

Weight gain may be influenced by fructose consumption

‘We saw that fructose did not cause feelings of fullness.’

—Kathleen Page, assistant professor of medicine at the Keck School

Feeling hungry after drinking something sweet? It could have something to do with the type of sugar you consumed, according to research at Yale University led by a Keck School of Medicine of USC scientist.

The research, conducted by principal investigator Kathleen Page, assistant professor of medicine at the Keck School, determined that fructose and glucose, the two forms of simple sugars, are processed differently in the brain. The difference was apparent after study participants consumed drinks containing fructose or glucose, and is a potential explanation for why we gain weight.

“We saw that fructose did not cause feelings of fullness, whereas the participants reported an increase in feelings of fullness after the glucose drink,” said Page, who is also chair of the Maternal-Child Health section of the

USC Diabetes and Obesity Research Institute.

The research was published in the *Journal of the American Medical Association*, and was conducted while Page was on the faculty at Yale. Research funding was provided by the Doris Duke Charitable Foundation.

The study used functional magnetic resonance imaging to map changes in the brains of 20 test subjects who consumed sugary drinks. The researchers found that the glucose drink suppressed activity in the hypothalamus and other brain regions that regulate appetite, motivation and reward processing, while the fructose drink did not. The different responses to fructose were associated with reduced levels of the hormone insulin, which sends signals to the brain that a person has had enough to eat.

Fructose, found with glucose in many fruits and

vegetables, as well as table sugar, is an ingredient in high-fructose corn syrup, a popular sweetener. High-fructose corn syrup is found in certain soft drinks and processed foods, and consumption of the sweetener has been on the rise over the past few decades. Rates of obesity

have increased in parallel, the researchers noted.

In continuing research, Page’s team is studying whether obese people have exaggerated brain reward and hunger responses to fructose and whether different ethnic groups respond differently to fructose and glucose.



Courtesy Jean-Pierre Touzeau estate

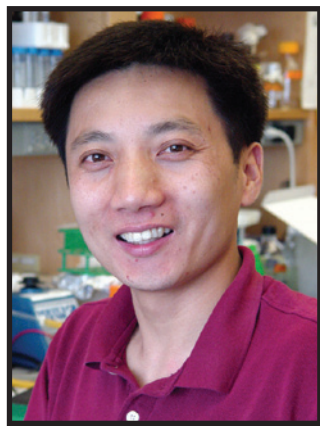
\$1.5 million bequest to endow lung cancer research at USC Norris Comprehensive Cancer Center—Lung cancer research has received new support at the USC Norris Comprehensive Cancer Center thanks to the generosity of Jean-Pierre Touzeau (left), pictured with longtime companion Janique Hervé. Touzeau created a \$1.5 million bequest for an endowment to support lung cancer research at USC Norris, in gratitude for the supportive treatment Hervé received for cancer there. The bequest was received last year. Lung cancer research at USC Norris is focused on quality of life and better outcomes for patients. In addition to providing robotic surgery and radiation oncology, the cancer center is developing new methods of early detection and new drugs to improve patient treatment.

USC-designed mouse mimics human immune response, speeding new disease treatments

By Alison Trinidad

Medical scientists at USC have bred a first-of-its-kind mouse model that possesses an immune response system more like a human’s. The discovery makes way for quicker and more cost-effective development of next-generation drugs to treat human diseases like cancer, diabetes and tuberculosis.

Medical researchers have long used mice and rats to help formulate new drugs and vaccines, in part because their genetic and biological characteristics closely parallel human physiology. But mice are not humans, and many experimental drugs that work extraordinarily well in rodents fail miserably when tested in people. One such



Weiming Yuan

drug, α -galactosylceramide (α -GalCer), essentially wipes out cancerous tumors in mice by activating the body’s immune system; for reasons not entirely clear, the drug does not trigger the same response in people with cancer.

Scientists hypothesize that the failure to translate

is due to subtle differences between the CD1d molecules in mice and humans and how they respond to tumors and infection. CD1d molecules are found on certain cells that trigger the body’s innate immune response. In a study published by the *Proceedings of the National Academy of Sciences* this week, USC researchers describe how they genetically engineered mice to express CD1d molecules that look more like those in humans and in more similar proportions. More importantly, the humanized CD1d molecules effectively trigger natural killer T (NKT) cells—a recently discovered type of white blood cell that attacks tumors and infection—in live animals when exposed to α -GalCer.

“It’s the best model we have in the field,” said Weiming Yuan, assistant professor of molecular microbiology and immunology at the Keck School of Medicine of USC and principal investigator of the study. “We’ve basically set a platform to fast-

USC celebrates grand opening of new Engemann Student Health Center

By Cristy Lytal

University officials unveiled the USC Engemann Student Health Center at the University Park campus on Jan. 29, showing off the new five-story, 101,000-square-foot health center now open to students, faculty, staff and community members.

Located on the University Park Campus at 1031 W. 34th St., the state-of-the-art health center houses multiple services, including Counseling Services, the Office for Wellness and Health Promotion, the faculty staff practice, the oral health clinic, physical therapy, occupational therapy, immunizations and the health insurance office.

It is also home to the newest Keck Medical Center of USC ambulatory practice—a 3,224-square-foot, five-day-a-week operation offering primary and specialty care services.

“The focus of this site

is to offer a convenient location for our University Park campus faculty and staff,” said Dana Habers, chief operating officer for USC Care Medical Group, Inc., who led efforts with a team of dedicated staff to open the facility. “We’re excited to extend the Health Sciences Campus downtown and be able to offer world-class services right in their own backyard.”

The office, which will be operated by USC Care, has six well-appointed exam rooms and one procedure room, offering same-day access to appointments. Internal medicine and rheumatology are among the specialties available now. There are already plans to expand those clinical offerings in the future to include an orthopedics presence, in response to a recently administered survey.

“We’ve designed this site

Nikias to address faculty Feb. 13

USC President C. L. Max Nikias will present his annual address to the Health Sciences campus faculty on Feb. 13 from 7:30-8:30 a.m. at the Aresty Conference Center.

All faculty and staff are welcome and encouraged to attend the event and the 7 a.m. breakfast immediately preceding.

To RSVP, visit: usc.edu/esvp and use code “HSC13.”

CHLA receives Magnet recognition for nursing excellence

Magnet recognition ‘confirms the unwavering dedication of our nurses and our nursing leadership and their commitment to providing the best in patient care.’

—Richard D. Cordova, CHLA president and CEO

For the second time in four years, the American Nurses Credentialing Center (ANCC) bestowed Magnet recognition for nursing excellence on Children’s Hospital Los Angeles, announced Richard D. Cordova, president and CEO of Children’s Hospital Los Angeles.

“Earning Magnet recognition the first time in 2008 was a milestone in the history of Children’s Hospital Los Angeles,” Cordova said. “To have achieved Magnet status a second time confirms the unwavering dedication of our nurses and our nursing leadership and their commitment to providing the best in patient care. It demonstrates why we are ranked among the top children’s hospitals in

the United States, if not the world.”

The Magnet Recognition Program was developed by the ANCC, the world’s largest nurse credentialing organization, to recognize health care organizations that demonstrate quality patient care, nursing excellence and innovations in professional nursing practice.

According to the ANCC, Magnet designation benefits consumers by identifying hospitals with superior nursing care and quality patient outcomes. It is the highest honor a health care organization can receive for professional nursing practice.

Only a select group of 395 hospitals out of almost 6,000 U.S. health care organiza-

tions have achieved Magnet status, recognizing only the very best hospitals across the country. In California, Children’s Hospital, which is affiliated with the Keck School of Medicine of USC, is one of only 28 recognized Magnet organizations.

Hospitals must reapply for Magnet recognition every four years. Children’s Hospital received word Jan. 16 from the Commission on Magnet leadership that it had achieved Magnet redesignation for another four years.

The Magnet commission reported that Children’s Hospital exceeded many of the high Magnet standards and stood out as an example to hospitals across the U.S. in several areas, including the hospital’s

transformational nursing leadership practices, its current and long-term strategic priorities in a changing medical market and the organization-wide adaptation to a new hospital building, the Marion and John E. Anderson Pavilion.

In addition, the commission cited many practices and programs that exceeded its stringent standards, including: daily interdisciplinary rounds with patients and families, efficient medication administration, outreach programs for homeless youth, children’s reading and library programs, spinal education for scoliosis patients, teleconferencing interpreter services, and bedside technology to enhance patient care and parent-nurse communication.

USC School of Pharmacy researcher sees microorganisms as key to new biofuels

By Gabrielle Olya

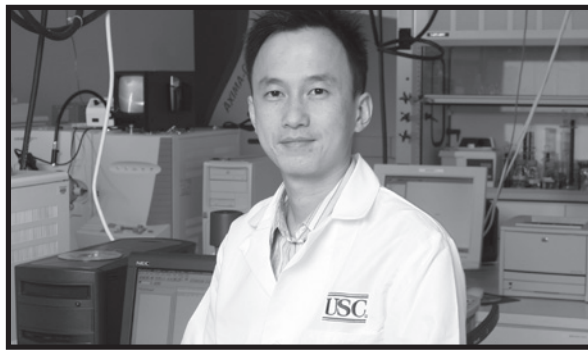
The Obama administration, along with the U.S. Department of Energy, has announced \$10 million worth of grants to aid in the development of alternative energy sources, namely novel biofuels.

Among the recipients of the grants is School of Pharmacy Associate Professor Clay Wang, who will be collaborating with The Pacific Northwest National Laboratory, other universities and industry representatives on a new project that aims to increase the production of fuel molecules in fungi growing on lignocellulosic hydrolysate. The grant is a two-year, \$2.4 million grant based

out of Richland, Wash.

“These projects use innovative synthetic biological and chemical techniques to convert biomass into processable sugars that can be transformed into bioproducts and drop-in biofuels for cars, trucks and planes,” the Department of Energy explained in a release.

Wang’s previous work has focused on exploring possible uses of naturally occurring microorganisms as drugs, with a particular emphasis on natural product biosyn-



School of Pharmacy Associate Professor Clay Wang aims to increase the production of fuel molecules in fungi.

Lee Salem

ces both have the ability to produce many more drugs than was previously believed. Wang has also developed a biosynthetic method to upregulate or downregulate these genes to change what is produced and to create new drugs.

His grant is one of five receiving funding from the Energy Department’s Office of Energy Efficiency and Renewable Energy, which was established to accelerate development and facilitate deployment of energy efficiency and renewable energy technologies and market-based solutions that strengthen U.S. energy security, environmental quality and economic vitality.

thesis—using genomics for natural drug development. His lab has discovered that the fungi *Aspergillus nidulans* and the bacteria *Streptomy-*

MOUSE: More accurate simulation of human immune response bolsters chance for success

Continued from Page 1

track the identification of immunotherapies that can kill cancer and also make vaccines stronger.”

Once activated, NKT

cells react in a matter of hours, whereas other T cells may take days. This rapid response makes them difficult to study, but also an ideal target for drug-makers.

Yuan’s humanized mouse allows scientists to more accurately test the viability of those NKT cell-targeting drugs before going to human clinical trials.

“Before, it would have been a guess as to whether the drug would work in people. Now, the chance of success goes from 1 out of 100 to 1 out of 5,” Yuan said.

Yuan and colleagues have yet to demonstrate the effects of inserting a more human-like version of the final component of the CD1d/NKT system, the T cell receptor. More experiments are necessary to determine why α -GalCer is ineffective in treating people with cancer and to develop novel α -GalCer derivatives that work with the human immune system.

Co-authors include Xiangshu Wen, Seil Kim

and Agnieszka Lawrenczyk of the Keck School of Medicine; Ping Rao of the UCLA Immunogenetics Center and Department of Pathology; Leandro J. Carreño and Steven A. Porcelli of the Albert Einstein College of Medicine at Yeshiva University; and Peter Cresswell of the Yale University School of Medicine. The research was supported by the National Institutes of Health (R01 AI091987, R01 AI059167, R01 AI045889), the Harry Lloyd Charitable Trust, the Margaret Early Medical Research Trust, and the Howard Hughes Medical Institute.

The Weekly

Next Issue: Feb. 15

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Can you really learn to be more understanding by watching ‘The Bachelor’?

By Robert Perkins

A new USC study finds evidence suggesting that the brain works hard to understand those who have different bodies when watching them in action.

According to the study’s lead author, the finding supports initiatives to include more individuals with physical differences in mainstream media—such as Sarah Herron, a contestant on ABC’s “The Bachelor” this season, who was born with a foreshortened left arm.

“Generally, it’s considered impolite to stare. But what these results suggest is that we need to look. It’s through this visual experience that we’re able to make sense of those different from ourselves,” said Sook-Lei

Liew, who is the lead author of a paper on the research that appeared online this month in *NeuroImage*.

Liew, now a postdoctoral researcher at the National Institutes of Health, completed the research while she was a doctoral student at USC, working with Tong Sheng, a fellow graduate student, and Lisa Aziz-Zadeh, an assistant professor at the USC Dornsife Brain and Creativity Institute and the Division of Occupational Science and Occupational Therapy.

Liew, Sheng and Aziz-Zadeh monitored the brains of 19 typically developed individuals using functional magnetic resonance imaging (fMRI) while showing them a series of video clips. First

they showed a typically developed person picking up objects and then a woman born without complete arms using her residual limbs to perform the same tasks.

The fMRI scans showed that parts of the motor network responsible for picking up objects by hand are activated when simply watching another person performing the task—physical evidence of participants attempting to use their own body representations to represent the people they are watching on screen.

The thing that surprised the researchers was that the same part of the motor network was activated to a greater degree when watching residual limbs doing the same activity. Participants’ brains worked

overtime to process the use of a type of limb that they did not have.

“Interestingly, we found that individual differences in trait empathy affected the result,” Aziz-Zadeh said. “That is, individuals who scored higher in their ability to empathize with other people showed more activity in motor regions when observing actions made by residual limbs.”

Further, when shown more clips of the woman with a residual limb—clips that lasted minutes instead of seconds—the fMRI scans showed similar motor network activity, which returned to a level comparable to when they were watching typically developed individuals, suggesting that increased

visual exposure improved understanding.

“Stigma is one of the main challenges for people with physical differences,” Liew said. “We need to examine why stigmas exist and what we can do to alleviate them. Learning about disabilities visually is one way that we can begin to map their experiences onto our own brains.”

This research was supported by the National Science Foundation Graduate Research Fellowship, The USC Provost’s Ph.D. Fellowship, the Division of Occupational Science and Occupational Therapy, the Dana and David Dornsife Neuroimaging Center and the Brain and Creativity Institute.

The Weekly NEWSMAKERS

A Feb. 4 broadcast on KPCC-FM featured an interview with **Daniel Arkfeld**, assistant professor of medicine at the Keck School of Medicine, about rheumatoid arthritis. “I think it’s important to understand that rheumatoid arthritis comes from the blood,” Arkfeld said. “The disease doesn’t start in the joints; it’s really in the blood.”

A Feb. 4 report in *Science Codex* featured research led by **Weiming Yuan**, assistant professor of molecular microbiology and immunology at the Keck School of Medicine, that describes a new breed of mouse that possesses an immune response more like a human’s.

A Feb. 4 article in *VOXXI* cited a 2008 study led by **Michael Goran**, who holds the Dr. Robert C. and Veronica Atkins Endowed Chair in childhood obesity and diabetes and is professor of preventive medicine, physiology & biophysics and pediatrics at the Keck School of Medicine, finding that overweight Hispanic children are at significant risk for pre-diabetes.

A Feb. 1 article by HealthDay News quoted **Sean Nordt**, assistant professor of clinical emergency medicine of the Keck School of Medicine, about the dangers that energy drinks pose to teenagers.

A Feb. 1 column in The Huffington Post quoted **Robert Kloner**, professor of medicine at the Keck School of Medicine, about his research that links the emotional stress experienced by fans of a losing Super Bowl team with increasing the risk of heart attack.

A Jan. 31 broadcast on American Public Media’s “Marketplace” quoted **David Agus**, professor of medicine at the Keck School of

Medicine, about cancer screening. “Countries that screen [for prostate cancer] have half the death rate of countries that don’t,” Agus said. “In the United States, since we started screening, the death rate is down over 45 percent.”

The Jan. 31 edition of *The Desert Sun* featured an article by **Kevan Craig**, assistant professor of clinical pediatrics at the Keck School of Medicine, about a Children’s Hospital Los Angeles patient’s recovery after a near-fatal hit-and-run accident.

A Jan. 31 column in *The New York Times* published SAT study strategies by Keck School of Medicine student **Shaan Patel**, who is the author of “SAT 2400 in Just 7 Steps.”

A Jan. 30 broadcast on KCET-TV’s “SoCal Connected” interviewed **Sean Nordt**, assistant professor of clinical emergency medicine of the Keck School of Medicine, about the dangers of designer drugs called “bath salts.”

A Jan. 28 article in *The Plain Dealer* featured research by **Wei-An “Andy” Lee**, assistant professor of clinical medicine at the Keck School of Medicine, on how geospatial video can help inform patients at his urban clinic in Los Angeles.

Using geospatial maps, doctors can learn what a patient’s immediate neighborhood is like, and then make healthful recommendations based on that information. “Along with a patient’s medical and family history, what I’d like to see is your spatial history,” Lee said. “By looking at that throughout time, how does that influence your health?” Andrew Curtis, now at Kent State University, also conducted research in this area while he was a USC faculty member.



Alison Trinidad

Volunteers sought for LA Marathon—For the second year, the Keck Medical Center of USC is the official medical sponsor of the 2013 LA Marathon, which will be held Sunday, March 17. The Keck Medical Center is seeking 150 medical and non-medical staff, faculty and student volunteers to staff the medical stations along the race course and to care for the runners from start to finish. Physicians and nurses from the Keck Medical Center are encouraged to participate, as well as students and faculty from the Keck School of Medicine of USC. Volunteers will provide on-the-spot care at mobile medical tents along the 26.2-mile course, which starts at Dodger Stadium and ends at the Santa Monica Pier. With 25,000 expected runners, thousands of volunteers and hundreds of thousands of spectators, the LA Marathon is one of the largest organized road races in the country. Above, at the 2012 LA Marathon, USC medical resident Allyson Estess and other volunteers assist a runner out of the medical tent. To volunteer and be a part of the event this year, email Assocdeanlac@usc.edu.

CENTER: USC celebrates grand opening

Continued from page 1
around our university patients,” Habers said. “We are just starting out, but this practice will continue to evolve as specialists join—including cardiology, dermatology and others—and as we adapt our operations to most effectively meet the needs of USC faculty and staff.”

To express the university’s gratitude, USC President C. L. Max Nikias invoked the words of the ancient Greek physician Hippocrates on Jan. 29: “Wherever the art of medicine is loved, there is also a love of humanity.”

Nikias called the Engemanns “two faithful philanthropists who have demonstrated their love of humanity and of this university through their

extraordinary legacy of generosity and support.”

Vice President for Student Affairs Michael L. Jackson, who served as the grand opening master of ceremonies, praised the leading-edge center as a great achievement.

“I am really proud to again celebrate another great accomplishment by the university, the Division of Student Affairs and our campus partners who played instrumental roles in the development of the Engemann Student Health Center,” he said.

The festivities concluded with a symbolic ribbon-cutting ceremony, a bright burst of cardinal and gold confetti, and a brassy performance by the USC Trojan Marching Band.

Calendar of Events

Monday, Feb. 11

4 p.m. NGP Distinguished Speaker Seminar Series. “The Circuit of Value and Incentive-Based Learning: Linking Connectivity to Function and Disease,” Suzanne Haber, University of Rochester Medical Center. BCC Conference Room. Info: (323) 442-7874

Tuesday, Feb. 12

Noon. Psychiatry Grand Rounds. “The Genetics of Bipolar Disorder and Lithium Response,” John Kelsoe, UC San Diego. CSC 250. Info: (323) 442-4065

Noon. Broad Center for Regenerative Medicine and Stem Cell Research at USC Seminar. “Epigenetic Mechanisms of Tumor Maintenance,” Paola Acaffidi, NIH. BCC Seminar Room. Info: (323) 442-8080

Thursday, Feb. 14

Noon. Cellular Homeostasis Lecture. “The Immune Response and Biliary Atresia: Guilt and Redemption,” Jorge Bezerra, Cincinnati Children’s Hospital Medical Center. MCH 156. Info: (323) 442-3121

Friday, Feb. 15

8:30 a.m. Surgical Grand Rounds. “Transplant Education Network—Liver Graft Survival and Beyond: Renal Function, HCV and HCC,” James Trotter, Baylor University. DOH 1st Floor Auditorium. Info: (323) 442-9064

Monday, Feb. 18

Noon – 2 p.m. Center for Technology Innovation in Pediatrics Industry Roundtable. “Commercializing Pediatric Medical Devices: Turning Challenges into Opportunities,” various speakers. CHLA Stauffer A Conference Room, Anderson Pavilion. Info: (323) 442-7874

Tuesday, Feb. 19

10:30 a.m. Keck Hospital of USC Guild Speaker Series. “Brain Wellness—Saving Our Brains from Arteriosclerosis,” Helena Chui, USC. DEI 3rd Floor Auditorium. Lunch immediately following. \$25. Info: (323) 254-0600

Noon. Broad Center for Regenerative Medicine and Stem Cell Research Seminar. “Characterizing Circulating Tumor Cells: Insights into Cancer

Metastasis,” Min Yu, Harvard. BCC Seminar Room. Info: (323) 442-8080

5 p.m. Clinical Research Ethics Forum. “Can You Draw the Line Between ‘Innovative Treatment’ and Human Subjects Research?” Alexander Capron and Donna Spruijt-Metz, USC. NRT Aresty Auditorium. Info: (323) 442-8281

Thursday, Feb. 21

Noon. Cellular Homeostasis Lecture. “Role of Nuclear Receptor HNF4 in Cancer,” Frances Sladek, UC Riverside. MCH 156. Info: (323) 442-3121

Noon. USC Global Health Lecture Series. “Entrepreneurial Approaches to Global Health Challenges,” Jacqueline Novogratz, Acumen Fund. UPC: TCC 450. Info: (323) 865-0419

5:30 p.m. – 7 p.m. Orthopaedic Surgery Grand Rounds. “Influences: What Does It Take to Change Our Minds?” James Kellam, Carolinas Medical Center. NRT Aresty Auditorium. Reception: 5:30 p.m. – 6 p.m. Lecture begins promptly at 6 p.m. Info: (323) 226-7204

Friday, Feb. 22

Noon. Center for Applied Molecular Medicine. “Can Cancer Be Reversed by Engineering the Tumor Microenvironment?” Donald Ingber, Harvard. CSC 250. Info: (323) 442-3849

1:30 p.m. KSOM Research Seminar. “The mTOR Pathways in Nutrient Sensing, Autophagy, Cell Growth, and Cancer,” Kun-Liang Guan, UC San Diego. NRT Aresty Auditorium. Info: (323) 442-7732

Monday, Feb. 25

11:30 a.m. KSOM Research Seminar. “Using Genomics to Search for New Viral Causes and Treatments for Cancer,” Patrick Moore, University of Pittsburgh. NRT Aresty Auditorium. Info: (323) 442-7732

Tuesday, Feb. 26

Noon. Women in Management Luncheon and Speaker Series. “HIV/AIDS: 30 Years of Successes and Challenges—A Personal Account,” Andrea Kovacs, USC. NRT LG 503/504. Cost: \$15 members/\$18 non-members. Info: (323) 442-2356



Steve Cohn

Honoring excellence—The Keck School of Medicine held an honors awards ceremony on Jan. 16, marking a yearly tradition of celebrating outstanding medical students for their academic performance, as well as their leadership outside of the classroom. Above at the event are: first-year students Alexandra Mihalek, Kevin Platt, Erin Cleveland, Erin McGuire and Samantha Spragg. For a full list of honorees, visit <http://usc.edu/1s1>.

Dying young: Americans now less likely to make it to 50

By Suzanne Wu

A report released in January by the National Academies paints a dire picture of American health.

Not only do people in the United States die sooner than people in other high-income countries, but American health is poorer than in peer countries at every stage of life—from birth to childhood to adolescence, in youth and middle age, and for older adults.

“The problem is not limited to people who are poor or uninsured,” said Eileen Crimmins, holder of the AARP Chair in Gerontology at the USC Davis School of Gerontology and a member of the National Research Council panel that compiled the report. “Even Americans with health insurance, higher incomes, college education and healthy behaviors, such as not smoking, seem to be sicker than their counterparts in other countries.”

In contrast to prior research on life expectancy that focused on people over 50, the 10-person panel, chaired by Steven Woolf of Virginia Commonwealth University, examined potential health disadvantages among younger Americans—and found that Americans are less likely to make it to age 50 at all.

Deaths before 50 account for about two-thirds of the difference in male life expectancy between the United States and other developed countries and about one-third of the difference in female life expectancy, the report found.

Among the 17 peer countries examined by the panel—all high-income democracies with relatively large populations—people in the United States are much more likely to die of almost everything, including injury, noncommunicable diseases, such as diabetes, and communicable diseases, such as HIV.

In particular, among the countries studied:

- Americans are the most likely to die in transportation accidents. The rate of violent death is also significantly higher in the U.S., especially death from firearms.

- Americans are much more likely than people in peer countries to die from maternal conditions related to pregnancy. Since the

1990s, among high-income countries, teenagers in the United States have much higher rates of pregnancy and are more likely to acquire sexually transmitted diseases.

- Though the incidence of AIDS has fallen in the last two decades, the United States still has the highest incidence of AIDS among peer countries. Overall, the United States has the fourth highest mortality from communicable diseases, behind Portugal, Japan and the U.K. The United States has the highest prevalence of diabetes and high rates of obesity, starting in childhood.

For an interactive chart of how the U.S. stacks up against peer countries in causes of death, visit bitly.com/deathfromallcauses.

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Visit the USC Web: <http://emergency.usc.edu> This page will be activated in case of an emergency. Backup Web servers on the East Coast will function if the USC servers are incapacitated.