WHY SO MANY ARE GETTING
DIABETES

Never have doctors known so much about how to prevent or
Control this disease, yet the epidemic keeps on raging.
How you can protect yourself
(by Christine Gorman and Kate Noble)

Hillary Carroll knew something was amiss. She had spent the day happily frolicking in her grandmother's swimming pool, but by that evening she was doubling over in pain every time she went to the bathroom. Her mother figured it was probably an infection and the next day took Hillary, then 10, to the pediatrician. Instead of getting a prescription for an antibiotic, however, the 100-kg youngster was immediately admitted to the hospital. Lab tests showed that she had something far more serious – Type 2 diabetes.

Hillary is not the first overweight child to learn she has this form of diabetes, a chronic metabolic disorder that used to be called adult-onset diabetes but was renamed partly because so many kids Hillary's age were getting it. As doctors have repeatedly warned, the world is experiencing a diabetes epidemic. In 1985, around 30 million people worldwide had the disease. But today in Europe alone, 48 million people – 7.8% of the population – are living with it. And although Type 2 diabetes still tends to strike people in their fifth or sixth decade, more children are getting it, a fact of grave concern to health officials.

Not only are these kids likely to face a life-time of problems – including higher risks of blindness, heart disease and stroke – they are also a warning sign that something in our way of life has gone terribly wrong.

And yet scientists in just the past decade have learned that the most devastating complications of diabetes – and in some cases the disease itself – are almost entirely preventable. There are better techniques for monitoring diabetes and more effective drugs for treating it, and two major studies have shown that by making only modest changes in diet and exercise, people at high risk of Type 2 diabetes can stave off the disease for at least three years and perhaps a lot longer (more on Type 1 in just a bit).

It's a puzzle. Never have physicians known so much about Type 2 diabetes and how to control it, yet the number of cases is expected to rise at an alarming rate. Epidemiologists predict that by 2025 the incidence will double in North America and rise by 20% in Europe; it will more than double in Africa, the eastern Mediterranean, the Middle East and Southeast Asia, and increase between 75% and 85% in the western Pacific and Latin America. With an estimated 35.5 million cases, India has the most people with diabetes; China has 23,8 million and the U.S. has 16 million.

Lots of doctors will tell you that the reason for the explosion is obvious: many societies are eating too much and exercising too little. There is no question that excessive weight increases your risk of becoming diabetic. But that only partly explains the problem. Diabetes has a strong genetic component, and scientists are beginning to suspect that certain evolutionary factors, as well as your mother's metabolic or nutritional status during pregnancy, may predispose you to develop diabetes.

A complex picture is emerging that is changing the way we think about what was already a complex disease. It turns out that patients are not as helpless against its ravages as was once thought, especially if they are warned at the disease's very earliest stages. Changes in lifestyle and diet can, in the vast majority of cases, make a big difference. The future for anyone with diabetes has never been brighter, provided he or she has access to the right treatments. But the consequences of inaction have never been more broadly devastating. Diabetes is the fourth main cause of death in developed countries, the leading cause of blindness and the most common cause of amputation.

WHAT IS DIABETES?

To understand the latest insights into the disease, it helps to know a little more about two key molecules – glucose and insulin – and the roles they play in the conditions doctors call Type 1 and Type 2 diabetes. We'll start with glucose, the sugar molecule that is a major source of fuel for the body. You can get your glucose levels tested at a doctor's office or at home with a device called a glucometer. What you're looking for is a reading measure in millimoles of glucose per liter of blood (or, on some glucometers, in milligrams per deciliter). Anyone whose glucose level before breakfast – the fasting level – is 7 mmol/L or higher is considered diabetic. A normal fasting level runs anywhere from 4 mmol/l to 7 mmol/L.

Insulin is a hormone made by specialized cells in the pancreas, whose job is to push glucose out of the blood into various cells in the body. Whenever the amount of glucose in the blood starts to rise, this happens just about whenever you eat, the pancreas pumps out more insulin to keep sugar levels stable.

Here's where the difference between Type 1 and Type 2 is clearest. Type 1 diabetics have high glucose levels because their pancreas can no longer make insulin. By definition, Type 1 diabetics must eventually take insulin shots to get their diabetes under control. Type 2 diabetics can still make their own insulin, but their bodies don't respond as well to it – a situation called insulin resistance.

Any scientists who can figure out why Type 2 diabetics are insulin resistant will probably be a candidate for a Nobel Prize. It's not a simple consequence of being overweight. Many obese people are not insulin resistant, and not everyone who is insulin resistant is overweight. Researchers at the Salk Institute in La Jolla, California, believe that at least part of the answer lies not in the pancreas but in the liver. In a study of mice published in the Nov. 13, 2003 issue of *Nature*, scientists identified a protein that tells the liver to

favor the metabolism of fat over that of glucose. The result is a buildup of glucose levels in the blood, a hallmark of insulin resistance.

Evolutionary biologists suspect that a predisposition toward diabetes developed among certain ethnic groups – such as Indians, Pacific Islanders or Americans of African decent – as a result of repeated, perhaps even recent, bouts of starvation. Those individuals who were better able to decrease energy expenditures during a famine survived and passed on the trait to their offspring. Unfortunately, that ability seems to cause insulin resistance when food is plentiful. In other words, says Terry Wilkins, professor of endocrinology at Derriford Hospital, in Plymouth, England, "We developed genes that allow us to put aside spare calories for a rainy day, and now we get to the 21st century when excess calories are all around us and our genes are maladapted to that situation."

THE SUGAR BLUES

What's so bad about being insulin resistant and having too much glucose in your blood? For reasons that researchers are still trying to figure out, having diabetes greatly increases your risk of suffering a heart attack or a stroke. A man with diabetes appears to have the same risk of cardiovascular problems as a non-diabetic who has had a heart attack. A woman who develops diabetes loses the cardiovascular benefits of being female. And kids with Type 2 diabetes are more likely to develop heart disease in their 20s and 30s.

The condition also damages small blood vessels throughout the body – particularly those in the eyes and kidneys. The damage causes sight-threatening retinopathy in around 10% of diabetics, kidney disease in up to 50% and a 15-fold increase in the chance of having a lower limb amputated. Diabetics are twice as likely as non-diabetics to suffer from depression.

It doesn't have to be this way. Back in 1993 doctors proved that Type 1 diabetics could greatly reduce their risk of complications by intensively managing their glucose levels to keep them as close to normal as possible (using a glucometer to measure the level of sugar in a pinprick of blood and an insulin shot when necessary to bring the level down). Similar results have since been seen with Type 2 diabetics.

But most Type 2 diabetics don't have to resort to insulin shots to manage their condition. Because the fundamental problem in Type 2 diabetes is insulin resistance – not the inability to produce insulin as in Type 1 – other options are available. Some of your best allies in this struggle are your muscles. Building them up and using them regularly in such pursuits as walking or dancing draws more glucose out of the bloodstream and increases insulin's efficiency. It also pays to avoid easily digested foods – like chips, non-diet soda and other junk food – which require large amounts of insulin to metabolize. Finally, losing a little weight usually makes insulin's job a lot easier.

Donna Black Bradley was driving home from work one evening when she suddenly was unable to read the freeway signs. When her doctor diagnosed diabetes, she felt

paralyzed. "Then I said, 'O.K., I got something I got to do here,'" Bradley recalls. "I got to change." And change she did. The 1.7-m-tall mother and grandmother started eating better and working out on a treadmill several times a week. Her weight dropped from 123 kg to 90 kg, and her fasting glucose fell from 16.7 mmol/L to 5.7 mmol/L. "It's amazing how your cravings diminish when you're eating the right food groups," Bradley says. Her vision problems have disappeared, and her doctor believes she will no longer need to take insulin-sensitizing drugs if she can get her weight under 90 kg – something she's determined to do, both for herself and for her grandson Isaiah. Says she: "I want to be around for that 2-year-old."

SMALL STEPS, BIG REWARDS

The more scientists learn about diabetes and the complications it causes, the more they find themselves looking at the conditions that precede it. At Plymouth's Derriford Hospital, Linda Voss is coordinating a research program among healthy children to try to identify environmental factors than can lead to insulin resistance, the precursor of diabetes. "If insulin resistance is the fuse that leads to the explosion that is diabetes," she says, "we're looking to see what lights the fuse and keeps it burning. Ultimately, we'll learn how to put it out." Three years into the study, Voss and Wilkins have already identified children who may be at risk. With nearly 30% of 5-year-old girls in the cohort overweight – "and 10% of them frankly obese," notes Wilkins – the team has identified a relationship between body-fat mass and insulin resistance, since as the body gains weight it becomes more resistant to the action of the chemical.

The effects of piling on the pounds, and playing on the computer instead of in the park, are wreaking havoc on our health. With 50% of Europe's population overweight, and around 50 million believed to be insulin resistant, we all need to note the simple but effective measures we can take to avoid serious illness. For 20 years, Finnish researcher Jaakko Tuomilehto of the Public Health Department at Helsinki University was puzzled by why people were so interested in finding out how to prevent cancer and cardiovascular disease but practically ignored diabetes. He was convinced that simple lifestyle modifications could prevent many cases of the disease.

In 1993 he initiated a clinical trial using only lifestyle changes – no drugs or other interventions – among more than 500 people though to be at high risk of developing Type 2 diabetes. The program he devised assigned participants five very simple tasks: weight reduction of at least 5 %, reduction of fat consumption to less than 30% of total energy intake, a decrease of saturated-fat intake to less than 10% of total energy, an increase of fiber in the diet to at least 15 g per 1,000 calories, and at least half an hour of physical activity a day. "It was very modest," he says. "We started the trial with the assumption that we could cut the risk by 35%."

In 2000, halfway through the study, Tuomilehto invited an independent statistician to scrutinize his progress. Instead of the expected 35%, the risk of developing Type 2 diabetes was cut by 58%. The results were so startling that Tuomilehto quickly published

a report. A similar study in the U.S., the Diabetes Prevention Program, was under way when Tuomilehto's research was published. The D.P.P. researchers did their own interim analysis and found an identical reduction. Their results were published in 2002. "We showed that of the people who managed to achieve all five targets, and even those who managed four of them, none became diabetic," says Tuomilehto. "It just shows how closely diabetes is related to these simple lifestyle patterns."

FAMILY FORTUNES

While most of us recognize that we should be thinking about modifying our lifestyles, losing weight and getting more exercise, the question really is: Why do some of us develop diabetes while the rest of us don't? it all comes down to your genes. If you have Type 2 in the family, you are up to 75% times more likely to see it yourself. Of course, that still leaves unexplained what triggers the onset of the full-blown disease. That's why researchers are prying into the human genome to find which genes are responsible and how they are affected by the environment. At England's Exeter University, Andrew Hattersley and his team are scouring the genome for clues. He likens the search to trying to find one misspelled word in a library full of books. "Once you have found what kind of misspelling it is," he says, "that will determine what treatment you give."

Hattersley has been working on a particular form of diabetes known as MODY (Maturity-Onset Diabetes of the Young), which accounts for about 2% of diabetes worldwide and usually strikes people under 25. While Type 2 diabetes is polygenic, meaning than many genes are involved, MODY involves just one, HNF1-alpha. In a study published in the British medical journal the *Lancet* in October, 2003, his research group reported that people with a defect on HNF1-alpha responded four times better to one standard treatment – metformin, a sulfonylurea that promotes insulin production – than to other drugs.

Because of the early onset age of the disease, some of the people in the study had been misdiagnosed as having Type 1, and had been injecting insulin for many years. Mary Lee, 46, a nurse from Essex with an extensive family history of diabetes, received her diagnosis when she was 16 and was on insulin for 27 years. Although she was used to injecting insulin twice daily – "It becomes part of your routine," she says, "like brushing your teeth" – she was eager to take part in the study. She's been on diamicron, a sulfonylurea, now for two years and is doing well. "I feel so much better," she says. The drug has stopped the dramatic fluctuation of her blood sugar, and she's thrilled that she no longer has to inject herself: "Even though I varied the sites of the injections, my skin had become dimpled, like cellulite, but now it's nice and smooth. I even venture into a bikini now."

AN OUNCE OF PREVENTION

Another clue in the search for treatments could come from a better understanding of the way our muscles use glucose. At Scotland's Dundee University, researchers Grahame Hardie and Dario Alessi recently reported the discovery of an enzyme that regulates the level of glucose in the blood. As we exercise, particularly during endurance types of activity like brisk walking, swimming or cycling, our muscles become more insulin sensitive (the opposite of insulin resistant).

The Dundee group found that during workouts an enzyme known as LKB1 switches on another called AMPK, which triggers the uptake into the muscles of glucose and fatty acids form the blood and turns them into energy. The discovery also helps explain why exercise not only reduces blood sugar but also keeps you slim and makes you less prone to Type 2 diabetes. Hardie concedes that these discoveries might make it possible to develop a drug that mimics exercise, but says that could never be a substitute for real physical activity. "I would never say, 'Take a drug instead of changing your lifestyle,'" he says, "but it could benefit people for whom taking more exercise or changing lifestyle fails."

Advances in diabetes research over the past few years have been swift and wide-ranging. Scientists are looking beyond glucose levels to gauge patient's health and progress. They have identified other pathways that may play a role in triggering diabetes. Every new insight into Type 2 diabetes, form tits biochemistry to its metabolic roots, makes clear that it can be avoided – and that the earlier you intervene the better.

The real question is whether we as a society are up to the challenge. When governments look at the math, they can see that something needs to be done – and fast. In Britain, diabetes accounts for €13 billion of the National Health Service budget, while in Germany the figure is a staggering €20 billion. Despite that cost, around 80% of Germany's 6 million diabetics have badly adjusted medication and are poorly informed – or not informed at all – about the disease. "As a result, many people simply ignore the disease," say Lutz Graf zu Dohna, head of the German Diabetes Association. "They claim that they would rather live a short but intensive life than one full of restrictions." But what happens if, as is predicted, the number of German diabetics reaches 10 million by 2010? "The health system will completely collapse," Dohna says bluntly.

Things are happening to stave off such dramatic outcomes. Based on the five-target lifestyle plan formulated by Helsinki University's Tuomilehto, Finland has this year started the world's first nationwide diabetes-prevention program. In 2002, Germany introduced a Disease Management Program that gives people with diabetes or high blood pressure a legal right to extensive training in how to deal with their illness. In January, 2003, the British government announced a National Service Framework for Diabetes to prevent people developing the serious complications that result from the disease.

Comprehensive prevention programs aren't cheap, but the cost of doing nothing is far greater. "If we don't take care of this issue now, we will have huge numbers of Type 2

diabetics, and we will be paying for them with our tax dollars," says Dr. Phyllis Preciado, an internist who runs a diabetes clinic in California's farming-rich Central Valley. As the U.S. loses productive members of the work force, she notes, more people will turn to public assistance for treatment. And the increased toll in human suffering will be staggering.

There are ways to keep costs down. It doesn't take a physician to teach a patient the principles of better nutrition or how to use a glucometer. Nurses, nutritionists and diabetes educators can play a key role. Experts say it's important to reach the communities that are hardest hit by diabetes, all the while taking cultural differences into account. "You can't give everybody the same diet to solve the problem," says Ann Albright, chief of the California Diabetes Prevention and Control Program. "People obviously eat the foods they've grown up with. So you have to try to help them get as much of those things that they like into their eating plan but also make the changes that will help lower the fat or moderate the carbohydrates."

Hillary Carroll and her family have taken those lessons to heart. While still in the hospital, Hillary went through a kind of diabetes boot camp in which she learned how to monitor her blood-sugar levels, change the way she eats and boost the amount of physical activity in her life. Her parents bought her a turquoise BMX bike, which she rides at least an hour every day. She has lost 11 kg so far, and her glucose levels have stabilized. "Before she was diagnosed, she was happy to sit here by herself, playing with her Barbies," says Tammy Carroll, Hillary's mother. "I thought she was so calm then, but now that we have her sugar under control, she's more active." Hillary, now 11, is taking charge of her life. To gain control of the diabetes epidemic, the rest of us may have to do the same.