THE DIABETES EPIDEMIC

IS IT YOUR FAULT IF YOU'RE FAT?

BY ELEFTHERIA MARATOS-FLIER, M.D. AND JEFFREY S. FLIER, M.D.

Why are more Americans overweight and developing diabetes? Is it fast food? No regular meals and precious little exercise? Our love affair with the TV and computer? The wrong advice about what to eat?

Very likely it's all these things – combined with something about the genetic makeup in many of us. Genes may program some to feel hungry when they aren't and others to be less able to tell when they are full.

Some extreme obesity in children is caused by an identifiable, single gene defect. Obesity is no more their "fault" than developing cystic fibrosis is the "fault" of a child who has the CF gene. Admittedly, perhaps only 5 percent of obesity is purely genetic. But research suggests that multiple genes control appetite and metabolism, and defects in one or more may make someone more prone to overweight. Fat cells, particularly in the abdomen, in turn release substances that can make people more prone to insulin resistance, which leads to type 2 diabetes.

Some people are genetically blessed and never gain much weight. Those with gene defects must expend huge effort to overcome messages their body is sending their brains to eat more.

For example, research at Rockefeller University and elsewhere suggests that people who lack leptin or lack receptors to make their cells sensitive to leptin have uncontrolled hunger, overeat and become extremely obese. The melanocortin pathway in the brain has recently been identified by scientists at Beth Israel Deaconess Medical Center and elsewhere as another target influencing both obesity and anorexia.

continued >

In addition, some researchers have shown that the absence of a peptide called MSH, which suppresses eating, leads to obesity. Research at Joslin and elsewhere suggests that another peptide, MCH, which stimulates eating, may also play a role.

Ghrelin, a stomach hormone that signals hunger, is another potential target. Interestingly, extremely obese individuals who undergo stomach bypass surgery (stomach stapling) may be less inclined to eat afterwards because food no longer passes through the section of the stomach that produces ghrelin.

Some overeating may be triggered by stress, boredom or depression. For example, food smells may stimulate production of certain peptides that make one want to eat—even if not hungry. Behavior modification may be needed to combat these stimulants of weight gain.

As our genes haven't changed in the last 20-30 years, societal influences are still the major culprit for growing obesity. We are more sedentary. Super-sizing meals makes it harder not to eat for those trying mightily to ignore the errant signals their bodies are sending. Until we can identify who has what gene defects, and medications are developed to treat them, we must remember that it is much easier to prevent weight gain than to lose weight once gained. Your body adjusts quickly to those extra calories. Life as overweight adults often has its roots in life as a child. For the moment, the best approach to obesity, and the type 2 diabetes it causes, is prevention—in ourselves and our children. As nationwide studies show, even modest weight loss—15 pounds—and 30 minutes of daily exercise is the best bet to prevent diabetes in those most likely to develop it.

Eleftheria Maratos-Flier is Chief of the Obesity Research Section at Joslin Diabetes Center and Associate Professor of Medicine at Harvard Medical School. **Jeffrey S. Flier** is George C. Reisman Professor of Medicine at Harvard Medical School and Chief Academic Officer at Beth Israel Deaconess Medical Center in Boston.

CASE STUDY #1

Photo: Steve Gilbert

Maureen Marinelli, 48, had a family history of type 2 diabetes when she was diagnosed four years ago as high risk for diabetes. So she joined a nationwide research program that has shown that modest exercise (30 minutes per day), combined with modest sustained weight loss (she lost 18 pounds) can help prevent full-blown diabetes. She's kept the weight off and has not developed diabetes. "I've cut back on the late night trips for junk food and started a walking club," she says.

DIABETES IN CHILDREN

BY LORI M. LAFFEL, M.D., M.P.H.

At one time called "adult-onset diabetes" because it almost exclusively developed in people over 40, type 2 diabetes is an alarming new phenomenon in rising numbers of overweight children.

Until recently, a child with diabetes almost certainly had type 1 or "juvenile-onset," caused by a malfunction in the body's disease-fighting immune system, that mistakenly destroys the body's insulin-producing cells. Today, there is significant growth in type 1 diabetes. It is occurring more frequently, and at younger ages, for reasons unknown. It develops most frequently in Caucasians.

Disturbingly, that growth is being joined by increases in childhood type 2, which appears more frequently in Hispanics, African-, Asian- and Native Americans. Scientists believe type 2 among children is caused by the same increase in obesity and inactivity seen in adults.

While every child or adult with type 1 diabetes must take insulin to survive, most with type 2 still produce insulin but are resistant to it. Many can manage their condition with diet, weight loss and physical activity. Some adults may also take pills that enhance the body's ability to use insulin effectively. But these medications are largely untested in children. And so many children (and even some adults) with type 2 take insulin to keep blood sugar levels under good control.

Diabetes complications can emerge after someone has had poorly controlled diabetes for about 20 years or more. With more children and teens developing type 1 and type 2 diabetes, complications such as eye, kidney, heart and nerve disease will occur during the years of greatest productivity in young and middle-aged adults. Complications are preventable with good control achieved through careful attention to medications, meal planning, exercise, blood sugar monitoring and timely medical follow-up. Balancing these demands is challenging for children and teens and begs for better approaches to prevention and care.

There is currently no way to prevent or cure type 1 diabetes. While type 1 diabetes develops slowly over years, tests can now identify persons at risk for type 1 diabetes long before symptoms strike. Clinical trials are underway to determine if the immune destruction that causes the disease can be arrested by medications either shortly after diagnosis or in pre-type 1 diabetes.

Lifestyle changes, including weight loss, nutritious eating habits and regular physical activity, can reduce the development of type 2 diabetes in at-risk adults and can be applied in children and teens to help arrest the epidemic of childhood obesity and type 2 diabetes. A recent study in the *New England Journal of Medicine* from researchers in New Haven, CT, found that one in four obese youths as young as four years of age already had abnormal blood sugars. To reverse this trend, our nation's schools can support physical education programs and develop after-school exercise opportunities that anyone can enjoy – regardless of athletic ability. Schools must offer more nutritious lunch programs and limit vending machines with high-calorie junk food and sodas. Over half of the daily calories for many children – especially those from racial and ethnic groups at highest risk for diabetes – come from free or reduced-cost school breakfast and lunch programs. Diabetes is also a family disease and families must work together to prevent it and manage it.

Lori M. Laffel is Chief of the Pediatric and Adolescent Diabetes Unit at Joslin Diabetes Center and Joslin Clinic in Boston and Assistant Professor of Pediatrics at Harvard Medical School.

CASE STUDY #2

Photo: Steve Gilbert

When Joshua and Carla McKenna's 4-year-old son, Nathyn, was diagnosed with type 1 diabetes in May, Joshua had just been laid off from his high-tech job and had no health insurance. Joslin Diabetes Center's JumpStart program — which offers free diabetes medical care in Boston to newly diagnosed children – enabled the family to get care for Nathyn during this tumultuous time without worrying how they would pay for it.

DIABETES AND MINORITIES: A DISPROPORTIONATE RISK

BY GEORGE L. KING, M.D.
AND JAMES R. GAVIN, III

Researchers have long known that ethnic groups living in the United States are far more likely to develop diabetes than Caucasian Americans. African-Americans, Asian-Americans and Latino Americans, for example, are twice as likely to develop diabetes as non-Latino whites. Among Native Americans, the rates are even higher: in one tribe in Arizona, half the adults between the ages of 30 and 64 have diabetes, compared to just six percent of whites.

CASE STUDY #3

Photo: Bill Curry

NBA star Jerry Stackhouse knows the devastating effects of diabetes. Although he doesn't have it, two of his sisters died from diabetes complications while in their 40s and both his parents have diabetes. "Managing diabetes is tougher than anything I do," he says. The Washington Wizards guard is establishing a charitable foundation called the Triple Threat Fund, committed to improving care and finding a cure for diabetes.

Not only do minorities experience a higher prevalence of diabetes, they are also hit harder by complications. The death rate among African-Americans with diabetes is 27 percent higher compared to whites, and both Mexican-Americans and Native Americans are as much as six times more likely to suffer end-stage renal disease (kidney failure).

Why are these figures so skewed?

There is no single explanation.

For example, among Latinos and African-Americans, the rise in diabetes appears to be related to obesity, just as it is among many white Americans. But among Asian-Americans, a high prevalence of diabetes can be found even among those who are not obese. What's more, the rate of diabetes for Asians and Latinos in their home countries is much lower, meaning it is only when immigrants settle in the United States that the disease develops at such disproportionate rates.

Studies of second-generation Japanese-Americans in Seattle found that developing a "westernized" lifestyle brought out an underlying susceptibility toward diabetes, triggered by the increase in dietary animal fat and reduced physical activity. And while Japanese-Americans need not be obese to develop diabetes, "a central pattern of body fat," or visceral fat, could be responsible for triggering the development of insulin resistance, which leads to diabetes, University of Washington studies found. A separate study, published in the September 2002 issue of *Diabetes Care*, found an association between visceral fat and increased risk for type 2 diabetes in Hispanic children.

The good news is that when it comes to prevention, what works for white Americans also appears to work for minorities. Recent studies have shown that losing five to seven percent of body weight and exercising for 30 minutes five times a week can reduce the risk of developing diabetes by nearly 60 percent, even among ethnic groups.

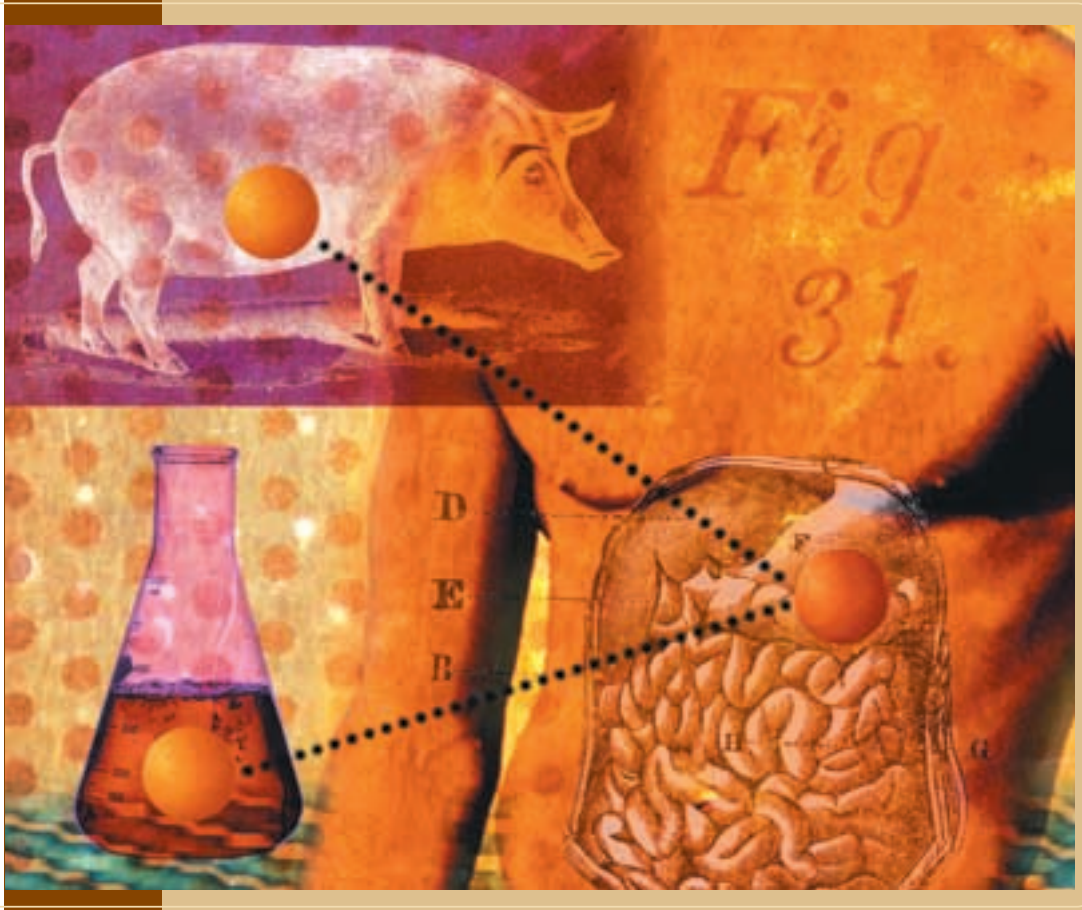
The problem is getting people to make those lifestyle changes. That's why the Joslin Diabetes Center and the American Diabetes Association have both developed diabetes education and awareness campaigns targeted specifically at African-Americans. Joslin is also developing programs targeted at Hispanics and a new Asian-American program that provides culturally sensitive diabetes education materials and research materials.

James R. Gavin, III is President, Morehouse School of Medicine. He is a past President of the American Diabetes Association.
George L. King is Research Director at Joslin Diabetes Center and Professor of Medicine at Harvard Medical School.

LATEST RESEARCH IN ISLET CELLS AND STEM CELLS

BY C. RONALD KAHN, M.D. AND GORDON C. WEIR, M.D.

There's good news and bad news in the quest to cure type 1 diabetes by transplanting insulin-producing islet cells.



The good news is that recent research at the University of Edmonton and elsewhere has shown that one of the major hurdles, namely rejection of transplanted islets, can usually be prevented. Thus, using new combinations of anti-rejection drugs, up to 80 percent of those receiving transplants are free from taking insulin injections for one year or more after the transplant. This is a marked improvement over previous results and gives hope that islet transplantation might be able to become widely available, if these immune suppressive drugs are found safe for the long-term.

The bad news is that there aren't enough islet cells to go around. Each transplant usually requires cells from at least two pancreases, i.e. two separate donors. Only about 4,000 donor pancreases from cadavers become available annually. With almost 1 million Americans with type 1 diabetes and 35,000 newly diagnosed each year, demand far outstrips supply.

Researchers at Joslin Diabetes Center in Boston and at other research institutions have been working on several solutions to this problem. One is to coax other cells of the pancreas, called duct cells, to become insulin-producing cells. If this works, it might be possible to take these cells from a patient's own pancreas (since they are not destroyed in the process that causes diabetes), multiply and convert them into islet cells in a test tube, and then transplant them back into the patient. This might limit the need for anti-rejection drugs, which can have significant short-and long-term side effects. In other approaches, researchers working on type 2 diabetes have shown that it may be possible to make islets grow and multiply after they are transplanted. If the growth factors in this form of diabetes can be identified, they may be helpful in restoring islets or growing more islets for patients with type 1 diabetes. It may also be possible to use islets derived from species other than humans, such as pigs, for transplantation or to genetically engineer other cells of the body, such as liver or pituitary cells, to produce insulin.

Embryonic stem cells are another promising source of islets. These cells can multiply indefinitely and, if the circumstances are correct, can then be triggered to differentiate into specialized cells such as muscle, blood or liver tissue. Work at the National Institutes of Health, Johns Hopkins and in Israel has shown that embryonic stem cells can also become insulin-producing islet cells, but currently the U.S. government has limited embryonic stem cell research, and most stem cell lines are owned by private industry. Scientists had thought that adult stem cells might also be capable of becoming insulin-producing, but they are clearly more limited in potential. The limits on embryonic stem cell research must be modified if we are to understand how islet cells develop and recognize the full potential of these cells.

While there is much hope that in the future diseases like type 1 diabetes will be prevented even before they occur, the many people who already have this disease and are waiting for a "cure" are a constant reminder of the urgency of research in this important area.

C. Ronald Kahn is President and Director of Joslin Diabetes Center in Boston and Mary K. Iacocca Professor of Medicine at Harvard Medical School.
Gordon C. Weir is Chief, Section on Islet Transplantation and Cell Biology at Joslin Diabetes Center in Boston and Diabetes Research and Wellness Foundation Professor at Harvard Medical School.

DEVELOPMENTS IN EVERYDAY DIABETES TREATMENT

BY ALAN C. MOSES, M.D.

Technology is having a major impact on the ability of patients to manage their diabetes more effectively.

Home blood sugar monitoring, a key to good diabetes control, is changing rapidly. New products enable patients to test blood from their arm or thigh, as well as from more painful fingertip samples. This summer, two companies received approval to sell devices that combine blood sugar monitoring with a personal digital assistant (PDA). The devices read glucose (sugar) levels, display them and store them in a database so patients and clinicians can analyze results over time and make adjustments in treatment.

Another new device is worn like a wristwatch. It measures sugar levels by testing tiny amounts of fluid from the skin, sending warnings when sugar levels are too high or too low (traditional blood sugar testing must then confirm readings before taking action). Another product uses a needle-shaped sensor under the skin to measure blood sugars every five minutes for three days. These readings are downloaded at the doctor's office for analysis to assist in treatment recommendations.

Researchers see this kind of sensor as an important step toward an implantable "artificial pancreas" that continuously measures blood sugars and releases correct amounts of insulin to keep blood sugars under control. Several companies are working on such a device, but won't have something ready for some time.

U.S. DIABETES STATISTICS

- 17 million Americans have it.
- 5.9 million of those don't know it.
- It's the fifth-deadliest disease in the U.S., causing more than 210,000 deaths annually.
- It's the leading cause of new cases of blindness in adults — 12,000 to 24,000 people lose their sight because of diabetes each year.
- It's the single most common cause of end-stage kidney disease requiring transplant or dialysis.
- Adults with diabetes are two to four times more likely to have a heart attack or stroke.
- Health care and other costs directly related to diabetes treatment, as well as the costs of lost productivity, run $98 billion annually.
- As many as 16 million Americans have pre-diabetes, putting them at high risk for diabetes and its complications.
- Of children newly diagnosed with diabetes, 8%-45% have type 2, which previously was only found in adults.

Source: American Diabetes Association

LOOKING FOR THE LATEST IN DIABETES INFORMATION? CHECK OUT THESE EXCELLENT WEBSITES:

www.joslin.org — from Harvard-affiliated Joslin Diabetes Center

www.diabetes.org — website of the American Diabetes Association

www.jdrf.org — from the Juvenile Diabetes Research Foundation

www.niddk.nih.gov — website of the federal government's National Institute of Diabetes & Digestive & Kidney Diseases

Looking for books, cookbooks and videos on diabetes that come from an authoritative source? Check out the online stores of Joslin Diabetes Center (www.store.joslin.org or call 1-800-344-4501 if within the U.S.) or the American Diabetes Association (on the web at http://store.diabetes.org or call 1-800 232-3472)

Need an expert diabetes doctor or diabetes education program? Joslin Diabetes Centers are located throughout the country. Get a complete list by state at www.joslin.org/jnationwide/sites_nationwide.shtml. The American Diabetes Association also certifies diabetes education programs and providers. Certified diabetes education programs are listed by state at www.diabetes.org/education/edustate2.asp?loc=x. Certified providers by state are listed at www.diabetes.org/recognition/physicians/ListAll.asp

Another new product allows patients to do hemoglobin A1c tests at home. Once only available in medical labs, hemoglobin A1c is a standard measure of overall blood sugar control and should be measured every three to six months in those with diabetes. This new product allows patients to measure A1c levels at home to help them work more effectively on diet, physical activity and use of medications to achieve target A1c levels of seven or less.

Scientists also hope to develop successful ways to deliver insulin by routes other than injection—be it inhaled into the lungs, taken by pill, absorbed through skin or sprayed by aerosol and absorbed through the lining of the mouth and throat. One drawback of many of these potential products is that they can't yet be used to supply insulin between meals. But for people with type 2 diabetes whose blood sugar may be most difficult to control right after meals, they could help. Several of these products are in clinical trials, but it will be some time before they are on the market.

Over time, it is likely these new technologies will have a major impact on the way patients with diabetes manage their disease.

Alan C. Moses is Chief-Medical Officer, Joslin Diabetes Center and Joslin Clinic in Boston and Professor of Medicine at Harvard Medical School.

WHAT ARE THE RESEARCH LABS DISCOVERING ABOUT TYPE 2?

BY STEVEN E. SHOELSON, M.D., Ph.D.

Research is rapidly increasing our understanding of how obesity, a fatty diet and sedentary lifestyle contribute to the development of type 2 diabetes. Scientists now think that there are many genetic factors out of our control that interact and potentially predispose some people to develop the disease. Acquired risks that aren't present at birth also play a role. And so, just as an unhealthy lifestyle substantially increases the risk of developing type 2 diabetes, lifestyle changes such as regular exercise, weight loss and a healthy diet can lower the risk of developing diabetes.

Why? Obesity, a fatty diet and lack of exercise all contribute to insulin resistance, a condition where cells in the body don't respond well to insulin produced by the pancreas. Since the cells don't respond, the pancreas overproduces insulin to overcome the resistance. At some point the pancreas can't compensate, and the combination of insulin resistance and "islet cell exhaustion" leads to elevated blood glucose levels. Researchers at Yale and the University of Texas are studying how fatty acids in the bloodstream promote insulin resistance and islet cell exhaustion. Scientists at MIT, Albert Einstein Medical College and the University of Pennsylvania have recently discovered substances produced by fat – hormones called ACRP and resistin—that seem to influence insulin resistance.

New research also links insulin resistance and type 2 diabetes to inflammation. Acute inflammation occurs when the body responds to injury—sending certain white blood cells to destroy and clean up damaged cells. Chronic inflammation in tissues like the joints leads to diseases such as rheumatoid arthritis. Scientists have found small but significant elevations of inflammatory markers in the blood of people who have, or are at risk for, heart disease or diabetes. Researchers at Joslin Diabetes Center in Boston recently discovered that salicylates, a class of anti-inflammatory drugs that includes aspirin, can reverse insulin resistance and lower blood sugar in patients with type 2 diabetes. While aspirin has too many side effects at the high doses needed to lower blood sugar, other salicylates may be safe and effective, and by identifying the enzyme that salicylate targets, scientists hope to create better "aspirins." Other drugs commonly used to lower cholesterol, the statins, may also reduce levels of inflammatory markers and improve insulin resistance and insulin production. An improved understanding of the disease and better treatments should follow as scientists close in on the altered molecular pathways in cells that cause insulin resistance and type 2 diabetes. ■

Steven E. Shoelson is Chief of the Section on Cellular and Molecular Physiology at Joslin Diabetes Center and Associate Professor of Medicine at Harvard Medical School.