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## DIABETES IN CONTROL.com NEWSLETTER

*The Newsletter for Professionals in Diabetes Care*

June 11, 2003 Issue #159

### From the Editor's Desk:

**Paul Chous, M.A., O.D. Doctor of Optometry**, and Type 1 diabetic since 1968, will be joining our writing staff to share information on Diabetic Eye Disease. His first article, The Many Faces of Diabetic Retinopathy, brings the different types of retinopathy to our attention.

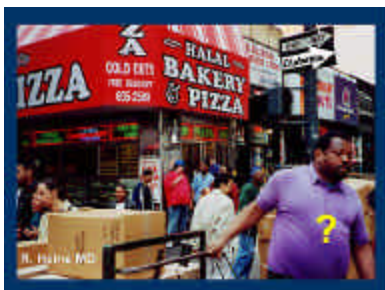
As President Elect of the Tampa Bay chapter of JDRFI, I was in Dallas last week for the Annual International Board Meeting. We were briefed on the latest research and I have put together an overview of the promising work being done in the area of complications.

**Melissa Diane Smith, Dipl Nutr**, author of the soon-to-be-published *User's Guide to Preventing and Reversing Diabetes Naturally* brings us part 3 of her series New Nutritional Agents for People With Diabetes and Pre-diabetes.

We will be attending the ADA in New Orleans Friday through Monday and will be bringing you the latest information on all the new products and discoveries that will be announced. Watch for next week's special ADA issue and stay informed

**Lawrence A. Wheeler MD, PhD**, is introducing his latest Computer Planned Nutrition Program and we are seeking 25 medical professionals who see patients in regularly to use the program and advise us on its functionality.

The results are in for the **Formula II Skin Cream Feedback Study**. Click here to find out why this could be one of the best skin products we have ever tried.



This weeks Photo: Click to enlarge and then tell us what's unusual about this photo? If your correct answer is chosen, you will receive a Medic Alert Diabetes Watch.

This week's overview:

**Item#2: New Diabetes Model: Treatment in a Group Setting**

**Item:#12: Color Vision Test Detects Diabetic Retinopathy**

**Item #15: Walking Less Than 20 Minutes A Day! Reduces Risk of Heart Disease 61%\***

**Check out this weeks "Test Your Knowledge" question. [Click Here](#)**

Dave Joffe, *Editor-in-Chief*

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### **New Product: Diachrome®**

A new nutritional product with scientific research showing Improved insulin sensitivity, Increased



glycogen production and improved lipid metabolism is now being made available. Diachrome® consists of a combination of biotin and chromium picolinate which has a synergistic effect on regulating glucose levels. To view the current research and for more information: [More Information](#)

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**NEWS FLASH!** The AADE is launching a new campaign to prevent toenail fungus, called "**Take the Right Steps to Foot Care.**" Toenail fungus can lead to serious complications for people with diabetes, such as skin or bone infections, tissue death and loss of mobility. A special web page, to help the 17 million Americans with diabetes prevent this problem is available at: [Take the Right Steps to Foot Care](#) Or <http://www.aadenet.org/News&Events/StepstoFootCare.html>  
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**Tools for your Practice: Diabetes 'Quality of Life Test'**

Check out a new test that determines the quality of life for people with diabetes. Use this tool to motivate your patients to improved self- management of their diabetes. Click here for more information and a brochure you can print. [Quality of Life Test](#)

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This newsletter is the condensed version. If you would like to see the full newsletter go to <http://www.diabetesincontrol.com/Issue159index.htm>  
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**New Study: Computer Planned Nutrition Program.**

This Program for health care professionals provides complete support for patient assessment, menu planning for individuals, development of integrated nutrition, exercise and medication plans, and menu recipe analysis. [Click here to learn more.](#)

**Study Results:** The results are in for the **Formula II Skin Cream Feedback Study.** Click here to find out why this could be one of the best skin products we have ever tried.  
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**This Week's Items:**

1. **New Method for Delivering Genes in a Pill to Induce Production of Insulin**  
[Click Here](#)
2. **New Diabetes Model: Treatment in a Group Setting**  
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3. **A Dog's Nose for Sniffing Out Signs of Diabetes....Can it replace the OGTT?**  
[Click Here](#)
4. **Topiramate's Side Effects Stops Weight Loss Study**  
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6. **Novel Drugs for the Treatment of Diabetes**  
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7. **Modified Pig Pancreas Cells Reverse Diabetes**  
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8. **Reversing Early Kidney Damage in Diabetics\***  
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9. **Walking Reduces Risk of CVD, CV Death and Total Mortality in Diabetic Men & Women**  
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10. **Tight Glucose Control In Diabetes Lowers Risk Of Atherosclerosis\***  
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11. **Edmonton Protocol Shows Safety, Efficacy of Islet-Along Transplantation**  
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12. **Color Vision Test Detects Diabetic Retinopathy Before Vision is Lost**

[Click Here](#)

13. **Fasting And Post-Challenge Hyperglycemia Indicates Distinct Pathways in Progression Of Type 2**

**Diabetes**

[Click Here](#)

14. **New Target for Antidiabetic Agents Identified**

[Click Here](#)

15. **Walking Less Than 20 Minutes A Day! Reduces Risk of Heart Disease 61%\***

[Click Here](#)

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**ITEMS For The Week:**

Item 1

**New Method for Delivering Genes in a Pill to Induce Production of Insulin**

*The first patent for a method of delivering normal genes in a pill to induce the production of insulin in people with diabetes was issued May 1 to the University of California, San Francisco.*

Sometimes referred to as a "gene pill," the oral delivery of normal genes has been a long-sought and elusive technique. Now, UCSF researchers have successfully demonstrated that raw DNA taken orally can find its way inside cells lining the intestinal tract and prompt those cells to express a protein, such as insulin, even though they are not specialized for that purpose.

The technique holds the potential for providing patients with more than 50 proteins normally secreted by the body into blood and which patients now receive by injection into muscles - including insulin, growth hormones, blood factors for treating hemophilia, and erythropoietin for treating anemia.

Generic, a biotechnology company in Alameda, Calif. has an exclusive, worldwide license agreement with the University to use the method for drug development.

Oral delivery of genes differs from many of the highly publicized gene therapy techniques now under investigation in clinical trials at research centers across the country. Gene therapy in those studies attempts to correct disease at its root by administering DNA to cells through the use of a modified virus or other microscopic delivery vehicle in order to provide a permanent or long-term cure or treatment for the disease. Oral delivery of genes is intended to provide short-term therapy by placing a specifically-engineered therapeutic gene with normal DNA in cells lining the intestinal tract, causing those cells to express a desired protein to be secreted into the blood - in the case of this patent, insulin.

Cells containing the therapeutic gene would continue to express the protein only for the few days they remain on the wall of the intestine before the body routinely sloughs them and replaces them with new cells. In effect, the therapeutic genes would remain "outside" the body on the surface of the gastrointestinal tract as they pass through the body, even as the protein drugs that are manufactured are released into the blood stream. As a consequence, the genes pass relatively quickly through the body creating less opportunity to access the blood stream or to enter other cells, including those in the ovaries or testes.

"Regular oral delivery of new genes would provide continuous production of insulin, and the natural removal of the affected cells would permit doses to be adjusted or stopped easily," said German, an expert on diabetes.

To demonstrate the validity of the method, the UCSF research team had to show, among other obstacles, that neither stomach acids nor intestinal enzymes would destroy the DNA.

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**FACT:** According to the results of the International DECS Survey on global diabetes educational practices, available soon in the *Diabetes Atlas from IDF*, Physicians provided 74%, pharmacists 20% and nurse educators 6% of diabetes education.

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<http://www.diabetesincontrol.com/tools.shtml>

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Item 2

### **New Diabetes Model: Treatment in a Group Setting**

*"We're learning that people who are living with a chronic condition really require an approach to medical care that is different than the acute care model."*

Managing diabetes can be confounding and all-consuming. Diabetics must test their blood sugar several times a day and adjust their medications accordingly. They have to watch what they eat, check their blood pressure, monitor the circulation in their feet. More than half of all diabetics eventually must inject themselves with insulin twice a day.

Now doctors and nurses at a Eugene medical clinic are trying a new model for diabetes management: treating diabetics in a group setting. Since January, the Volunteers in Medicine Clinic has provided monthly group visits at its office.

The setting provides diabetics with much needed support and gets them into regular, continuing care for their chronic disease.

About 70 people are enrolled in eight different groups at Volunteers in Medicine and a ninth group will begin soon, said Cheryl Ana Moore, a diabetes nurse educator who coordinates the program.

Three of the groups are for Spanish-speaking patients; Mexican-Americans are twice as likely to develop diabetes as white people, according to the federal Centers for Disease Control and Prevention.

The Volunteers in Medicine Clinic, which provides free health care to low-income, uninsured Lane County residents, is one of a handful of clinics in Oregon to try the group approach.

Studies have shown that diabetics who participate in group visits reported improvement in their blood sugar levels, improved quality of life and diabetes knowledge compared with patients who received conventional diabetes care. More study is needed to determine why, according to an article in the latest issue of the journal Diabetes Spectrum.

In Oregon, the group visit model is used at the Clackamas Public Health Clinic in Sandy and at the Samaritan Internal Medicine Clinic in Corvallis, said Linda Dreyer, who manages the Oregon Diabetes Prevention and Control Program for the state Department of Human Services.

"We're learning that people who are living with a chronic condition really require an approach to medical care that is different than the acute care model that most of us are exposed to with our medical care provider," she said.

Under the acute care model, people see their doctor only when they get sick. They get a prescription, go home and don't think about seeing a doctor until next time they get sick, she said.

"Chronic conditions aren't going away," she said. So doctors and nurses need to figure out a better way to treat such conditions, she said.

The group meetings are combination of a regular visit to a doctor and a support group. A doctor and nurse are there to provide education, check blood pressures and adjust medications, but much of the good seems to come from the support and information the diabetics provide to each other.

At a group visit last Thursday morning at the Volunteers in Medicine Clinic, Dr. Hugh Johnston, the clinic's medical co-director, explained how different diabetes drugs work, why some are effective and some aren't. Then he talked with the patients individually.

The setting allows doctors and nurses to cover the bases more efficiently.

"Essentially you get better management," Moore said. "You're giving the same information to six or seven or eight people instead of one, so you don't start dribbling off details after the fourth or fifth patient."

Each patient also brings a binder to document their self-treatment.

"The object of the notebook is that they learn they are managing the disease and I am not," Johnston said.

Group members also talked together informally, sometimes offering advice. For example: Mark Royce gave Sheila Werth a tip to liven up her diet without compromising its healthfulness: Tabasco. Diabetics often must eat bland diets to keep their blood sugars in check.

Werth said she's tired of trying to eat a healthy diet. "I'm in rebellion," she said. "I want to eat Cheetos."

But the group, she said, has been a big help. "I never learned anything about diabetes before I came here," she said. "It's like any support group. You've all got the same problem. You learn what other people are going through." For more information: Contact Volunteers in Medicine at 685-1800. [New Diabetes Model:](#)

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Item 3

**A Dog's Nose for Sniffing Out Signs of Diabetes....Can it replace the OGTT?**

*Technology based on a dog's ability to smell can detect a range of illnesses, including diabetes, cancer and schizophrenia*

SMELL is an important indicator of well- being, and has been used as a diagnostic tool since ancient times. The Romans gave the distinctive odor of renal failure its own term — "fedor hepaticus" — while even today many diseases are known to have a characteristic smell, such as a "sweet acetone breath" for diabetes, and "putrid breath" for streptococcal throat infections.

But now this principle is being harnessed with the latest technology to provide a sophisticated way of diagnosing disease. In one advance, researchers at the University of Rome have designed an electronic nose ("e-nose") for detecting lung cancer in patients. In recent trials at the Forlanini Hospital, the e-nose correctly identified patients with lung cancer tumors simply by smelling their breath.

The "nose" is actually a chemical sensing system — a spectrometer — and a computer system that matches patterns of smells. The technology is pretty much the same whether you are detecting lung cancer or sniffing for salmonella. Each system is "trained" to pick up certain chemical signatures, usually a complex combination of smells. People with lung cancer tend to exhale a mixture of alkanes and benzene derivatives — the University of Rome e-nose has been calibrated to pick up these chemical signatures.

The e-nose is non-invasive, quick and apparently accurate (the lung cancer patients were diagnosed in a minute). The technology is based on the olfactory model of dogs, known for their acute sense of smell (the human nose is too blunt an instrument).

In a case reported in *The Lancet* some years ago, a dog was said to have “discovered” a melanoma on her owner’s leg. The border collie/doberman cross kept on sniffing and even biting the mole, so finally her owner went to the doctor to have it looked at — a biopsy confirmed that the mole was in fact a malignant melanoma. “This dog may have saved her owner’s life by prompting her to seek treatment when the lesion was still at a thin and curable stage,” wrote the researchers.

While it may not be practical to have a canine cancer-sniffer in every dermatology clinic, the fact that melanomas and diabetes can be detected through smell means that one day an e-nose could be adapted to do the same job.

Professor Donald Broom, of the department of clinical veterinary medicine at the University of Cambridge, is currently looking to test the viability of using dogs to sniff out prostate cancer in urine samples. Again, if dogs can detect prostate cancer, then so could an electronic nose. The advantage that e-noses have over dogs is that they don’t get tired (sniffer dogs can suffer from smell “burnout” if they are kept working on a smell for too long). Electronic noses could be used as a diagnostic tool for other pathologies, too, such as diabetes, liver cirrhosis and renal failure — each has its own chemical signature.

The team at the University of Rome is also studying the correlation between schizophrenia and skin odor. It was nearly 30 years ago that scientists first discovered that schizophrenic patients have a specific skin odor. Now that the technology is available, this information can be put to use.

According to Professor Corrado Di Natale, who is leading the study: “We have been measuring axilla “armpits” odor in patients and results are encouraging.”

He envisages the e-nose being developed to screen smokers and other high-risk groups for lung cancer as part of a routine check-up. Of course, it may not replace the precision offered by scans and blood tests, but it could be a useful tool for early detection.

But even at this stage — with a correct diagnosis in one minute — the e-nose future looks promising. **For information on e-noses:** [www.nose-network.org](http://www.nose-network.org)

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Item 4  
**Topiramate’s Side Effects Stops Weight Loss Study**  
*Patients had a mean weight loss of 26 pounds when the study was ended.*

The epilepsy drug topiramate has been shown to be an effective weight loss agent for a period of one year to 18 months, but it was associated with side effects that resulted in the study being halted.

Study author Dr. Luc Van Gall, from the University of Antwerp, in Antwerp, Belgium, presented the study’s findings here May 30<sup>th</sup> at the 12<sup>th</sup> European Congress on Obesity.

Dr. Van Gall and colleagues enrolled 484 patients -- 381 randomized to various doses of topiramate and 103 received placebo treatment.

Patients on two of three higher doses used in the study (192 mg and 256 mg) had a mean weight loss of 12-13 kg when the study was ended. At this time the patients had been taking the drug for between 60 and 76 weeks. By comparison, patients in the placebo arm lost a mean of 2.9 kg. These losses corresponded to a mean decrease of 12% to 13% from baseline for the two highest dose groups.

One unusual trend observed during the study was a consistent decline in weight over the entire study period, said Dr. Van Gall. "Beyond Week 26 to 28, where we usually see a plateau in weight management trials, there continues to be a small gradual fall in weight," he said.

"If further trials also show this [result], topiramate would be the first drug with such a long term weight loss effect," he added.

The proportion of patients who responded to treatment by losing more than 5% of their body weight was high -- 80% to 88% for the two highest topiramate doses. The proportion of patients who lost 10% or more of their body weight was also high -- 59% to 64% for the higher dose patients. Only 27% of placebo patients lost more than 5% of their body weight and only 10% of them lost 5%.

There was a small but significant decrease in blood pressure seen in patients given the higher doses of topiramate, with a mean decrease of 6.8 mm Hg systolic and 3.3 mm Hg diastolic in patients on the 192-mg/day dose of topiramate.

The researchers observed benefits in low-density lipoprotein (LDL) levels, and high-density lipoprotein (HDL), as well as in the LDL-to-HDL ratio with topiramate.

Among benefits seen early in the course of topiramate treatment: two of the 484 patients in the study decreased their body mass index to below 25 by the end of the study, and were no longer judged to be overweight or obese.

However, the study's sponsors, Johnson & Johnson, which manufacturers topiramate, decided to end the study early because of the high incidence of side effect. "I should stress that this decision does not affect any other seizure-control indications for topiramate," Dr. Van Gall said.

During the study, 19% of patients withdrew because of side effects. Mild to moderate paresthesia was the most common. There were 57 reports of paresthesia and 5% of patients withdrew due to this side effect.

Other adverse effects included headache, dizziness, anorexia, depression and problems with concentration and depression. Dr. Van Gall said the majority of adverse events and discontinuation of the drug occurred early in the course of treatment.

"New trials with a new formulation need to be carried out to look at efficacy in relation to side effects," he said.

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**DID YOU KNOW:** In a new study, 15 postmenopausal women with high blood pressure added an extra 4,000 to 5,000 steps a day by making small changes in their daily routines. The results: Six achieved normal blood pressure. Another three dropped their pressure from the danger zone to borderline normal. Blood pressure dropped an average of 11 points (*Medicine & Science in Sports & Exercise*, Nov 2001). Start your own Step Program to Health: [More Information](#)

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## **High Protein Diets More Effective At Maintaining Weight Loss**

*Higher protein diets are more effective at maintaining weight loss in overweight people who previously lost weight on very low-energy diets.*

Dr Manuela Lejeune, of the University of Maastricht in the Netherlands, presented study findings at the European Congress of Obesity, being held here.

One hundred and twenty subjects who lost an average of 6 kg in 4 weeks while following a very low-energy diet were then randomized to follow either a moderately restricted diet (control group), or a diet similar in calories but higher in protein content (study group). The initial weight loss on the very low-calorie diet was equivalent to a mean loss of 7.5% of initial body weight.

The high protein group followed a similar diet but also received a drink containing 48.2g/day protein, resulting in an additional 30g of protein per day, when checked by objective nitrogen balance techniques. The high-protein drink was a partial replacement for lunch.

Those on the high protein diet regained a mean 0.8 kg in the 6 months after the initial weight loss, compared to 3.0 kg regained on the control diet. The difference was statistically significant. Body mass regain in patients on the high protein diet was of fat-free mass, Dr. Lejeune said.

The control diet provided 15% of its energy as protein, while 18% of the higher protein diet by energy was protein.

The subjects, well matched at baseline, also showed a difference in waist circumference at the end of the 6-month study period. Those on the high-protein diet lost an average 1.2 cm around the waist, compared to a gain of 0.5 cm for those on the control diet.

Similarly, those on the high-protein diet reported high feelings of satiety than did the control group, and they had a higher respiratory quotient.

There were no statistically significant differences between the 2 groups in blood test results, physical activity or fat free mass.

Dr Lejeune concluded: "Despite no differences in attitudes to eating, a protein intake of 18% as energy versus 15% as energy resulted in improved weight maintenance, as well as improved fat distribution based on body waist circumference, and improved substrate oxidation and satiety."

She explained: "In the short term, weight loss is often successful, but weight maintenance in the long term is more difficult. Additional protein intake may contribute to the storage of fat free mass, may increase satiety and have a lower energy storage efficiency during overfeeding. The result may be that higher protein diets have a higher cost of weight gain."

In answer to questions from the floor of the congress, Dr Lejeune said that the patients in the control group had not received a lunchtime drink and acknowledged that this left open the possibility that some of the difference between the two groups could be accounted for by the placebo effect.

[ECO: Study title: *Additional protein intake limits weight gain after weight loss in humans. Abstract t4:02*]

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Item 6

**Novel Drugs for the Treatment of Diabetes**

A new family of possible drugs to treat type 2 diabetes are being developed from D-Xylose, a sugar found in fruits.

A new approach to providing medication for adult diabetics (type 2 diabetes) that is not dependent on insulin has been developed by a doctoral student at the Hebrew University of Jerusalem. For his work, which he did for his Ph.D. thesis in pharmacology, Arie Gruzman was awarded one of this year's Kaye Innovation Awards at the Hebrew University.

Unlike other conventional drugs that require active insulin-producing cells in the pancreas and that often fail to overcome a companion problem of insulin resistance, the novel compounds developed by Gruzman and his supervisor, Prof. Shlomo Sasson, in collaboration with Prof. Yehoshua Katzhendler and Prof. Erol Cerasi of the Hebrew University School of Pharmacy and the Faculty of Medicine, are unique in that they can reduce hyperglycemia (above-normal levels of glucose in the blood) by increasing the rate of glucose disposal in the blood in a non-insulin-dependent manner.

The new drugs, when fully developed, may provide a treatment to diabetic patients who have especially serious problems of insufficient natural insulin production and/or resistance to insulin.

A patent for these new compounds -- which, perhaps surprisingly, are based on D-Xylose, a sugar found in fruits -- has been obtained through the Hebrew University's Yissum Research Development Company. The laboratory work was supported financially by the Deutsch Foundation of Venezuela and the Nophar Program of the Israel Ministry of Trade and Industry.

Source: Hebrew University of Jerusalem 06/05/2003

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**DID YOU KNOW:** . After 6 years of follow-up, researchers found that watching TV was associated with both becoming obese and developing diabetes. After adjusting for confounding factors, each additional 2 hours per day of TV watching was associated with a 23% increase in obesity and a 14% increase in type 2 diabetes.

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Item 7

### **Modified Pig Pancreas Cells Reverse Diabetes**

*Genetic engineering has improved the survival rate of diabetic monkeys that receive pig pancreas cells.*

The data was presented by the University of Minnesota's Diabetes Institute for Immunology and Transplantation. and Immerge BioTherapeutics on June 3 at the American Transplant Congress.

The study involved the transplantation of islet cells purified from genetically modified pigs into the pancreas of diabetic cynomolgus monkeys.

"In this swine, we have been able to 'knock-out' the gene that is irresponsible for beginning the immediate and overwhelming rejection process that happens in transplants between species," says Julia Greenstein, CEO and President of Immerge BioTherapeutics.

Immediately after the transplant, the monkeys achieved normal glucose levels and no longer required insulin injections. They were treated with an immunosuppressive cocktail and didn't require injections for up to 70 days.

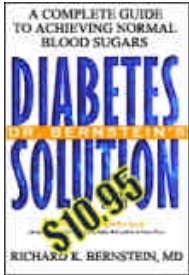
"This data is very significant because while we have been able to reverse diabetes in past islet studies, we had only seen two to three week survival times before the graft was lost due to the overwhelming rejection response," says Bernhard Hering of the Diabetes Institute for Immunology and Transplantation at the University of Minnesota.

In addition, there was no evidence of antibody-mediated rejection, which is common in transplantations involving solid organs such as kidneys and hearts.

And Greenstein says that research by Immerge BioTherapeutics has found that cells from the modified pigs are also unable to spread pig retroviruses to human cells in culture.

The findings could benefit a small subset of diabetics, known as "brittle" diabetics, who suffer from a condition that is defined by the overreaction of blood glucose levels from minute changes in diet, exercise and insulin. Researchers are also now looking at the potential of both islet and solid organ xenotransplants from the modified pigs.

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Item 8

### **Reversing Early Kidney Damage in Diabetics**

*Patients with type 1 diabetes who have slightly elevated levels of protein in their urine are not necessarily destined to develop kidney failure years later.*

In fact, during the study's six-year follow-up period, the condition, known as microalbuminuria, actually regressed in nearly 60 percent of patients with this form of diabetes, who must take insulin to live.

"Microalbuminuria has this label as a dire finding, that kidney disease is inevitable," said study author Dr. Bruce A. Perkins of the Joslin Diabetes Center in Boston, Massachusetts.

But the new findings "give hope that with the right medical care people can get rid of this condition" before it progresses, he says.

When the kidneys, which filter blood, become damaged by diabetes, protein from blood can leak into urine. While doctors have thought this damage was irreversible, Perkins said, the new results indicate it may be repaired in patients who have small protein elevations in the urine that are suggestive of lesser amounts of damage.

Extensive damage leads to kidney failure, which requires that a patient undergo regular dialysis or a kidney transplant.

In the study, published last Thursday in *The New England Journal of Medicine*, microalbuminuria was most likely to regress in patients who had their blood sugar under tight control and had healthy levels of cholesterol, triglycerides and blood pressure.

The findings suggest that quality medical care that detects microalbuminuria early and addresses these other factors may afford the kidneys an opportunity to heal, Perkins said.

"If one develops microalbuminuria, there are still measures that can be taken to try to reverse it," he said.

The study involved 386 patients who had microalbuminuria during a two-year evaluation period and were then followed for the next six years to see whether the condition persisted. While microalbuminuria regressed in 58 percent of patients, 19 percent developed a more advanced condition called proteinuria, which is marked by higher levels of protein in the urine that signal greater kidney damage.

Statistics show that about half of patients with type 1 diabetes will develop microalbuminuria at some point in their lives, and the odds are even greater for those with type 2 diabetes, according to Perkins.

He said that while the study did not include people with type 2 diabetes, which is the more common form of the disease, the findings could possibly apply to them as well.

"It's likely, but it definitely should be studied," Perkins said.

In an accompanying editorial, Dr. Eberhard Ritz of the University of Heidelberg in Germany writes that the study provides "welcome documentation that a widely accepted surrogate marker for the progression of (kidney) disease can be favorably influenced." *NEJM May 29, 2003*

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**FACT: Two studies reported in the June 5 issue of the *New England Journal of Medicine* offer hope for those with microvascular complications of type 1 diabetes. The first study shows regression of microalbuminuria with aggressive management of diabetes, and the second shows that intensive therapy can slow the progression of carotid intima-media thickness.**

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Item 9

**Walking Reduces Risk of CVD, CV Death and Total Mortality in Diabetic Men & Women**

*Two studies validate that walking was associated with reduced CVD risk and total mortality for Men and Women with type 2 diabetes.*

The present study was conducted to examine the relationship of physical activity with risk of cardiovascular disease (CVD) and mortality among men with type 2 diabetes. CVD risk and mortality are increased in type 2 diabetes. Few epidemiological studies have investigated the effect of physical activity on these outcomes among type 2 diabetics.

Of the 3058 men who reported a diagnosis of diabetes at AGE 30 years or older in the Health Professionals' Follow-up Study (HPFS), we excluded 255 who reported a physical impairment. In the remaining 2803 men, physical activity was assessed every 2 years; 266 new cases of CVD and 355 deaths of all causes were identified during 14 years of follow-up. Relative risks of CVD and death were estimated from Cox proportional hazards analysis with adjustment for potential confounders. The multivariate relative risks of CVD incidence corresponding to quintiles of total physical activity were 1.0, 0.87, 0.64, 0.72, and 0.67 (*P* trend=0.07). The corresponding multivariate relative risks for total mortality were 1.0, 0.80, 0.57, 0.58, and 0.58 (*P* trend=0.005). Walking was associated with reduced risk of total mortality. Relative risks across quintiles of walking were 1.0, 0.97, 0.87, 0.97, and 0.57 (*P* trend=0.002). Walking pace was inversely associated with CVD, fatal CVD, and total mortality independently of walking hours.

From the results of the study it was concluded that physical activity was associated with reduced risk of CVD, cardiovascular death, and total mortality in men with type 2 diabetes. Walking and walking pace were associated with reduced total mortality. *Circulation. 2003;107:2435-2439.*

In the second study, they used 5125 female nurses with diabetes In the Nurses' Health Study. The objective of the study was to determine whether physical activity decreases risk for cardiovascular disease among diabetic women.

Physical activity was first assessed in 1980 and was updated in 1982, 1986, 1988, and 1992 through validated questionnaires. Average hours of moderate or vigorous exercise and a metabolic equivalent of task (MET) score were computed.

During 14 years of follow-up (31 432 person-years), 323 new cases of cardiovascular disease were documented (225 cases of coronary heart disease and 98 cases of stroke). The age-adjusted relative risks according to average hours of moderate or vigorous activity per week were 1.0, 0.93, 0.82, 0.54, and 0.52. These figures did not change materially after adjustment for smoking, body mass index, and other cardiovascular risk factors (1.0, 1.02, 0.87, 0.61, and 0.55, respectively; *P* = 0.001 for trend).

In separate analyses, levels of physical activity were inversely associated with coronary heart disease and ischemic stroke. Among women who did not exercise vigorously, the multivariate relative risks for

cardiovascular disease across quartiles of MET score for walking were 1.0, 0.85, 0.63, and 0.56 ( $P = 0.03$  for trend). Faster usual walking pace was independently associated with lower risk.

From the results it was concluded that among diabetic women, increased physical activity, including regular walking, is associated with substantially reduced risk for cardiovascular events. *Ann Intern Med.* 2001;134:96-105.

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Item 10  
**Tight Glucose Control In Diabetes Lowers Risk Of Atherosclerosis**

*Strict glucose control in type 1 diabetes reduces the risk of atherosclerosis, a benefit that persists for years.*

Since 1993, when the Diabetes Control and Complications Trial (DCCT) ended, researchers have known that intensive glucose control greatly reduces the eye, nerve, and kidney damage of type 1 diabetes. Now, researchers conclude, the benefits of tight control also extend to the heart.

"Intensive control is difficult to achieve and maintain, but its benefits are even greater than we realized," says study chair Dr. Saul Genuth of the Case Western University. "The earlier intensive therapy begins and the longer it can be maintained, the better the chances of reducing the debilitating complications of diabetes."

The DCCT was a multicenter study that compared intensive versus conventional management of blood glucose in 1,441 people with type 1 diabetes. Patients on intensive treatment kept glucose levels as close to normal as possible with at least three insulin injections a day or an insulin pump and frequent self-monitoring of blood glucose. Intensive treatment aimed to keep hemoglobin A1c (HbA1c), which reflects average blood sugar over 2 to 3 months, to as close to normal (6 percent) as possible. Conventional treatment at that time consisted of one or two insulin injections a day with daily urine or blood glucose testing.

After 6½ years of the DCCT, HbA1c levels averaged 7 percent in the intensively treated group and 9 percent in the conventionally treated group. When the DCCT ended, those who had been assigned to conventional treatment were encouraged to adopt intensive control and shown how to do it, and researchers began a long-term follow-up study of the participants, called the Epidemiology of Diabetes Interventions and Complications (EDIC) study.

The DCCT could not study atherosclerosis because the participants were relatively young, and heart disease takes years to develop. In 1994-95 and again in 1998-2000, EDIC researchers used ultrasound to measure the thickness of participants' carotid arteries, the two blood vessels in the neck that carry blood from the heart to the brain. Carotid wall thickness reflects the amount of atherosclerosis, or plaque build-up, in the artery: the thicker the arterial wall the greater the risk of later heart attack and stroke.

At the time of their first ultrasound, the diabetic participants' carotid wall thickness was similar to that of non-diabetic controls matched for age and gender. Five years later, however, the participants had thicker arterial walls than those of the non-diabetic group. In addition, the thickness of the carotid walls had increased less in the intensively treated group during the 5 years than in the conventionally treated group. "This finding strongly suggests that atherosclerosis progressed more slowly in the intensively treated group," noted Dr. Genuth.

Carotid thickening was also linked to known cardiovascular risk factors including age, higher systolic blood pressure, smoking, LDL:HDL cholesterol ratio, and urinary albumin (a measure of kidney function). After adjusting for these factors, the study found that the differences in carotid wall thickness between the two groups were due to the differences in blood glucose levels during the DCCT.

"The risk of heart disease is about 10 times higher in people with type 1 diabetes than in people without diabetes, but it was unclear to what extent blood glucose contributed to the development of heart disease," said Dr. David Nathan of Massachusetts General Hospital, who co-chaired the DCCT/EDIC research group. "Now we know that *intensively controlled glucose significantly reduces the atherosclerosis underlying heart disease just as it reduces damage to the eyes, nerves, and kidneys in people with type 1 diabetes*. What's striking is that the benefits of intensive control persisted despite a gradual rise in the HbA1c levels of the intensively treated group during the 5 years after DCCT ended."

"For many people, diabetes is difficult to manage with today's tools. Every new finding about the importance of blood glucose control in preventing complications heightens our determination to foster research that results in new therapies that take the burden off the patient," said Dr. Judith Fradkin, director of the Diabetes, Endocrinology, and Metabolic Diseases Division of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). *June 5, 2003 issue of the New England Journal of Medicine. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)*

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Item 11

**Edmonton Protocol Shows Safety, Efficacy of Islet-Alone Transplantation**

*Islet-alone transplantation is safe and effective, and the Edmonton Protocol used to accomplish this can be safely replicated.*

Preliminary findings were presented last Sunday during the first plenary session of the American Transplant Congress, the joint meeting of the American Society of Transplantation and the American Society of Transplant Surgeons.

On behalf of the Immune Tolerance Network, James Shapiro, MD, from the University of Alberta in Edmonton, Canada, presented the results of islet-alone transplantation in the first 36 patients enrolled at nine international sites. A total of 49 transplants have been performed. The first transplants took place in November 2001. The immunosuppression regimen included daclizumab, sirolimus, and tacrolimus. Median follow-up is 9.4 months.

To be eligible for the study, patients had to have type 1 diabetes with stable insulin requirements, a weight limit of 70 kg or less, an adequate renal reserve defined as a creatinine clearance of greater than 80 mL/min, and no progressive diabetic complications. There are 14 men and 22 women in the study. Average age is 48 years, and average duration of diabetes is 26 years.

The primary endpoint of the trial is insulin independence. Secondary endpoints include metabolic parameters, such as stable hemoglobin A<sub>1c</sub>, glucose tolerance, and stimulation tests.

To date, 52% of the patients who have received any transplants are insulin-independent, while 82.3% of those in whom transplants have been completed are insulin-independent; some patients have required up to three transplants.

As a whole, glucose control was abnormal in 92% of patients prior to islet transplantation. Glucose control is normal in 75% afterward.

There have been no deaths in the study. There have been two cases of severe neutropenia, which are the only two life-threatening events to date, and 15 cases of severe adverse events, including bleeding at the percutaneous portal access site, transient elevation in liver function tests, mouth ulcerations, neutropenia, leukopenia, thrombocytopenia, and hypercholesterolemia. All patients were C-peptide negative prior to surgery and 94% are C-peptide positive now.

Nineteen percent of patients were receiving statin therapy for hyperlipidemia prior to transplantation, and 39% began taking statins afterward. The remaining 42% remain statin-free.

"There was a considerable variation in success of islet transplantation between the different sites," Dr. Shapiro reported. It ranged from a high of 90% at the Edmonton site to 23% success rate in some of the other sites. "This reflects a learning curve here," he noted. "[The findings] emphasize a need for dynamic training and...longer follow-up to define safety, quality of life issues, and the impact of possible secondary complications."

Rodolfo Alejandro, MD, from the University of Miami in Florida, reported the results of the 15 patients to undergo islet transplantation at that institution. Thirteen are insulin-independent at this point under a steroid-free immunosuppressive regimen, he said. He added that there appears to be partial islet loss or a loss of islet mass over time, a finding that needs further exploration.

Thierry Berney, MD, from Geneva University Hospital in Switzerland, reported results of islet transplantation in five patients at his center. He said that three, or 60%, are insulin-free at this point, and "I am confident that we can raise that number to 80% with a third transplantation in one patient," he told Medscape. Two patients have undergone two transplants to date.

"Personally, what I'm most concerned about is the complication rate," Dr. Berney said. "There is about a 10% procedural complication rate, which is what you would expect. But almost all of the patients have at least one side effect of rapamycin. And almost all have dyslipidemia and are on statin therapy."

"Islet transplantation holds potential as augmentation in the treatment of diabetes, possibly as an alternative option to pancreas transplantation," Dr. Turka said. Even further down the road, he speculated that islet transplantation could even replace pancreas transplantation. "That's certainly nowhere near the case now," he hastened to add.

The primary endpoint of this trial has been achieved, the investigators reported at the American Transplant Congress. "Clearly the Edmonton Protocol has been successfully replicated," Dr. Shapiro announced.

*ATC 2003 Annual Meeting: Abstract 3, presented June 1, 2003; abstract 401, presented June 2, 2003.*

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**Did YOU KNOW:** Those over 18 years with blood pressure ranging from 120/80 to 139/89 mm Hg belong to the new category "prehypertension," a high-risk precursor to hypertension. That, according to the Joint National Committee 7 report.

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Item 12

**Color Vision Test Detects Diabetic Retinopathy Before Vision is Lost**

*Automated tritan contrast threshold (TCT) assessment identifies sight-threatening diabetic retinopathy before vision is lost.*

Color vision often deteriorates before visual acuity is lost and morphological changes are detectable, Dr. Anthony G. Casswell, of Sussex Eye Hospital in Brighton, and colleagues explain. However, conventional color discrimination tests are not sensitive enough for widespread screening purposes.

The authors performed automated TCT testing on 510 patients with best corrected visual acuity exceeding 20/30, and findings were compared to those obtained by slit lamp biomicroscopy. TCT was measured using a computerized, cathode ray tube-based system with a custom-made plug-in card stimulus generator. The TCT was 42.5 for patients with no retinopathy and 41.7 for those with background retinopathy.

Seventeen eyes exhibited STDR, and TCT correlated significantly with the presence of STDR ( $p < 0.001$ ), with a sensitivity of 94% and a specificity of 95%. The sensitivity for detecting proliferative retinopathy and maculopathy was 100%. Among the 3 patients with pre-proliferative retinopathy, mean TCT was

29.6. For the 2 with proliferative retinopathy, the mean TCT was 21.7, and for the 12 with maculopathy, the TCT was 24.0.

TCT deficits showed no association with duration of diabetes or the latest glycosylated hemoglobin results.

Because it directly measures visual function, Dr. Casswell's team believes that TCT testing will "also identify early those subjects who will progress to develop more severe retinal disease." *Br J Ophthalmol* 2003;87:747-752.

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Item 13

**Fasting And Post-Challenge Hyperglycemia Indicates Distinct Pathways in Progression Of Type 2 Diabetes**

*Two measurements may represent distinct phenotypic pathways in the evolution of type 2 diabetes, new research suggests.*

People with abnormal fasting and post-challenge hyperglycemia appear to have different rates of progression to diabetes; therefore, these 2 measurements may represent distinct phenotypic pathways in the evolution of type 2 diabetes.

Impaired fasting glucose (IFG) refers to a mildly elevated glucose level immediately after an oral glucose tolerance test (OGTT), whereas impaired glucose tolerance (IGT) indicates a mildly elevated plasma glucose levels 2 hours later. In the United States, detection of diabetes relies on measurement of fasting plasma glucose levels alone, and it is assumed that the value is predictive of impaired glucose tolerance and ultimately type 2 diabetes. This assumption has not been validated in longitudinal studies, however.

James B. Meigs, MD, MPH, with the Massachusetts General Hospital and Harvard Medical School, Boston, and colleagues studied this progression using biennial oral glucose tolerance tests and survival analysis to assess progression from normal glucose tolerance (NGT) to abnormal fasting plasma glucose (FPG; >110mg/dL or 6.1 mmol/L); abnormal 2-h plasma glucose (2hPG; >140mg/dL or 7.8 mmol/L); impaired fasting glucose (IFG) (FPG 110mg/dL or 6.1-6.9 mmol/L, 2hPG <140mg/dL or 7.8 mmol/L); and IGT (FPG <110mg/dL or 6.1 mmol/L, 2hPG 140mg/dL or 7.8-11.0 mmol/L). It was also used to assess progression from IFG-IGT to diabetes (FPG >126mg/dL or 7.0 mmol/L or 2hPG >200mg/dL or 11.1 mmol/L).

At baseline, 815 subjects of the Baltimore Longitudinal Study of Aging had a mean age of 57 years, 35% were women, and 60% (n=488) had NGT. Of those, over half were followed for at least 10 years.

By 10 years, 14% had progressed to abnormal FPG, and 48% had progressed to abnormal 2hPG, the researchers report. Of the 267 subjects who progressed to IFG-IGT, 216 were followed for an additional 10 years. During that time, 8% of them progressed to diabetes by FPG whereas 27% progressed by 2hPG. However, of the subjects developing abnormal FPG, 42% did not develop abnormal 2hPG, and vice versa.

"These data suggest that abnormal FPG and 2hPG levels are not necessarily part of a continuum in the evolution of hyperglycemia," the researchers conclude.

Dr. Meigs and colleagues note that detection programs "relying solely on elevated FPG levels using current diagnostic thresholds may only detect the more uncommon IFG phenotype, and miss a substantial number of subjects at risk for diabetes on the basis of abnormal 2hPG levels."

They also point out that specifying a lower "abnormal" FPG level (in the 100mg/dL-103mg/dL or 5.55-5.7 mmol/l range), using the OGTT, or identifying clusters of insulin resistance-related traits may be required to maximize identification of subjects at risk for developing type 2 diabetes. *Diabetes*. 2003 Jun;52(6):1475-1484

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**FACT:** Intensified blood glucose monitoring improved glycemic control in a large cohort of stable, insulin-treated veterans with type 2 diabetes. SMBG provided a strong stimulus for improved self-care resulting in clinically important and sustained reductions in HbA<sub>1c</sub>. *Diabetes Care* 26:1759-1763, 2003

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Item 14

**New Target for Antidiabetic Agents Identified**

*U.S. researchers identify a protein that could serve as a new target for drugs designed to treat type II diabetes.*

The protein, known as TRB3, is actually a homolog of a protein found in the fruit fly *Drosophila tribbles*, senior author Dr. Marc Montminy, from the Salk Institute for Biological Studies in La Jolla, California, and colleagues note.

The focus on TRB3 was the result of a search to identify proteins that modulate the activity of Akt, a main target of insulin that blocks hepatic glucose output when glucose is available from food. Mice lacking the Akt gene demonstrate insulin resistance similar to that seen in humans with type II diabetes.

Dr. Montminy's team found that TRB3 acts as a negative modulator of Akt and that its expression is increased under fasting conditions. By binding to Akt, TRB3 prevents the enzyme from being activated by insulin, leading to increased glucose output from the liver.

Elevated hepatic levels of TRB3 RNA and protein were identified in diabetic mice compared with wild-type mice, the authors report. Hepatic overexpression of TRB3 was associated with hyperglycemia and glucose intolerance.

Based on these findings, the researchers suggest that TRB3 may be an "attractive drug target in the treatment of type II diabetes." *Science* 2003; 300: 1574-1577.

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Item 15

**Walking Less Than 20 Minutes A Day! Reduces Risk of Heart Disease 61%**

*Moderation is the key to sustaining exercise. Two studies show that exercise for less than 20 minutes a day and in moderation can reduce the risk of heart disease by 61%*

The first study shows that physical activity during leisure time, but not at work, is linked to a reduced risk of heart problems.

We already know that exercise is beneficial for the heart. What has been less clear is what kind of physical activity is best.

Researchers in Ulm, Germany, have been investigating whether the context of physical activity matters. They studied a group of 312 people aged between 40 and 68 with heart disease, to determine levels of physical activity during leisure time and in the workplace. They were compared to a group of 479 healthy people. This revealed that leisure activity, but not workplace activity, can reduce your risk of heart disease.

Those spending less than an hour a week of physical activity during their free time were 15 per cent less likely to develop heart problems compared to those who took no activity. Those spending between one and two hours in physical activity had a 40 per cent reduced risk and those who spent more than two hours had a 61 per cent reduced risk.

The study is interesting in highlighting the importance of the leisure context for physical activity. It

suggests that people should do more than just rest during their time off - they should get moving too!  
*Archives of Internal Medicine 26th May 2003*

In a second study they found that participants in an exercise study were more likely to keep up moderate, rather than intense, physical activity in the long term.

While intense exercise gives the most health benefit, it is important to be realistic and focus on what people can, and will, do. Researchers at Duke University have studied what happens when people are taken through supervised exercise of differing intensity. A group of 87 'couch potatoes' was assigned to either high, moderate, or low intensity exercise for nine months. The high intensity activity involved the equivalent of 18 miles a week of brisk walking or jogging, moderate was 11 miles of the same, while low intensity was just 11 miles of walking.

When they finished the program, a high proportion of the group kept up their exercise. But those in the high intensity group cut back on time spent, while those in the low intensity group increased the intensity of their exercise. This suggests that people do tend to gravitate to a moderate level of activity. Those who abandoned their exercise gave lack of time as the main reason. Walking was the preferred activity, although some used elliptical trainers and other machines, or went swimming. *American College of Sports Medicine Meeting 29th May 2003*  
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### Quote of the Week-----

**"Patience and perseverance have a magical effect before which difficulties disappear and obstacles vanish"**

-----John Quincy Adams

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