For most of the last century, diabetes research has focused mainly on the pancreas, liver and fat. But research by Einstein’s Dongsheng Cai, M.D., Ph.D., shows that the brain—specifically the region known as the hypothalamus—plays a crucial role in determining whether we develop diabetes.

The hypothalamus performs essential roles in the body, such as controlling body temperature, hunger and thirst. “We have been studying whether some types of hypothalamic changes might be important for a network of disorders known as metabolic syndrome [involving obesity, prediabetes and hypertension] and even aging,” says Dr. Cai, a professor of molecular pharmacology at Einstein.

Dr. Cai hypothesized that an inflammatory reaction in the hypothalamus might cause metabolic syndrome. He knew that overeating can chronically inflame certain tissues and lead to insulin resistance—an early step in type 2 diabetes. In the mid-1990s, scientists discovered that leptin (a protein pro-
The global epidemic of diabetes requires a multidisciplinary approach to studying and treating this complex disease. Our Diabetes Research Center scientists integrate the full spectrum of diabetes research—from laboratory science to clinical studies to community-engaged research—in their efforts to combat diabetes.

This issue highlights Dr. Dongsheng Cai’s discovery that both diet and aging can cause inflammation by activating a specific molecular pathway in the hypothalamus. This activated pathway causes insulin resistance, obesity and type 2 diabetes. Meanwhile, Dr. Claire Bastie has identified a gene in mice that, when knocked out, improves insulin sensitivity in mice fed a high-fat diet even as they become obese. The findings of both researchers suggest future therapies that could decrease the likelihood of developing diabetes and extend the life span.

Beyond the lab, a recent paper by Dr. Eric Epstein describes using a new index of glucose metabolism to predict insulin resistance in patients and detecting an intriguing difference in insulin resistance among ethnic groups. In addition, Dr. Rita Louard recently received the Excellence in Community Service Award for developing comprehensive community health education classes for patients with diabetes, who are taught to develop “a sense of mastery over their disease.”

With these advances we look forward to another productive year of partnership and innovation across multiple disciplines of diabetes research.

**Diabetes and Aging: Brain-Body Connection (continued)**

Dr. Cai's discovery that both diet and aging can cause inflammation by activating a specific molecular pathway in the hypothalamus. This activated pathway causes insulin resistance, obesity and type 2 diabetes. Meanwhile, Dr. Claire Bastie has identified a gene in mice that, when knocked out, improves insulin sensitivity in mice fed a high-fat diet even as they become obese.

Inflammatory reactions occur in human cells via a signaling pathway involving NF-κB and an enzyme called IKK-β. Dr. Cai found that the IKK-β/NF-κB pathway is also present in the hypothalamic neurons of mice. He then showed that a high-fat diet triggers this inflammatory pathway in the hypothalamus. And interrupting this pathway—by knocking out the gene for IKK-β—not only suppresses inflammation in hypothalamic neurons, but also stopped the animals from overeating and becoming obese or diabetic.

Digging deeper, Dr. Cai recently showed that aging— independent of a high-fat diet—also causes inflammation by activating the IKK-β/NF-κB pathway in the hypothalamus. By interrupting this pathway in the hypothalamus of animals, Dr. Cai was able to extend their life span.

Together, these discoveries place hypothalamic inflammation at the center of obesity, diabetes and aging. They point to a wholly new approach to controlling obesity and, possibly, aging-related disorders as well, with the potential to improve the lives of many people.

That’s precisely what Dr. Cai wants to do. Growing up in rural China, where disease was common and doctors scarce, Dr. Cai vowed to become a physician so he could help his community. Later, he realized that he could have a broader impact by discovering better treatments for disease, so he decided to become a researcher. Dr. Cai earned his M.D. and Ph.D. degrees in China and then relocated to the United States, which he considered the best place to hone his investigative skills. “I’m not biased toward this or that country,” he explains. “I’m more of an internationalist. I think of the whole world as one family.”

Dr. Cai joined Einstein in 2009. His work is currently funded by grants from the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute on Aging and the National Heart, Lung and Blood Institute, and by an American Diabetes Association research award.

**Q&A**

**Q: What led you to suspect that inflammation of the hypothalamus might contribute to aging?**

**A:** “We first found that chronic overeating triggers inflammation that leads to obesity and diabetes,” says Dr. Cai. “Since we knew that inflammation is also involved with aging, we suspected that inflammation of the hypothalamus might also play a role in the aging process—which was indeed the case, at least in mice.

“We also found that the undesirable effects of the NF-κB pathway in the hypothalamus can be counteracted by GnRH [gonadotropin-releasing hormone], a hormone that is synthesized in the hypothalamus and is associated with reproduction,” he adds. “When we injected GnRH into aged mice, it slowed down aging, probably because it stimulated neurogenesis, or growth of new brain cells. The exciting conclusion of this study is that it’s possible—at least in mice—to alter signaling within the hypothalamus to slow down the aging process and increase longevity.”
Discoveries

New Diabetes Target
Claire C. Bastie, Ph.D.
Assistant Professor of Medicine (Endocrinology)
Albert Einstein College of Medicine

Mice lacking Fyn, a member of the kinase family of enzymes, are leaner and have better insulin sensitivity when kept on a low-fat diet. But does lack of Fyn protect mice from the ill effects of a high-fat diet?

In a recent study, Claire C. Bastie, Ph.D., and her colleagues found that even when put on a high-fat diet, mice lacking Fyn showed better glucose tolerance and insulin sensitivity despite accumulating fat tissue. On the positive side, their fat tended to be under-the-skin fat rather than the more dangerous variety found around the gut that releases inflammatory chemicals. These findings point to inhibiting Fyn as a possible treatment for obesity-induced diabetes. The study was published in a 2013 issue of Diabetes.

Diabetes in the Bronx
Eric J. Epstein, M.D.
Assistant Professor of Medicine (Endocrinology)
Albert Einstein College of Medicine
Medical Director, Department of Medicine
Faculty Practice
Montefiore Medical Center

Diabetes is common in New York City, particularly in the Bronx. Insulin resistance—the body’s inability to use the insulin it produces—is a hallmark of diabetes. One way to assess insulin resistance is the estimated glucose disposal rate (eGDR), calculated using three clinical measures: waist circumference, glycosylated hemoglobin levels (HbA1c) and the presence of hypertension.

In a recent study of people with type 1 diabetes, Eric J. Epstein, M.D., and his colleagues found that ethnic groups in the Bronx tend to have different eGDR scores. Compared with Hispanics and whites, African Americans had greater insulin resistance as measured by eGDR, and those scores were associated with a greater risk of diabetes complications. Further studies should determine whether the eGDR can be used to guide treatment. The study was published in a 2013 issue of Diabetes Care.

A Smorgasbord of Solutions
Fajun Yang, Ph.D.
Assistant Professor of Medicine (Endocrinology)
Assistant Professor of Developmental and Molecular Biology
Albert Einstein College of Medicine

What do a glass of red wine and the Indian spice turmeric have in common? Both contain natural compounds that have anti-inflammatory, anticancerous and antioxidant properties. Resveratrol in red wine and curcumin in turmeric belong to a family of natural compounds known as polyphenols. But it’s not clear how these compounds might protect against cancers, heart disease, diabetes and neurological disorders.

In a recent study, Fajun Yang, Ph.D., his Ph.D. student Arian Abdulla and their colleagues found a possible explanation for the beneficial effects of resveratrol and curcumin. Both inhibited the activity of lysine-specific demethylase 1 (LSD1), a protein important for cell growth and nutrient metabolism. The study was published in a 2013 issue of the Journal of Biochemical and Pharmacological Research.

Diabetes Facts and Stats

1. The United States has the third-largest number of confirmed diabetes cases in the world: 17.9 million. Undiagnosed cases add another 5.7 million.
2. In the United States, 1.6 million new cases are diagnosed yearly.
3. One in 10 U.S. adults has type 2 diabetes.
4. One in 400 to 600 children and adolescents in the United States has type 1 diabetes.
5. The cost of diabetes in the United States is $220 billion per year.
6. Projections indicate that one in three Americans will have diabetes by 2050.

Sources: American Diabetes Association, Centers for Disease Control

Rifkin Lecture
On April 25, Andrew F. Stewart, M.D., director of the Diabetes, Obesity and Metabolism Institute at the Mount Sinai School of Medicine in New York, came to Einstein to deliver the annual Rifkin lecture. Dr. Stewart works in an area critical to both types of diabetes, but especially type 1: He strives to develop ways to encourage insulin-producing beta cells in the pancreas to replicate and regenerate. His lecture, held in the Ethel and Samuel J. LeFrak Auditorium of the Michael F. Price Center for Genetic and Translational Medicine/Harold and Muriel Block Research Pavilion, was titled “Advances and Obstacles in Molecular Control of Human Beta Cell Proliferation for Diabetes.” Dr. Stewart is also a professor of medicine, endocrinology, diabetes and bone disease at Mount Sinai.
UPDATE
Dr. Louard Receives Excellence in Community Service Award

Bronx residents are learning to manage their diabetes or avoid developing the disease thanks to Rita Jean Louard, M.D., an associate professor of clinical medicine (endocrinology) at Einstein and director of the Clinical Diabetes Program at the Moses Division of Montefiore, the University Hospital and academic medical center for Einstein. She and her colleagues—a nurse practitioner, a nutritionist and an in-patient nurse—plan and organize educational programs at Montefiore throughout the year. These programs range from classes in Spanish for the Latino community to support groups for children and teens.

In addition to caring for patients at the clinic, Dr. Louard and her associates conduct classes for adults with type 2 diabetes. Participants learn, for example, the importance of a healthy diet and regular exercise. The classes also help patients feel less isolated and imbue them with a sense of mastery and control over their disease,“ says Dr. Louard.

Community outreach is a strong component of Dr. Louard’s work. “Partnering with a core group of practitioners and organizations, we marshal our limited resources to increase awareness and improve health outcomes,” she says.

November is National Diabetes Month (NDM) and a special time of year for Dr. Louard and her team. They reach out to senior centers, schools and libraries and engage diabetes educators to help communicate key health-promotion messages to the public. Prevention will be the focus of NDM in 2014. Dr. Louard looks forward to working with Montefiore’s healing arts group (which explores crafts, painting, writing and music as therapies) to come up with creative ways to spread the word about the importance of a healthier lifestyle in preventing the disease.

One challenge is fighting preconceived notions about diabetes. “We promote the message that ‘the complications of diabetes don’t have to be in your future,’” says Dr. Louard. “We tell people with diabetes that they can handle it through lifestyle changes, and that the new medications allow us to tailor their care.”

Last September, Dr. Louard received an Excellence in Community Service award from Doctors for a Healthier Bronx. It was presented by Judy L. Aschner, M.D., a professor of pediatrics and the Michael I. Cohen, M.D., University Chair in the department of pediatrics at Einstein, at a neighborhood Walkathon and Health Fair co-sponsored by Einstein and Montefiore. Dr. Aschner is also a professor of obstetrics & gynecology and women’s health at Einstein and chair of pediatrics and physician-in-chief of The Children’s Hospital at Montefiore.

“I love spreading awareness,” says Dr. Louard. “By arming people with information and knowledge, we can offer them a really hopeful future.”

Congratulations!
The Diabetes Research Center is pleased to announce the appointment of Meredith A. Hawkins, M.D., as an associate director of the center. Dr. Hawkins, founding director of Einstein’s Global Diabetes Institute, travels the world investigating the reasons for the dramatic rise of diabetes and what can be done about it. She studies the role of nutrients and inflammation in causing diabetes, and the use of vitamin D in diabetes management and treatment. Dr. Hawkins is also the Harold and Muriel Block Chair in Medicine, a professor of medicine (endocrinology) at Einstein and an attending physician in medicine (endocrinology) at Montefiore.

To learn more about supporting the work of the DRC, please contact:
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Our mission:
• To support and conduct basic and clinical research related to diabetes and its causes, treatment and complications
• To encourage research that will rapidly lead to diabetes therapies, especially in minority and underserved populations

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