Hospital Boston aims to determine how diabetes modifies the response to statins using mouse models of Type 1 and Type 2 diabetes, potentially setting the stage for further studies of statins and lipoprotein metabolism in patients with Type 1 diabetes.

Sarosh Rana of the Department of Obstetrics, Gynecology and Reproductive Biology, Beth Israel Deaconess Medical Center, will investigate whether measuring angiogenic biomarkers in pregnant women with symptoms of preeclampsia results in a more accurate, quicker diagnosis of the condition, and whether alterations in these markers correlate with adverse pregnancy outcomes.

Aaron Styer of the Department of Obstetrics, Gynecology and Reproductive Biology at Massachusetts General Hospital will investigate the utility and application of microRNA (miRNA) technology to improve the diagnosis, treatment and surveillance of uterine fibroids, which have a disproportionately higher incidence in African-American women. This project aims to delineate the impact of ethnicity-specific fibroid miRNA expression on clinical outcomes.

Mary Townsend of the Department of Medicine at Brigham and Women's Hospital aims to build upon epidemiologic methods relevant to research on aging, a multi-dimensional outcome that encompasses survival, chronic diseases, mental health and physical and cognitive function.

Neurobiologists 'Crawl' the Brain to Map a Neural Circuit

The brain is a black box. A complex circuitry of neurons fires information through channels, much like the inner workings of a computer chip. But while computer processors are regimented with the deft economy of an assembly line, neural circuits are impenetrable masses. Think tumbleweed.

Researchers in Harvard Medical School's Department of Neurobiology have developed a technique for unraveling these masses. Through a combination of microscopy platforms, researchers can crawl through the individual connections composing a neural network, much as Google crawls web links.

"The questions that such a technique enables us to address are too numerous even to list," said Clay Reid, HMS professor of neurobiology and senior author on a paper reporting the findings in the March 10 edition of *Nature*.

The cerebral cortex is arguably the most important part of the mammalian brain. It processes sensory input, reasoning and, some say, even free will. For the past century, researchers have understood the broad outline of cerebral cortex anatomy. In the past decade, imaging technologies have allowed us to see neurons at work within a cortical circuit, to watch the brain process information.

But while these platforms can show us *what* a circuit does, they don't show us *how* it operates.

For many years, Reid's lab has been studying the cerebral cortex, adapting ways to hone the detail with which we can view the brain at work. Recently they and others have succeeded in isolating the activities of individual neurons, watching them fire in response to external stimuli.

The ultimate prize, however, would be to get inside a single cortical circuit and probe the architecture of its wiring.

Just one of these circuits, however, contains between 10,000 and 100,000 neurons, each of which makes about 10,000 interconnections, totaling upwards of 1 billion connections—all within a single circuit. "This is a radically hard problem to address," Reid said.

Reid's team, which included Davi Bock, then a graduate student, and postdoctoral researcher Wei-Chung Allen Lee, embarked on a two-part study of the pinpoint-sized region of a mouse brain that is involved in processing vision. They first injected the brain with dyes that flashed whenever specific neurons fired and recorded the firings using a laser scanning microscope. They then conducted a large anatomy experiment, using electron microscopy to see the same neurons and hundreds of others with nanometer resolution.

Using a new imaging system they developed, team members recorded more than 3 million high-resolution images. Researchers at the Pittsburgh Supercomputing Center at Carnegie Mellon University stitched them into 3-D images. Using the resulting images, Bock, Lee and laboratory technician Hyon Suk Kim selected 10 individual neurons and painstakingly traced many of their connections, crawling through the brain's dense thicket to create a partial wiring diagram.

ON THE WEB

Watch a video of neural circuitry in action at **focushms.com**.

This model also yielded some interesting insights into how the brain functions. Reid's group found that neurons tasked with suppressing brain activity seem to be randomly wired, putting the lid on local groups of neurons all at once rather than picking and choosing. Such findings are important because many neurological conditions, such as epilepsy, are the result of neural inhibition gone awry.

"This is just the iceberg's tip," said Reid. "Within ten years I'm convinced we'll be imaging the activity of thousands of neurons in a living brain. In a visual circuit, we'll interpret the data to reconstruct what an animal actually sees. By that time, with the anatomical imaging we'll also know how it's all wired together."

For now, Reid and his colleagues are working to scale up this platform to generate larger data sets.

"How the brain works is one of the greatest mysteries in nature," Reid added, "and this research presents a new and powerful way for us to explore that mystery."

—David Cameron

For more information, students should contact Clay Reid, HMS professor of neurobiology, at clay_reid@hms.harvard.edu.

Genome Anniversary

Continued from page 1

HMS. "We've been able to read out the lab notebooks of evolution."

Lander was part of a panel of scientific experts who talked about the Human Genome Project and its legacy at an event at Sanders Theatre.

The event, "Mapping the Human Genome: Ten Years After," was hosted by Harvard President Drew Gilpin Faust and webcast by *USA Today*. Other panelists were Margaret Hamburg, head of the U.S. Food and Drug Administration; M. Susan Lindee, chair and professor of history and sociology of science at the University of Pennsylvania; Vamsi Mootha, associate professor of systems biology and of medicine at HMS and associate member of the Broad Institute; and Vicki Sato, former president of Vertex Pharmaceuticals and today professor of the practice of molecular and cellular biology in the Faculty of Arts and Sciences and professor of management practice at Harvard Business School.

"Has sequencing of the human genome been transformative, and in what ways?" Faust asked in her introductory remarks. "How are we all … different than we otherwise would have been, and what will the coming decades hold?"

The Human Genome Project started in 1990 and involved scientists from 20 centers in six countries. At a cost of $3 billion, the first draft of the genome was published in 2001, and the full sequence was published in 2003. The resulting map shows 21,000 genes that contain the instructions for making a human being and provide the foundation for better understanding our basic biology, how we differ from other animals, and what happens when things go wrong.

"I'm really excited about the future. If I were a student or graduate student, I don't think there's a better time to embark on biomedical research."

—Vamsi Mootha, HMS associate professor of systems biology and of medicine

Lander reeled off a list of advancements made possible by the project. In barely the time it takes to get a single drug developed and approved for use in humans, the number of genes tied to common diseases such as diabetes and Alzheimer's has increased from just 20 to 1,100, with more on the way. Scientists have decoded the genomes of dogs, chimpanzees, laboratory animals and a host of other creatures. The cost of reading a genome has fallen dramatically in just 10 years. Technology today can do in five minutes a decoding task that would have taken a year to complete a decade ago, Lander said.

The revolution extends to students and young researchers, who have at their disposal not only a new understanding of the foundation of life, but an array of equipment and techniques that until recently didn't exist.

"They have the tools to do things today that it used to take armies to do," Lander said. "My expectations have been blown away."

When it comes to the public's expectations, however, hype surrounding the project may have led some to imagine an era of rapidly developed genetic cures, Sato said.

Instead, as our understanding has advanced, the complexity of many diseases has emerged.

But that's not to say the Human Genome Project hasn't had an effect on some illnesses, Mootha said.

"I'm really excited about the future. If I were a student or graduate student, I don't think there's a better time to embark on biomedical research."

One problem, Mootha said, is that there is a tsunami of data from all the genetic analyses going on, so much so that equipment can't handle or even store it.

Another problem is the nature of the information, Lindee said. Though people are getting more information about their genetic tendencies, some of the information is ambiguous and difficult for doctors and patients to interpret, leading to an increase in what she called "uninformative information."

Sato said it has taken time for pharmaceutical companies to change how they operate so that they may take advantage of a flood of genomic data. They have had to change the way they look at disease, but they also have gained a better understanding of the differences between patients and of the fact that certain medicines work better on some people than others.

"If they have a mutation, we know this drug won't work even though it is the same cancer [as in another person who is without the mutation]," Sato said. "So much has changed in a relatively short period of time, I can't imagine what the medicine of the future will look like."

— Alvin Powell, Harvard Gazette

A Welcome Bridge to the Future

Medicaid waivers give states the flexibility to innovate, and doctors feel the winds of change

Courtesy of Ellen Rothman

"Well, at least it's good to see a doctor who is excited about health care reform," my sister-in-law's aunt said to me at Thanksgiving dinner. "For the insurance companies, it just looks like more regulations." As it turns out, she works as a lawyer for a health insurance company.

It is often said that one should avoid discussing religion and politics at family gatherings, advice that I typically take to heart. But in California, where I work at a community health center, health care reform is building steam. The topic has become unavoidable.

With the passage of the California "Bridge to Reform" Medicaid Waiver on Nov. 2, 2010, the federal government granted California a $10 billion health care package that will expand access to Medicaid for adults, provide more funding to safety-net hospitals, and streamline care for seniors and chronically ill children. It will increase the capacity for demonstration projects—innovative programs designed to optimize comprehensive care. Financial gains from improved efficiency will be reinvested in the health care system. More recently, President Barack Obama signaled on Feb. 28 that he supported even greater flexibility for states, offering to waive requirements of the 2010 health care law for those that find other ways to expand coverage and control costs.

By using federal waivers to modify their Medicaid practices, many states gain the flexibility to better serve their local communities. Waivers allow these states to set aside the requirement to dispense Medicaid services according to standard federal operating practices. Although California has implemented waivers in the past, waivers claimed through the Bridge to Reform program are explicitly designed to usher in the new generation of health care.

Of course, the general elections Nov. 2 also resulted in a change in the congressional makeup—the Democrats lost their majority in the House of Representatives and lost influence in the Senate as well. This has spurred significant debate over the past weeks as to the fate of health care reform. Will it survive intact? Will it survive at all?

From my perspective, it feels as though federal programs have fueled a burst of creativity and energy that cannot be reversed. The transformation has come in two parts: the first is health information technology and the second is the Bridge to Reform.

I first felt the winds of change in spring of 2009. A new president continued a stimulus plan to bolster our failing economy. Almost immediately, money became available for the installation of health information technology. But the money wasn't simply for purchasing electronic records systems. The rules demanded "meaningful use." They paid not just for expanding access to technology, but also for ensuring it was fast and meaningful. They require not only that doctors use the system, but also that patients be able to review personal health information. They require doctors to share information with additional health services providers, like pharmacists and specialists.

My clinic will spend more than $1 million to implement an electronic records system, and every other community clinic in the Los Angeles coalition will also be working to implement their own systems. We live on the financial brink. There is no way that this would be possible without this direct government intervention.

When health care reform was signed into law Sept. 17, 2009, we felt it on the ground the next day. My husband, Carlos, who works as a pediatrician at UCLA, was seeing a child with a rare genetic metabolic syndrome. When Carlos first met this boy, the child was considered to be uninsurable because of his pre-existing condition. The boy's family was petrified by the thought that their son would become ill and require hospitalization. But under the new law, in one day's time, the child became insured.

Now, with the Bridge to Reform Medicaid Waiver, we are considering ways to accommodate the increased number of patients seeking primary care because of expanded access to health insurance. We also are embarking on collaborative projects to restructure Medicaid compensation to reward better health outcomes.

The flip side of improved access for some is a lack of access for those specifically left out—the undocumented. Those of us working in South LA have started to further categorize our patients into the "uninsureds"—those who will potentially become insured—and the "uninsurables"—those who have no hope for insurance coverage at all. Although the undocumented can now be lumped with the uninsured masses of LA, as the number of uninsured decrease because of provisions in health care reform, it may become increasingly difficult to advocate for those left behind.

In a previous issue of *Focus* (April 3, 2009), I wrote about Lakeesha, a 40-year-old woman who ultimately died of a delayed diagnosis of uterine cancer. She was caught in the catch-22 of California Medicaid. At that time, adults needed a documented diagnosis with proven disability to be eligible for the program. To receive the diagnosis, however, patients needed access to insurance. Lakeesha died because she did not receive a CT scan when she most needed one. If health care reform had come two years earlier, she might have lived.

Those of us working in health care in California are beyond the tipping point. Electronic records are the new reality, along with the improved quality control and enhanced communication they bring. Change isn't coming. Change is here.

— Ellen Rothman, HMS '98, practices at a community health center in Los Angeles

The opinions expressed in this column are not necessarily those of Harvard Medical School, its affiliated institutions or Harvard University.

$1 Million Prize Recognizes ALS Discovery

Bruce Wahl/Beth Israel Deaconess Medical Center

HMS Associate Professor of Neurology Seward Rutkove has won a $1 million challenge prize for developing a method that is expected to hasten the development of treatments for amyotrophic lateral sclerosis (ALS), a neuromuscular condition for which there are neither cures nor life-extending therapies.

Awarded Feb. 7 by the nonprofit Prize4Life, the ALS Biomarker Prize is among the largest in a recent wave of cash incentives offered by individuals and organizations to ignite scientific breakthroughs.

Rutkove's innovation was to develop a reliable way to quantify the small muscular changes that signal progressive deterioration. Interestingly, he says, the technology itself is nothing new.

Rutkove, chief of the division of neuromuscular disease at Beth Israel Deaconess Medical Center, worked with two Northeastern University physicists to reliably measure the health of a muscle using a technique called electrical impedance myography (EIM). EIM passes a tiny alternating electrical current through muscle, producing a small, measurable voltage.

"As the disease progresses," Rutkove said, "the muscle atrophies, undergoing changes in composition and internal structure that alter the muscle's electrical properties."

Committed to curing ALS, Prize4Life was founded in 2005 by a group of Harvard Business School students after one, Avichai Kremer, was diagnosed with the disease. In 2006, the group launched the biomarker challenge to find a better method for assessing the disease's rate of progression, with the goal to cut in half the cost of Phase II clinical trials.

Although the prize comes with no strings attached, Rutkove said he plans to put the funds to good use—freeing up his time for research and to support the company he has co-founded to make EIM technology widely available.

— Valerie Wencis

The Evidence Adds Up

- Between 1980 and 2008, the percentage of obese men worldwide more than doubled, to 9.8 percent. Obesity's prevalence in women climbed by three-fourths, to 13.8 percent.
- BMIs were highest in the island of Nauru: 33.9 for men, 35 for women. Eight other island nations in the South Pacific region known as Oceania saw steep increases.
- Of high-income countries, the United States had the highest BMIs: above 28 for both men and women. Next came New Zealand. Japan's were lowest: about 22 for women, 24 for men.
- Some of the largest increases were in wealthy countries: the United States first, followed by New Zealand and Australia (women) and the United Kingdom and Australia (men).
- Women in Singapore, Italy, Belgium and Switzerland saw virtually no rise in BMI.
- In 1980, female BMIs in several countries in sub-Saharan Africa and South and Southeast Asia were below 19; by 2008, the lowest BMIs hovered around 21.

Group—showed that mean body mass index (BMI) increased in most countries, and in high-, middle- and low-income nations alike. Among high-income countries, the United States had the largest rise, more than 1 kg/m^2/decade, as well as some of the higher mean BMIs for both men and women, greater than 28 kg/m^2. (A standard measure of body weight, BMI is based on height and weight and is expressed as kilograms per square meter of height.)

The health implications of these findings are dire, said JoAnn Manson, the Elizabeth Fay Brigham Professor of Women's Health and chief of the Division of Preventive Medicine at Brigham and Women's Hospital.

"The numbers are staggering and portend an enormous burden of future disease," Manson said. "Many countries that are now experiencing a higher prevalence of obesity have populations that, because of genetic determinants, recently adopted Westernized lifestyles, or even *in utero* factors, are particularly vulnerable to developing Type 2 diabetes because of weight gain. Asian populations, people in India, Native Americans, Hispanics, Pacific Islanders—each group is susceptible to developing diabetes with more moderate levels of overweight than other populations are."

In Manson's view, the data should give policymakers the incentives and tools they need to bring about change. "It's important that health ministers and government officials have these numbers," she said. "Social and cultural factors contribute to the prevalence of overweight and obesity, so whether nations choose to encourage physical activity through the built environment or to work with the food industry to address nutrition, they need reliable statistics to help them make decisions about their use of resources."

The study was designed to provide that information. "We measured the performance of individual countries so that nations might use the data for benchmarking," Ezzati said. "Studying what the best-performing countries are doing could inform other countries of ways they might work to decrease obesity in their populations. We can't simply address this issue by reversing things; we're not going to get rid of cars or supermarkets. We need to look for imaginative and effective policies and programs that are doable in the current social context."

The researchers swept together published and unpublished information from health examination surveys and epidemiological studies involving 9.1 million people in 199 countries and territories. Using a statistical method known as a Bayesian hierarchical model, they estimated BMI by age, country and year. Overweight signifies at least 25 kg/m^2, obese 30 kg/m^2 and above.

To understand how those numbers translate to what the scale says, consider that if you are five feet, five inches tall and weigh 140 pounds, your BMI is 23. Add 10 pounds, and you are overweight; another 30 pounds, and you are obese.

In the United States, the impulse is to finger a bad guy. Ban super-sized burgers. Tax sugary soft drinks. Advise mom and dad to put junior on a diet. Eat less, exercise more.

But the problem defies easy solutions. Companion studies by the research team on serum cholesterol and blood pressure changes in the course of the same 28 years show that pharmaceutical interventions and nutritional policies have led to improvements in some parts of the world. In high-income regions such as the United States, Australia and Europe, serum cholesterol levels, although still high, actually declined among both men and women. In East and Southeast Asia and the Pacific, however, levels increased.

Blood pressure measures showed similar regional and national variations. Although levels for men and women in North America, Australasia, Asia-Pacific and Western Europe declined, blood pressure levels rose for men and women in East Africa, South and Southeast Asia, and the island nations in the South Pacific. Despite some gains in hypertension control, population growth and aging pushed up by 62 percent the number of people diagnosed with the condition, from an average of 605 million in 1980 to 978 million in 2008.

The decline in cholesterol and hypertension in some countries together with a rise in obesity has created a "wild card" situation, noted Ezzati: Will blood pressure and cholesterol go down so much that they will offset the rise in BMI, or will they not?

"Everyone with good intentions has ideas on how to reduce obesity," Ezzati said. "The reality is that in most of the world, those good intentions don't seem to be working. These data provide an empirical dimension to a debate that tends to be emotional."

—Ann Marie Menting

For more information, students may contact Majid Ezzati, chair of Global Environmental Health at Imperial College London, at majid.ezzati@imperial.ac.uk.

CALENDAR

Wednesday, March 23
Countway Library, Minot Room, 5th Floor
4:30–5:45 p.m.
The $1,000 Genome: The Revolution in DNA Sequencing and the New Era of Personalized Medicine
Kevin Davies, editor-in-chief of Bio-IT World, founding editor of *Nature Genetics.*
Davies will focus his talk on the subject of his newly released book, *The $1,000 Genome,* which reports that "2011 marks not only the tenth anniversary of the first draft of the human genome, but also the year that researchers coined the catchphrase 'the $1,000 genome.' " Davies will discuss prospects in next-generation sequencing technologies with a focus on clinical and diagnostic applications, as well as issues surrounding the delivery of that information to the public. This lecture is followed by a book signing and reception in the Lahey Room. Contact: Roz Vogel, rvogel@hms.harvard.edu, 617-432-4807.

Friday, April 1
Building C, Cannon Room. 9 a.m.–noon
Resiliency and Learning: Implications for Teaching Medical Students and Residents
George Everly , Jr., The Rockefeller University; Bruce McEwen, Johns Hopkins School of Public Health.
The 2011 Symposium on the Science of Learning: Implications for Medical Education from the Neurosciences and Social Sciences will pose the question, "How do we maintain resiliency during stressful experiences?" Recent studies document high rates of depression and burnout among medical students, residents in many specialties, and physicians in practice. George Everly and Bruce McEwen, both distinguished scholars, will present research on the impact of stress on the brain, factors contributing to resiliency, and evidence that resiliency can be taught. They will describe interventions that change brain function and foster resiliency. RSVP at www.hms.harvard.edu/academy. Direct questions to academy@hms.harvard.edu.

Monday, April 4–Tuesday, April 5
Joseph B. Martin Conference Center
1–6 p.m Monday; 8 a.m.–12:30 p.m. Tuesday
Global Health Delivery: Challenges and Opportunities for Advancing Excellence and Equity
Jeffrey Sachs, Columbia University; Paul Farmer, HMS Department of Global Health and Social Medicine.
A lively exchange will focus on the "know–do" implementation gap: methodologic limitations and possibilities in evaluating the impact of global health interventions; and the potential role of academe in advancing global health equity through science and policy. Register free at ghsm.hms.harvard.edu/ghd_symposium/. For more information, e-mail Kathleen Lebel at kathleen_lebel@hms.harvard.edu.

FOCUS ONLINE
For all events, see Events Calendar online