

mance for the endowment—Mendillo describes “the great talent working at Harvard Management Company” now, and Kaplan envisions “strong prospects” in the future. But for the next few years, they foresee the likelihood of a much rougher ride.

Stem-Cell Progress

THIS PAST SUMMER and fall saw the announcement of five important breakthroughs by University stem-cell scientists—a forceful validation of the Harvard Stem Cell Institute’s (HSCI; www.hsci.harvard.edu) approach, says executive director Brock Reeve. HSCI funds research throughout Harvard and its affiliated institutions and hospitals, organizing its investigations by disease areas, such as diabetes, cancer, neurodegeneration, and diseases of the blood or heart. The developments ranged from successful muscle-stem-cell transplants in mice, to the creation of disease-specific stem-cell lines using adult cells, to an extraordinary “direct conversion” of one adult cell type to another. (For background on stem-cell research at Harvard, see “Stem-Cell Science,” July-August 2004, page 36.)

The most stunning advance arose from diabetes research conducted by HSCI co-director Douglas Melton, Cabot professor of the natural sciences, and postdoctoral fellow Qiao “Joe” Zhou, who figured out how to transform one type of cell into another in a living animal by using a new process their research team has dubbed “direct reprogramming.” Specifically, Zhou and Melton created insulin-secreting pancreatic beta cells. But reprogramming holds promise, as well, for treating other diseases that involve missing cells, including cardiovascular and neurodegenerative conditions such as Parkinson’s disease and ALS (or Lou Gehrig’s disease).

Melton, Zhou, and their colleagues achieved this result by delivering a combination of three transcription factors (a class of genes known to regulate cell fate during early development) to target cells in the pancreas of a mouse. During a multiyear process of elimination,

Yesterday’s News

From the pages of the *Harvard Alumni Bulletin* and *Harvard Magazine*

1923 Ninety-six women with degrees from the School of Education have been listed in the new *Harvard Alumni Directory*. “To publish their names,” the *Bulletin* points out, “is simply an unavoidable recognition of their standing...it does not invite them to attend meetings of the Associated Harvard Clubs nor necessitate a ladies’ dining room in the Harvard Club of New York or Boston...there is no reason to assume the admission of women to a professional school is the ‘entering wedge’ of coeducation throughout the institution.”

1958 An informal survey of drugstores in and around Harvard Square the morning following *The Game* finds them entirely out of aspirin.

1963 Dean of students Robert Watson criticizes lax undergraduate attitudes toward parietal rules, insisting that Harvard “must be concerned that its students do not set an example for the relaxation of morals among youth...fornication must also be understood as an offense punishable by the University on the same grounds as thievery, cheating, and lying.”

1973 In response to the energy crisis, a new University-wide energy-conservation program lowers the temperature in all Harvard offices

and student rooms from 75 degrees to 68 degrees.

1983 Forty coin-operated word processors have been loaned to Harvard in a trial; if enough students demonstrate interest, “additional word processors and possibly computer equipment will be installed on the same basis.” An hour of operation costs \$2.

1988 Harvard drops its objections to the conduct of the preceding spring’s union election (the victory margin was 44 votes), clearing the way for the National Labor Relations Board to certify the Harvard Union of Clerical and Technical Workers as the collective bargaining agent for more than 3,000 support-staff members after a 13-year struggle.

1993 The Yard is wired to 2.7 million feet of fiber-optic cable, prompting the editors to note that the class of 1997 is “the first in Harvard history to be bonded electronically....Many students correspond daily by E-mail.” (The Quad and Lowell House are to be hooked up by midyear, the river Houses in the spring.)

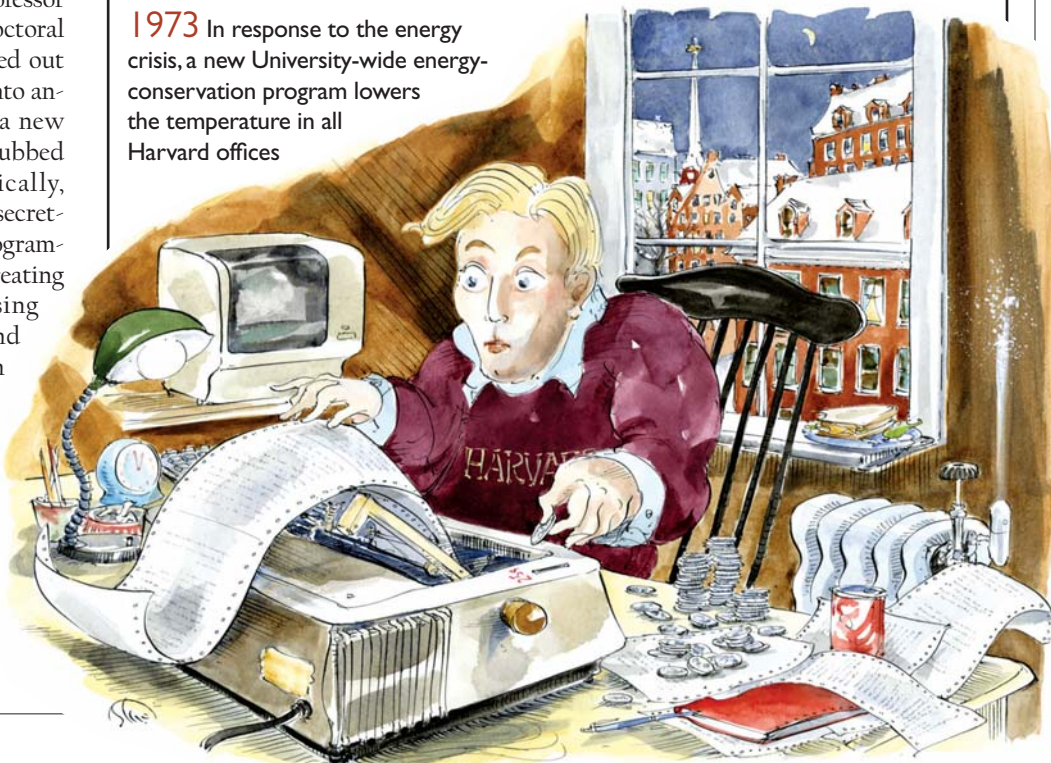


Illustration by Mark Steele

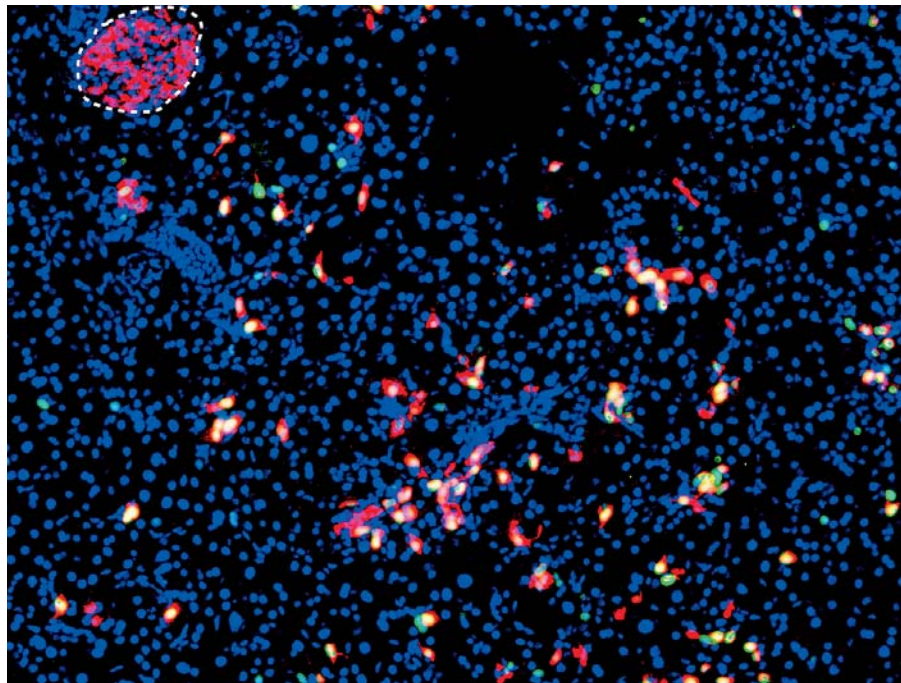
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they chose the three genes—which were delivered by means of a virus—from among more than 1,100 potential candidates they had identified as being expressed in the embryonic pancreas. In adult mammals, just 1 percent of the pancreas consists of beta cells that produce insulin, critical for the regulation of blood-glucose levels, while 95 percent consists of exocrine cells, which secrete digestive enzymes. Using their three introduced genes, Melton's team has been able to “flip”

exocrine cells, causing them to become rare beta cells that are indistinguishable in shape and function from preexisting beta cells. (For more on the disease, see “Decoding Diabetes,” page 50.)

Unlike conventional stem-cell science, which involves using *undifferentiated* cells and then figuring out how to coax them to become a particular cell type, Melton and Zhou's work points the way to a potential shortcut for treating any disease in which a cell type is missing. The trick was learning which genes to use. “The idea of reprogramming one differentiated cell type of adult tissue into another is very exciting, and it is applicable to achieve the regeneration of different types of cells in the body,” says Paola Arlotta, an assistant professor of surgery and of stem-cell and regenerative biology affiliated with Harvard's new interschool department of stem-cell and regenerative biology (www.scrb.harvard.edu). Arlotta is performing related work to reprogram neurons of the central nervous system. Although different combinations of genes will be needed to cause reprogramming in different individual tissues, substantial progress toward their identification is now being made.

“It's a wonderful piece of work,” says Sir John Gurdon, an emeritus professor of developmental biology at the University



Viral delivery of a three-transcription-factor cocktail has transformed pancreatic exocrine cells (blue) into scattered insulin-producing beta cells (red). A preexisting islet, or grouping of beta cells, is outlined at the upper left.

of Cambridge who oversaw Melton's graduate work at Oxford. “Particularly impressive is the idea of trying to derive the required cells from a related cell type, rather than going from adult cells back to the beginning and out again. It's much more logical, really.”

In some ways, Melton's departure from strict adult-stem-cell research was guided by a paper he published in *Nature* in 2004. There he described his finding that new beta cells in adults don't derive from adult stem cells, as so many other tissues in the body do; instead, they are produced by replication of existing beta cells. This showed there would be no way to coax stem cells in adults to become beta cells. (He nevertheless continues to try to create beta cells from *embryonic* stem cells, which are totipotent—they can make *any* cell type.)

Melton's feat echoed that of Shinya Yamanaka of Kyoto University, who in 2006 employed viruses to reset adult cells to a primordial state. These induced pluripotent stem cells (iPS cells), as they are known, can in theory be prodded to differentiate into more specialized kinds of

cells, but no one has figured out all the steps to do this yet. Melton's simpler approach—directly changing one adult cell type into another—is the first method to achieve such success. Yamanaka's technique also uses retroviruses that become permanently integrated into the genome and can induce cancer; the virus employed in Melton's technique does neither. Melton nevertheless hopes to identify a drug that will mimic the ac-

tion of the gene transcription factors he has identified as critical for pancreatic cell transformation. That would facilitate approval of potential treatments in humans, which could be as little as two to five years away.

In announcing his discovery, Melton emphasized the importance of continuing to work with embryonic stem cells derived from fertilized human eggs because of the critical insights they continue to provide in the field of developmental biology, and with iPS cells, which were at the heart of some of the other Harvard advances this past summer.

TWO SEPARATE TEAMS of HSCI researchers, employing variations of the Yamanaka technique, created disease-specific iPS stem-cell lines using adult cells from human patients. Kevin Eggan, an assistant professor of stem-cell and regenerative biology, announced in *Science* that he had used the technique to create motor neurons from the cells of an 82-year-old patient with ALS. George Daley, an associate professor of biological chemistry and molecular pharmacology and of pediatrics at Harvard Medical School (HMS), writing in *Cell*, announced that his laboratory had created 20 stem-cell lines representing a variety of afflictions, from “bubble-boy” disease to Parkinson's. The iPS

cell lines created by Eggen and Daley, made freely available to researchers throughout the world, will allow study of the development of these diseases in a petri dish, making them powerful tools for research even though they cannot be used in human therapy because of their cancer-causing potential.

But there was progress on that front, too. Konrad Hochedlinger, an assistant

professor of medicine and of stem-cell and regenerative biology, has discovered a way to create iPS stem cells in mice without causing cancer. Instead of the retroviruses employed by Yamanaka, he used adenoviruses that “infect the cells” carrying the genes needed for cellular reprogramming, “but are cleared... after a few cell divisions.”

In the wake of these discoveries, HSCI

announced that it would create a new “core laboratory” dedicated to iPS techniques, augmenting its four existing shared core facilities devoted to specialized aspects of stem-cell science.

At the Harvard-affiliated Joslin Diabetes Center, the viability of using stem cells in clinical treatments was demonstrated in principle using mice carrying an induced form of muscular dystrophy.

Morning Prayers: All Creatures

President Drew Faust's Morning Prayers address in Appleton Chapel on September 16

This chapel, this church represent places where we stop for a moment or an hour outside our usual work and lives to consider the larger meaning of what we do. It is also a place where we think beyond our own individual ambitions and achievements to reflect upon our obligations to one another and to a wider world.

Today I want to speak about one such obligation, one I am asking our community to take on with new focus and new force. It is an obligation to our children and to their children, and it is in one sense a quite simple matter of human self-interest and survival. But it is also a question with deeply spiritual implications concerning what we owe not just to one another and our descendants but to whatever god or transcendent being or divine force we might believe in. What I want to talk about today is the preservation of the world—its glaciers, its forests, its waterways, its species—in the face of the crisis of global warming and environmental change.

Among the most powerful memories of my childhood experiences in church and Sunday School are hymns that still echo in my mind. And a great many of those hymns are songs of praise and thanksgiving for creation's wonders. “Fair are the meadows; fairer still the woodlands.” Or perhaps for me and so many others, most memorably:

All things bright and beautiful,
All creatures great and small,
All things wise and wonderful,
The Lord God made them all.

Each little flower that opens,
Each little bird that sings,
He made their glowing colors,
He made their tiny wings.

Written in 1848, the words to this hymn are steeped in Victorian romanticism, extolling the glowing colors of each little flower, the tiny wings of each little bird. Its rather treacly senti-

mentality and continuing popularity in a far more cynical age moved Monty Python to parody:

All things dull and ugly
All creatures short and squat
All things rude and nasty
The Lord God made the lot.

Each nasty little hornet,
Each beastly little squid
Who made the spiky urchin?
Who made the sharks? He did!

But Monty Python's mockery actually reinforces, rather than rejects, my fundamental point: Urchins, squid, hornets, sharks matter too. They play an essential part in what we might call the wonders of biodiversity.

Yet we humans of the twenty-first century seem to be doing our best to destroy that wondrous creation. Pollution and climate change, habitat destruction and species extinction are growing threats to the world we have inherited and the world we will bequeath to our descendants—the creation we steward for purposes far larger than ourselves.

In July, I announced a new initiative for Harvard indicating that Harvard would be making an ambitious commitment to reducing its emission of greenhouse gases in an effort to lessen our carbon footprint and our contributions to global warming.* The goals we have set will not be easy to attain; they will require all of us to change assumptions and behavior; to live with enhanced consciousness and responsibility about our stewardship of the earth. And we will at the same time commit our intellectual resources as an institution devoted to learning and discovery, to explore policies and technologies that can make a significant difference in the crisis of sustainability that we face. In our work as students and scholars, in our lives as members of this community we must commit ourselves to preserving this wondrous creation all around us. However we may differ in our religious explanations and understandings, our lives are deeply intertwined and interdependent—with one another and with this world which we cannot permit to perish. To borrow words from the old hymn: “We must be wise to preserve what is wonderful.”

*See “Environmental Action,” September–October, page 57.

Amy Wagers, an HMS assistant professor of pathology, figured out a way to identify adult stem cells in muscle by means of the unique protein markers on their surfaces. She then transplanted stem cells from the muscles of healthy mice into mice with the disease. The stem cells not only restored partial muscle function, she reported, but also replenished the pool of stem cells that "could be reactivated to repair the muscle again during a second injury." For now, the technique works only on a muscle-by-muscle basis, making it impractical for treatments, but the work proves the viability of stem-cell transplantation.

THE SUMMER'S announcements were not isolated successes, but proof that HSCI works as a model for catalyzing collaborative research, says executive director Reeve. HSCI faculty members "are publishing on average 30 papers a month in peer-reviewed journals," he adds. The organization's budget for scientific research and operations has increased from \$5 million to just over \$16 million in the last three years, with 80 percent of the funding to date coming from individuals. (That will change with increasing sponsorship from industry: GlaxoSmithKline recently pledged \$25 million to support HSCI during the next five years. Reeve notes that the development of disease-specific iPS stem-cell lines is of particular interest to the pharmaceutical industry, because it will not only provide therapies, but also offer the ability to test drugs against specific diseases on an unprecedented scale.)

The growth in stem-cell research at Harvard has been even more rapid than anticipated: a shared therapeutic screening facility designed to handle the work of HSCI researchers until the opening of the first science building in Allston three years from now is already operating at capacity. New courses are being offered this year through the department of stem-cell and regenerative biology, with plans to introduce a concentration in the 2009-2010 academic year. And the number of principal HSCI faculty members has increased from 40 a year ago to 65 this year (there are also a hundred affiliated faculty). Looking ahead, HSCI ex-

pects to fill the space allocated to stem-cell researchers in the new science building within the first two years of occupancy.

Speaking of the summer's successes at HSCI's annual stem-cell summit in September, President Drew Faust noted,

Creating Space to Contemplate Success

"RICH LIVES INCLUDE continuing internal conversations about who we are, what we want to achieve, where we are successful, and where we are falling short," Hobbs professor of cognition and education Howard Gardner and his coauthors write in *Good Work: When Excellence and Ethics Meet*. Yet these conversations—both internal and among friends—seem to happen less frequently for today's undergraduates than for previous generations. Members of the Millennial Generation "plan every single moment of every day," says dean of freshmen Thomas A. Dingman. "I think all of us who work with them are struck by how purposeful they are." Students and administrators alike worry that in the absence of introspection, material success becomes the focus by default.

Students' busy schedules are crowding out the proverbial 2 A.M. philosophical discussions in a dorm room—but that is only part of the problem, says Sheila Reindl '80, M.Ed. '88, Ed.D. '95, a counselor at the Bureau of Study Counsel (BSC). Especially at Harvard, she says, "There is this pressure to be prematurely polished, to look as though you know where you're going."

The moral-reasoning component of the Core curriculum aims to get students to mull and elaborate their personal moral codes, but for many, the experience falls short. And striking up a conversation with friends over dinner about how concepts from class might apply to one's own life is practically a *faux pas*, says Lois Beckett '09. "There's this sense that it's somehow embarrassing. It's like walking into dinner with your fly unzipped."

Disappointed with this aspect of her freshman year, Beckett approached Dingman. The seed was planted for an optional,

"This may well be the first time since the end of World War II when major progress in basic biomedical science in the United States has been enabled primarily by farsighted private individuals, foundations, corporations, and institutions rather than by the federal government."

extracurricular discussion series; around the same time, Gale professor of education Richard J. Light, author of *Making the Most of College* (see "The Storyteller," January-February 2001, page 32), was hearing similar complaints in his survey of the classes of 2006 and 2007. Dingman and Light assembled a working group of three students (including Beckett), director of freshman programming Katherine Steele, and Gardner (who had led similar efforts at Amherst and Colby) to help design Harvard's discussions. The group selected faculty members and administrators to lead discussions and then invited the entire class of 2011 to participate. About 8 percent of the class—130 students—took part in "Reflecting on Your Life."

Each group met a minimum of three times for 90 minutes last spring. Leaders could decide how to structure the meetings, but, Steele says, one widely used exercise that proved "illuminating" was asking the first-years to state their core values, then account for how they spent their time in a given week, and see how closely their everyday pursuits and values corresponded.

Judith Kidd, who oversees student life and activities as associate dean of the College, explains that today's students "are used to having their activities planned for them." This is the play-date generation; its members feel more comfortable airing young-adult angst in an officially sanctioned forum. "It's sad that if they are going to have these conversations, we need to arrange them," she says, "but I think we need to do it."

In the "Reflecting" program for first-years (which will be repeated this year) and in "The Big Question," a dinner discussion series arranged by student members of the Phillips Brooks House Association, undergraduates can say what they think without worrying that it will affect